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Are Coumarin Derivatives The New Keys in Depression Treatment? In silico Key-lock Fitting Analysis of Coumarin Derivatives with Monoamine Oxidase-A

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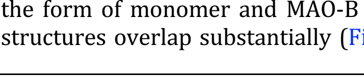
Abstract: The research of ligand-protein interactions with *in silico* molecular modeling studies on the atomic level gives an opportunity to be understood the pharmacokinetic metabolism of anti-depressant drug candidates. Monoamine oxidase (MAO) enzymes are important targets for the treatment of depressive disorder. MAOs have two isoforms as MAO-A and MAO-B being responsible for catalyzing of neurological amines. In this study a new series of coumarin derivatives were designed for selective and reversible inhibition of MAO-A enzyme. 3rd, 5th and 7th positions were selected to be placed of five different side groups. Docking procedures of each ligand in M series of these novel 125 compounds were executed with 10 runs by using AutoDock4.2 software. Docking results were analyzed via Discovery Studio 3.1 (Biovia Inc.). The most promising compounds were M118 and M123 according to selectivity index, SI (MAO-B/MAO-A)=180 fold and 209 fold and K_i values 7.25 nM and 12.01 nM, respectively. Overall, the current study provided significant knowledge for the development of new anti-depressant drugs.

Keywords: coumarin derivatives; monoamine oxidase; de novo drug design; molecular modeling; docking

1 Introduction

Monoamine oxidase (MAO, EC 1.4.3.4) is a flavoenzyme placed at the outer membrane of mitochondria as an integral protein in all mammalian tissues. MAO enzymes are responsible for catalytic reactions of biologic and xenobiotic amines in the nervous system.[1, 2] According to their substrate specificity,[3] sequence difference and cellular location[4] two isoforms as MAO-A and MAO-B have been identified. Both isoenzymes hold flavin adenine dinucleotide (FAD) coenzyme in hydrophobic binding site as a redox cofactor.[5] Although MAO-A is in the form of monomer and MAO-B is a dimer, their 3D structures overlap substantially (Figure 1). MAO-A and



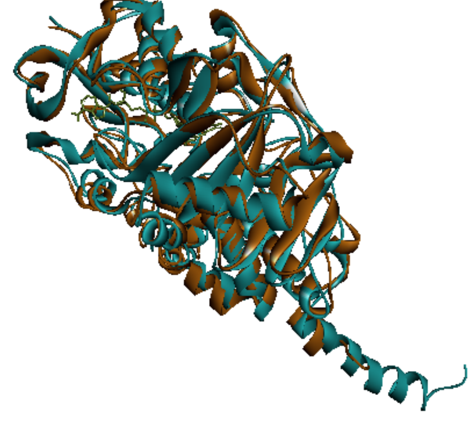


Figure 1 Superimpose of MAO isoenzymes. The blue structure represents MAO-A, and the orange structure represents MAO-B enzyme

MAO-B isoforms show 85% sequence similarity and 72% identity.[1] This high sequence similarity is one of the essential factors to consider in selective inhibitor design. Another important point is the correct estimate of how the modifications in the ligand's scaffold will affect their potency. In the nervous system, norepinephrine, and serotonin inhibition achieved with MAO-A, phenylethylamine, and benzylamine inhibition achieved with MAO-B. However, dopamine, tyramine, and tryptamine are non-selective substrates for MAO-A, and MAO-B.[6] Selective and reversible inhibition of MAO-A is an essential target for depression treatment. MAO-A is primarily responsible for the oxidation of tyramine. Therefore MAO-A's peripheral inhibition has been associated with the risk for an acute hypertensive syndrome known as the "cheese reaction".[7,8] The neurotransmitters that effected by MAO enzymes are responsible for changing myocardial function. Since heart tissues are affected by free radicals in the neural and hormonal system, the decreasing of tissue monoamines increases MAO-derived H_2O_2 production

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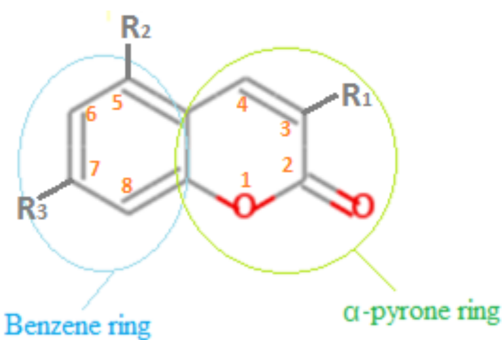

Figure 2 Coumarin Scaffold and Selected Positions

in heart tissue.[9] Because of these types of risks, reversible inhibitor design has become essential for researchers. Corresponding to previous studies providing information about *de novo* designed MAO inhibitors, one of the most available scaffold models is also coumarin[10-15] (Figure 2). Coumarin with other name 2-H-Chromen-2-one is a white lactone. Coumarins comprise a large family of compounds. Approximately 1300 coumarin derivatives are obtained from plants, bacteria, and fungi.[16] Coumarins possess several biological activities such as anticoagulant, anti-inflammatory,[17] analgesic,[18] anticancer,[19] antimicrobial, antiviral,[20] anti-malaria,[21] antioxidant, antifungal,[22] and antinociceptive.[23] Some coumarin derivatives also have MAO-A inhibition property[11]. In this study, 125 different coumarin derivatives were tested with MAO-A and MAO-B enzymes in terms of *in silico* key-lock fitting analysis and comparison of their inhibition properties of these ligands was given.

In order to discover the appropriate molecule in the drug development, it may be necessary to investigate the inhibition coefficient of hundreds of molecules with the target enzyme. Using computational tools to reduce the significant workload and cost of all these researches contributes significantly to the studies. The current study showed inhibitory activity of some coumarin derivatives against monoamine oxidase enzymes by using computational modeling methods via AutoDock4.2 software[24], AutoDock Tool (ADT)[25, 26], and Discovery Studio 3.1 (Biovia Inc.)[27] programs (Figure 3). AutoDock 4.2 is a very available molecular docking program used computational methods to find the free energy of binding and lowest inhibition binding constants (K_i) values by calculating a scoring function using AMBER force field for proteins and ligand interactions additionally RNA and DNA molecules.[26] *In silico* molecular modeling methods have been used more frequently in rational drug design for inhibition of MAO enzymes. [28, 29, 30, 31,32] Thus, data is provided on which molecules are worth synthesizing. In the present study, our aim is to reach more efficient binding and selectivity results by designing new reversible MAO-A inhibitors based on coumarin scaffold in the treatment of depression.

2 Result and Discussion

In the present study, the interest of *de novo* designed 125 coumarin derivatives was found to be higher on MAO-A than MAO-B. This result showed that the selection of the 3rd, 5th and 7th positions for the placement of F, Br, Amide, Methoxy, and Phenyl is important in MAO-A inhibition. All compounds were

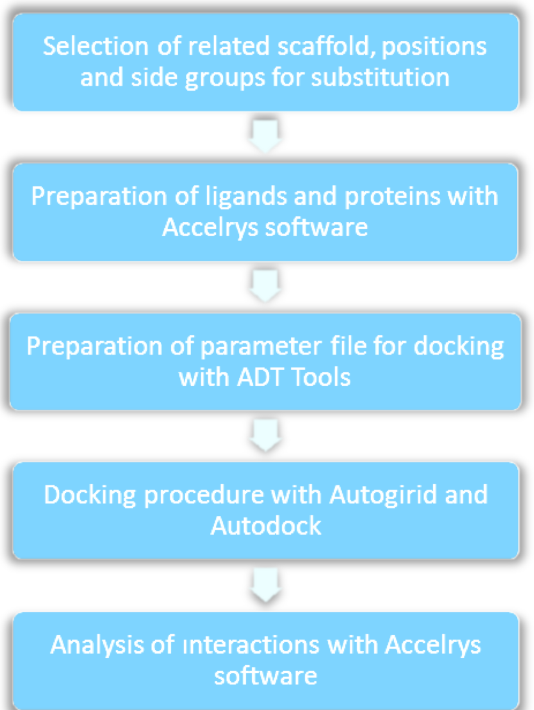

Figure 3 Steps for de novo drug design via computational tools

disposed of in the hydrophobic binding site of MAO enzymes as near to N5 atom of FAD coenzyme (Figure 4). Compound M118 (3-amide-5,7-diphenylcoumarin derivative) has an essential place in this study in terms of K_i value and free binding of energy (ΔG). M118 is the most available inhibitor candidate for MAO-A in the 125 ligands. A π-π interaction had 3.43 Å distance was installed between TYR407 and α-pyrone ring of coumarin nucleus. The same residue made another π-π interaction with the benzene ring of coumarin had 4.25 Å distance. As shown in Figure 5A and 5A-1, two polar interactions were established. Polar interactions had 4.9 Å, and 5.9 Å distances were established between TYR197 and Nitrogen atom of the ligand; and TYR444 and Oxygen atom of the amide group, respectively. Strong electrostatic interactions were performed between compound M118 and FAD coenzyme, GLY443, ASN181, and THR201 residues. Some van der Waals interactions were improved between M118 and THR314, TYR407, GLN215 GLY67, ALA68, LYS305, TYR69, ILE207, ILE180, PHE208, ASP399, TYR60, ASP329, THR327, LEU171, GLN206, PHE103 and VAL82

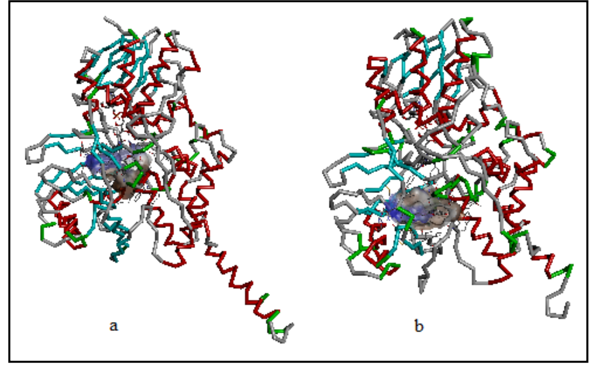

Figure 4 Hydrophobic binding sites. a) MAO-A, b) MAO-B enzymes. Blue surface represents lower and brown surface represents higher hydrophobicity.

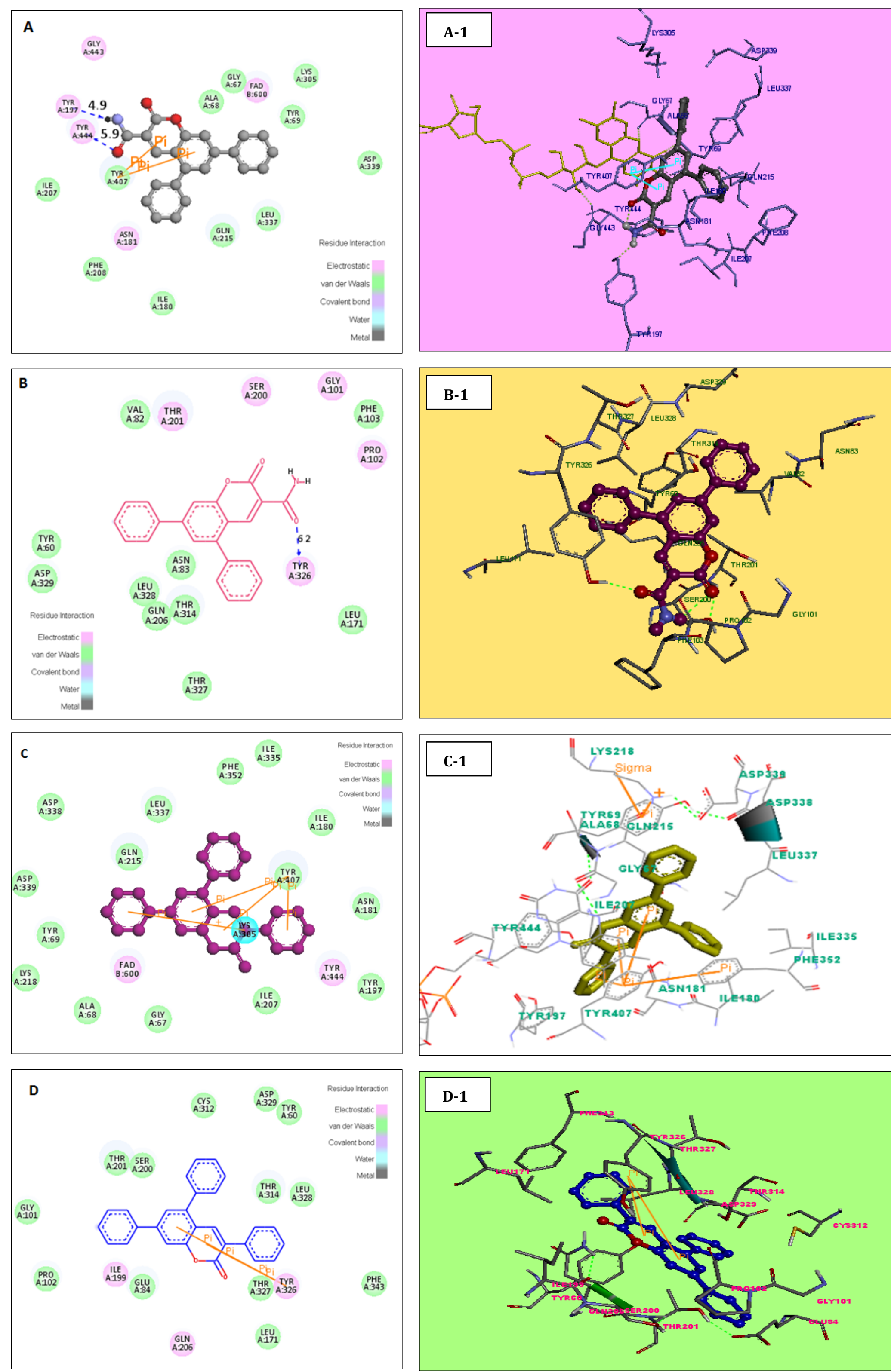

Figure 5 Interactions between ligands and enzymes. A) 2D and A-1) 3D representations of M118 and MAO-A. B) 2D and B-1) 3D representations of M118 and MAO-B. C) 2D and C-1) 3D representations of M123 and MAO-A. D) 2D and D-1) 3D representations of M123 and MAO-B.

residues (Figure 5A). As shown in Figure 5A-1, the side chain of THR314 was very near to ligand's atoms. In Figure 5B and Figure 5B-1 what was interesting about the M118's interaction with MAO-B was that the ligand made an aromatic sandwich between TYR60 and TYR326. M118 was found to be placed in a position similar to co-crystallized position of another coumarin derivative in MAO-B (pdb code: 2V60). It was a significant result signing the correctness of prediction. Compound M123 (3,5,7-triphenylcoumarin derivative) had various π interactions with certain residues which are in the MAO-A enzyme binding site. As shown in Figure 5C and Figure 5C-1 a π-caution interaction was formed that had 4.9 Å distance between Nitrogen atom

Table 1 Best ten ligands for MAO-A inhibition.

Code	Structure	K_i (nM) MAO-A	K_i (nM) MAO-B
M118		7.25	1310
M123		12.01	2520
M029		13.30	916.8
M109		17.70	1600
M115		23.54	597.98
M122		35.07	640.62
M120		35.20	1420
M061		37.39	623.5
M087		50.43	1700
M080		50.59	802.8

of LYS:305:NZ and phenyl ring at the 7th position of ligand. TYR407 installed three π-π interactions with ligand. One of them occurred with benzene ring of coumarin nucleus with 5.1 Å distance; other interaction was formed with the α-pyrone ring of coumarin nucleus had 3.7 Å distance. A π-π interaction had 4.6 Å distance was formed with phenyl ring existent at the 3rd position of the ligand. FAD coenzyme and TYR444 had electrostatic interactions with the ligand. GLY215 and LEU337 made strong van der Waals interactions with M123. Compound M123 is the best selective ligand and the best second inhibitor in terms of affinity for MAO-A (Table 1). M123 has double π-π interactions and electrostatic interactions with TYR326 residue of MAO-B (Figure 5D and Figure 5D-1). One of them had 6.68 Å distance installed between benzene ring of M123 and TYR326, and the other had 4.75 Å distance was formed with α-pyron of coumarin nucleus. Two other electrostatic interactions have occurred with ILE199 and GLN206. Other residues interacted with M123 in MAO-B active site were THR201, LEU171, THR327, PRO102, GLY101, TYR60, SER200, TYR327, CYS312, ASP329, LEU328, GLU84, and PHE343. The present study provides some new information in understanding the design of which side groups coumarin derivatives change and increase selectivity and affinity. Previous studies have demonstrated the importance of positions 3rd, 4th, and 7th for MAO inhibition.[13, 15, 23] In this study, results support the view that the 3rd and 7th positions have an important role in the inhibition of the MAO-A enzyme. In addition, it was understood that position 5th is more important in terms of influencing selectivity than position 7th. Especially, placing of aromatic groups in the 3rd and 5th positions allowed a large number of chemical interactions with the tyrosine residues in the active region of MAO-A. A study of Matos et al. (2009) with resveratrol-coumarin hybrid components showed that the substitution of methoxy or hydroxy groups in 3rd position increases the potency against MAO-B.[13] In another study, coumarins with electronegative groups substituted at the position 3rd of the γ-pyrone nucleus were found related to a decreasing of selectivity against human MAO-B.[8, 14] In the current study, it was observed that the presence of F and Br electronegative groups in position 3rd reduced selectivity for MAO. The most unfavorable ligand in 125 ligands was M062 (3,5,7-triflourocoumarin) with K_i for MAO-A = 48.15 µM and Ki for MAO-B = 77.99 µM. According to Abdelhafez et al. (2013), AutoDock binding affinities of 7-oxycoumarin derivatives (4-methyl and/or 3,4-dimethylumbelliferone with acyclic acetohydrazide moiety) was found at pM levels for MAO-A and at µM levels for MAO-B. The interacted residues of MAO-A were ASN181, TYR444, GLN215, and ALA111.[11] Another study showed that the placing of bulky groups such as cyclohexyl or phenyl in the 3,4-positions of the 7-acetonyl coumarin derivatives increase inhibitory activities of them with both MAO-A and MAO-B but decrease the selectivity.[12] It is unclear why the inhibitory potency against MAO-B is affected by the length of the side chain.[33] Coumarin analogs interact with noncovalent bonds to human MAO-B complexes.[34] Some resveratrol-coumarin hybrid compounds such as 6-methyl-3-para hydroxy phenyl coumarin and 6-methyl-3-para methoxy phenyl coumarin were found high selective for the MAO-B with the inhibitory activity in the nano to picomolar range.[13]

As a result of the present study, it is estimated that it will be beneficial to take advanced studies the coumarin derivatives with *in vitro* and *in vivo* experiments for researching in the treatment of depression since most

of the 125 coumarin derivatives (88 compounds, 70%) have inhibition binding constants (K_i) values being lower than -8 with MAO-A. K_i values of 125 components showed that especially the presence of amide, phenyl, and Bromine increases the potency. The presence of fluoride and methoxy does not much affect or reduce the potency of ligand for MAO-A and MAO-B. Regarding best five selective ligands M123 was 209 fold, M118 was 180 fold, M109 was 90 fold, M029 was 68 fold, and M115 was 67 fold selective for MAO-A. The ranges of K_i values were between 0.00725-48.15 µM for MAO-A and 0.5861-77.99 µM for MAO-B. The ranges of free energy of binding (ΔG) values were between -11.10 kcal/mol and -5.89 kcal/mol for MAO-A and between -8.50 kcal/mol and -5.60 kcal/mol for MAO-B enzyme. K_i values of the most appropriate 10 ligands for MAO-A affinity were shown in Table 1. Accordingly, the selection of phenyl as a side group affects selectivity for MAO-A. The result of the analysis has shown that presence of phenyl at the 5th and 7th positions of coumarin reduces compatibility with MAO-B. This reduction may be due to the wider binding region of MAO-A compared to MAO-B's.

3 Conclusion

In this study, possible binding modes of coumarin derivatives with MAO isoenzymes were estimated. Based on *in silico* calculations, these estimations provided information on which side groups and positions changed the potency and selectivity of drug candidates. Since these *de novo* designed 125 coumarin derivatives were found more suitable for MAO-A, the selection of the 3rd, 5th, and 7th positions for the placement of the side groups was outstanding in the inhibition of MAO-A. According to the results of this study, the third position of the coumarin has a significant effect on potency. The presence of amide in position 3 enhances the affinity to MAO-A. It allows M118 to adapt very well to an area surrounded by three tyrosine residues (TYR197, TYR444, and TYR407) in the MAO-A enzyme. Aromatic groups in positions 3, 5, or 7 increase the selectivity and number of interactions with residues in MAO-A. Generally, the coumarin nucleus was essential to perform effective π-π interactions with the aromatic cage of MAO-A and MAO-B enzymes. Inhibition constants of 125 coumarin derivatives for MAO-A were found at nanomolar and micromolar levels. The K_i values and selectivity index values revealed that M118 and M123 ligands are 180 and 209 fold selective components, respectively. The presence of phenyl in the third position increased selectivity while reducing potency slightly. The presence of phenyl in all three positions allows the most selective inhibition. The results of this study can be used to select the ligand to be used in synthesis studies and to compare with K_i values to be found *in vitro* experiments.

4 Experimental

While the placements of coumarin derivatives within MAO isoenzymes were examined according to the key-lock fitting model, docking procedure was performed with ADT and AutoDock 4.2. Possible chemical interactions of ligands in the binding region of protein were examined by Discovery Studio 3.1. Linux OS was used for performing of log files in Toshiba Satellite with Intel core processor 2GB RAM.

4.1 Ligand Preparation

125 different ligands structures were drawn using 5 different side groups on coumarin scaffold. 3rd, 5th and 7th positions were selected to add side groups to observe changes in the activity. The selected five side groups were; Methoxy ($-OCH_3$), Fluorine (-F), Bromine (-Br), Amide ($-C(=O)NH_2$) and Phenyl ($-C_6H_5$). Ligands were drawn by Discovery Studio 3.1 (Biovia Inc.). All hydrogens were added. "Clean Geometry Tool" was used for optimization. All ligands were prepared as .mol2 and .pdb formats.

4.2 Protein Preparation

Proteins had been prepared formerly in the Modelling Laboratory of Prof. Dr. Kemal Yelekci. Protein preparation was conducted by using Discovery Studio 3.1 (Biovia Inc.). For this aim, crystal structures of MAO isoenzymes were obtained from Brookhaven Protein Databank (http://www.rcsb.org/pdb). Human MAO-A enzyme in complex with harmine (PDB code: 2Z5X, Resolution: 2.2 Å)[35] and MAO-B enzyme in complex with safinamide (PDB code: 2V5Z, Resolution: 1.6 Å)[34] were chosen. All water molecules, non-interacting ions and inhibitors were removed. FAD were become oxidized form. All hydrogen atoms were added. Protein were minimized with fast Dreiding-like force field, "Clean Geometry" tool was used for last optimization.

4.3 Docking Simulation

N5 atom of FAD was selected as the center of docking. Protein was retained rigid, but hydrogens were allowed free in their moving that were only in the active site of the protein. The dielectric constant was adjusted as 10, and ionic strength was set to 0.145, grid box was 70x70x70, and grid point was 0.375Å. Since rotational bond number was smaller than 10, the number of generations was adjusted to 27.000 and evaluation of mutation was 5.000.000. Lamarkian genetic algorithm was used. Autodock4.2 was chosen for all docking procedure. Docking was comprised as 10 runs.

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