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RESEARCH ARTICLE

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Molecular Docking Studies on (Hetero)arlylidene(4-substituted-thiazol-2-yl)hydrazines as MAO-B Inhibitors

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Abstract

Docking simulations were performed on series (Hetero)arlylidene-(4-substituted-thiazol-2-yl)hydrazines as MAO-B inhibitors. This was done by analyzing the interaction of these compounds with the catalytic site of the MAO-B enzyme. Assuming that the enzyme inhibition is a function of the interaction energy, from a comparison with pIC_{50} a good correlation between theoretical and experimental data was observed. This suggests that identified binding conformations of these inhibitors are reliable. The results of docking studies provide an insight into the pharmacophoric structural requirements for the MAO-B inhibitory activity of these class molecules.

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INTRODUCTION

In humans Monoamine oxidase-B inhibitors (hMAO-BIs) are useful in the treatment of PD and AD especially after the 60th year of life; hMAOBIs have proven to be beneficial in prolonging the anti-parkinsonian action of *L*-DOPA. HMAO-BIs, which decrease the rate of MAO-B, catalyzed oxidative deamination and, consequently, the production of reactive oxygen species (ROS), might contribute to the treatment of other neurodegenerative diseases, such as Alzheimer's disease. The rational design of new agents targeted to MAO could be based on the recent description of the crystal structure of the two isoforms of human MAO Binda *et al*. provides relevant information of the mechanism underlying the selective interactions between these proteins and their ligands. In order to probe the catalytic mechanism and gain a better understanding of the pharmacophoric requirements, the rational design of potent and selective enzyme inhibitors is needed with oligomeric states and active site structures. Authors have previously reported the synthesis and inhibitory activity of a series of selective 2-thiazolylhydrazone MAO-B inhibitors; they studied the inhibitory activity of 2 – methylcyclohexylidene - (4-arylthiazol-2-yl) hydrazones on hMAO-B numerous compounds among the great variety of substituted hydrazines behave as MAO-B inhibitors. A common structural feature of substrates and inhibitors is an amino or imino group that is assumed to play an essential role in orientation and complex formation at the active site of the enzyme. In earlier papers by Cambria and others, it was shown that numerous hydrazinothiazole derivatives inhibit MAO-B activity in the range of μM concentration. Moreover, benzylidene-hydrazinothiazole derivatives were reported to be the most active, with their activity being further enhanced by the presence of a methyl group at 4th position of the thiazole nucleus in a computational study performed with docking techniques on the most active inhibitor benzaldehyde-4-methyl-(4-phenyl-2-thiazolyl)hydrazone.

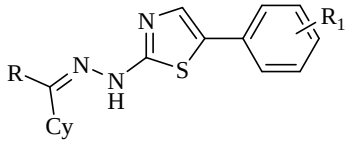
Substituents on the aromatic ring at 4th position of thiazole ring also influenced the activity as demonstrated by the introduction of several groups (NO_2, CN, CH_3, and OCH_3) or halogens (F and Cl) in the *ortho* and *para* positions in our previous works, while the introduction of more steric hindered coumarin and naphthalene nucleus at 4th position of thiazole led to a decreased hMAO inhibitory activity. That prompted us to evaluate the presence of an electron-donating group such OCH_3 in the meta-position of the aryl ring. The choice of different aliphatic, cycloaliphatic, heterocyclic, and bicyclic moieties on the C≡N group allowed a better comprehension of the steric and electronic influence on the enzyme–inhibitor interaction and a modulation of the chemical structure of these derivatives. The above studies elucidated some factors responsible for selectivity against the A and B isoforms, such as the lipophilicity of the inhibitor that is important for achieving effective binding to MAO-B, the presence of electron-rich aromatic moieties, typical of selective MAO-A inhibitors, and the role played by some amino acid residues in the active sites, such as Tyr326 for hMAO-B and Ile335 for hMAO-A. Finally, the choice of different aliphatic, cycloaliphatic, heterocyclic, and bicyclic moieties on the C≡N group (C2 of the thiazole) allowed us to better comprehend the steric and electronic influence on the enzyme-inhibitor interaction and to modulate the chemical structure of these derivatives. Indeed, treatment of pre-Parkinson's patients with selective hMAO-B inhibitors has been shown to be effective in reducing the development of this neurodegeneration. A disadvantage of the first selective hMAO-B inhibitor, (*R*)-deprenyl, was its sympathomimetic effect related to its chemical structure because it is metabolized in vivo to methamphetamine compounds with sympathomimetic activity. One advantage of rasagiline, therefore, was that it was not an amphetamine derivative and showed no sympathomimetic activity. hMAO-B. The results from this study should be useful in understanding the inhibitory mode of the (hetero) arlylidene (4-substituted-thiazol-2-yl) hydrazines and in designing new drugs leads against neurodegenerative diseases [1-8]

Computational Methods

Molecular structures and optimization

Computational model studies will increase the chances of finding the required drugs before synthesizing the hundreds of model compounds. This will both fasten the time needed to develop a target compound and will decrease the cost drastically. The biological activity data of (Hetero)arylidene-(-4-substituted-thiazol-2-yl)hydrazines) (45 molecules), reported by Deniela Secci *et al.* is used in present study (Table 1) [9]. The structures of all compounds reported in Table 1 were constructed using the Builder module. The geometries of these compounds were subsequently optimized by MOE2011.10 (Molecular Operating Environment) [10] using MMFF9X77 force field for energy minimization with an energy convergence gradient of 0.001 kcal mol^{-1}. The coordinates were saved in mol2 format for use in GOLD. In order to relieve the crystal structure tension and to make the protein available to use in the GOLD docking simulation program, all polar hydrogen atoms were added with the M.O.E modelling package [11-12]. The structures of MAO-B protein (PDB code 4CRT) was obtained from Protein Data Bank [Research Collaboratory for Structural Bioinformatics (RSCB) (http:/www.rcsb.org/pdb)]. A study was carried out on

only one subunit of the enzymes. The PDB files were edited and the β-chains were removed.



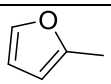
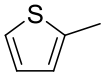
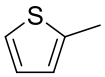
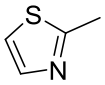
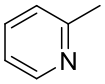
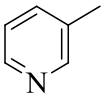
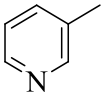
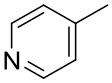
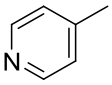
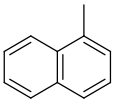
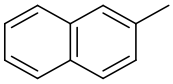
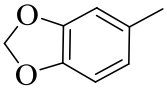
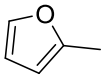
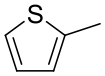
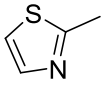
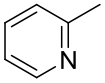
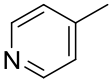
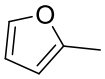
Comp. No.	Substitution			Observed (-log IC_{50})	Chemplp Score
	Cy	R	R_1		
1		H	4-CN	5.82	112.04
3		H	4-CN	6.81	90.26
4		CH_3	4-CN	5.50	97.22
5		CH_3	4-CN	5.69	95.67
7		CH_3	4-CN	6.00	102.23
8		H	4-CN	6.02	100.43
9		CH_3	4-CN	8.67	95.63
10		H	4-CN	5.17	96.18
11		CH_3	4-CN	6.36	94.42
12		H	4-CN	5.95	105.83
13		CH_3	4-CN	6.11	105.56
15		H	4-CN	6.52	104.97
18		CH_3	4-NO_2	5.44	101.46
20		CH_3	4-NO_2	6.52	95.18
21		CH_3	4-NO_2	6.43	97.67
23		CH_3	4-NO_2	7.57	101.11
27		CH_3	4-NO_2	7.88	97.50
33		H	4-F	6.18	93.02

Table 1 continued

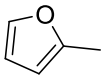
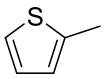
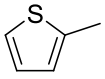
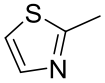
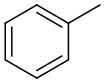
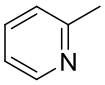
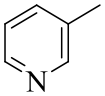
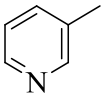
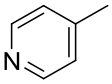
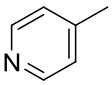
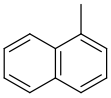
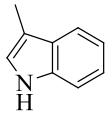
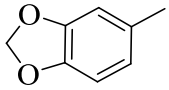
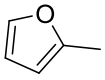
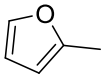
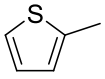
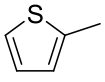
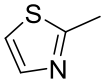
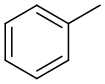
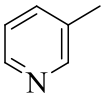
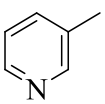
34		CH_3	4-F	6.49	93.81
35		H	4-F	6.47	92.49
36		CH_3	4-F	7.80	93.90
37		CH_3	4-F	5.91	94.88
38		CH_3	4-F	6.45	97.88
39		CH_3	4-F	7.61	99.28
40		H	4-F	6.31	93.59
41		CH_3	4-F	8.76	95.48
42		H	4-F	6.94	95.67
43		CH_3	4-F	8.59	111.75
44		H	4-F	4.89	109.02
46		H	4-F	6.23	102.21
47		H	4-F	5.96	95.83
49		H	2,4-F	6.66	92.99
50		CH_3	2,4-F	7.39	92.93
51		H	2,4-F	7.78	98.76
52		CH_3	2,4-F	8.52	99.98
53		CH_3	2,4-F	7.88	100.21
54		CH_3	2,4-F	7.04	96.68
56		H	2,4-F	6.70	98.78
57		CH_3	2,4-F	7.73	100.98

Table 1 continued

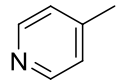
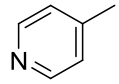
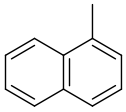
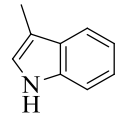
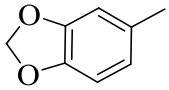
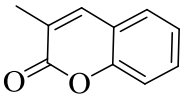
58		H	2,4-F	6.26	102.14
59		CH_3	2,4-F	7.77	114.80
60		H	2,4-F	6.86	116.85
62		H	2,4-F	6.27	106.44
63		H	2,4-F	5.93	104.76
64		CH_3	2,4-F	5.84	90.09

Table 1: MAO-B inhibitory activity and their chemplp scores of (Hetero)arlylidene-(4-substituted-thiazol-2-yl)hydrazines

Docking Study

Docking study was carried out by GOLD 5.1 docking program interfaced with Hermes 1.4.1. [13]. Based on previously reported structural information, the active-site regions by using comparative macromodel software they did docking simulations of substituted thiazole hydrazone with MAO-B were constructed [14]. The proposed interaction modes of the ligand with the MAO-B binding site were determined as the highest scored conformation (best-fit ligand) among the 45 conformations. The binding modes were generated according to the ChemPLP scoring (Table 1), which was represented by the structure with the most favorable binding free energy (ΔG bind). The ChemPLP uses a purely empirical scoring function [15]. The binding free energy of a protein/ligand complex was estimated as the sum of the free energy contributions from hydrogen bonding, ion-pair interactions, hydrophobic and pi-pi stacking interactions of aromatic groups, and lipophilic interactions. A scaling function was used to penalize deviations from the ideal geometry. The docking simulations obtained were scored further using the CScore program, which is a consensus-scoring program that integrates well-known and extensively applied multiple scoring functions available with MOE CScore scoring function include root mean square deviation (RMSD) values, GScore (scores ligand-receptor complexes having many polar interactions), GOLD score (based on empirical functions) [13].

Hardware and software

MOE2011.10 (Molecular Operating Environment) and GOLD 5.1 docking program were used for molecular modeling study.

RESULTS AND DISCUSSION

Monoamine oxidase B has a hydrophobic bipartite elongated cavity with the first cavity the entrance cavity, the second substrate cavity, or active site cavity between both an isoleucine199 side-chain serves as a gate. Depending on the substrate or bound inhibitor, it can exist in either an open or a closed form, which has been shown to be important in defining the inhibitor specificity of hMAO B. At the end of the substrate cavity is the FAD coenzyme with sites for favourable amine binding about the flavin involving two nearly parallel Tyr (398 and 435) residues that form what has been termed an aromatic cage [16] with help of crystal structure it has been possible to delineate amino acids involved in noncovalent interactions with MAO-B. Gly11, Gly13, Ile14, Ser15, Leu33, Glu34, Ala35, Arg36, Gly41, Arg42, Gly58, Ser59, Tyr60, Val235, Ala263, Ile264, Trp388, Tyr393, Cys397, Tyr398, Gly425, Thr426, Gly434, Tyr435, Met436 residues are in MAO-B which are interacting with FAD [17]. To date, numerous crystal structures of MAO-B have been reported. With the help of crystal structures it has been possible to define amino acids involve in various type of interaction with MAO-B enzyme. These crystal structures provided not only insight into the interaction mechanism of the MAO-B with the inhibitors, but also valuable idea for designing new inhibitors. In the present study we have selected the ASS234/MAO-B complex (PDB code-4CRT [18] for the docking study of Hetero) arlylidene (4-substituted-thiazol-2-yl) hydrazine.

Docking Validation

To ensure that the ligand orientation and the position obtained from docking studies were likely to represent valid and reasonable binding modes of the inhibitors, the GOLD 5.1 docking program docking parameters first had to be validated for crystal structure used (4CRT). The ligand ASS234, in the conformation found

in the crystal structure was extracted and docked back into the corresponding binding pocket to determine the ability of GOLD 5.1 to reproduce the orientation and position of the inhibitor observed in the crystal structure. The results of control docking showed that GOLD 5.1 determined the optimal orientation of the docked inhibitor, ASS234 to be close to that of the original orientation found in the crystal. The low RMSD of 1.14 Å between the docked and crystal ligand co-ordinates indicate very good alignment of the experimental and calculated positions, especially considering the resolution of the crystal structure (1.18 Å). The 4 structural waters are conserved among all the MAO-B crystal complexes, the docking experiments were performed with these water molecules in the catalytic site. To test this procedure, ASS234 was docked into the binding pocket in the presence of four water molecules located within the pocket in the crystal structure. The best scoring results were in the identical relative positions to those calculated in the presence of the water molecules.

To study binding modes of (Hetero)arlylidene-(4-substituted-thiazol-2-yl)hydrazines in the catalytic binding site of MAO-B on which docking simulations were performed by means of GOLD and interaction energies calculated from the docked conformations of the MAO-B-inhibitor complexes. The docked 3D-structures of hetero)arlylidene-(4-substituted-thiazol-2-yl)hydrazines were compared with the X-ray crystallographic structure of ASS234. All the inhibitors were docked at the binding site of MAO-B enzyme. In MAO-B, the important residues involved in D-R interactions were found as Gly11, Gly13, Ile14, Ser15, Leu33, Glu34, Ala35, Arg36, Gly41, Arg42, Gly58, Ser59, Tyr60, Val235, Ala263, Ile264, Trp388, Tyr393, Cys397, Tyr398, Gly425, Thr426, Gly434, Tyr435, Met436 residues. The literature reports also showed that these are crucial residues for inhibition activity. All the docked compounds show similar kind of interaction. The inhibitor 41 and 60 were taken as representative compounds to discuss D-R interaction in detail because they have shown many important D-R interactions (Fig. 1). All these compounds show hydrogen bond interaction with MAO-B enzyme that is shown in (Fig. 1a and 1b). Reversible and selective MAO-B inhibitors (1-45) with varying structural features and inhibition constants were selected from the literature and were docked into the catalytic site of MAO-B. The docked models of compound 41 and 60 are shown in Fig. 1. Contrary to most of the docking modes, the model for compound 41 shows hydrophobic interaction in between the benzyl moiety and amino acids like Phe168, leu171, Ile199, Ile316. N-H group shows hydrogen bonding interaction with amino acids like Gln 206, Tyr326 and Tyr60 shows hydrophobic interactions with arylidene moiety. In the binding of inhibitor 60 in which benzyl moiety shows hydrophobic interaction in between the benzyl moiety and amino acids like Leu171, Cys172, Ile 199, Gln206 and Tyr326. N-H group shows hydrogen bonding with Tyr60. Arg42 shows hydrophobic interaction with arylidene moiety of thiazole hydrozone.

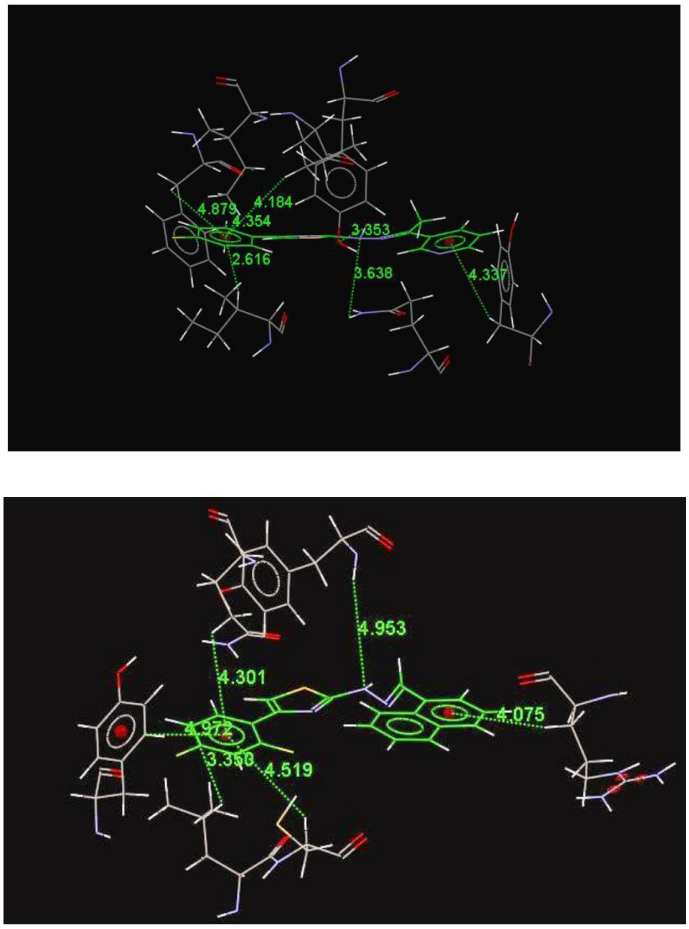


Figure 1: D-R interaction between MAO-B and its inhibitors **a.** inhibitor 41; **b.** inhibitor 60

CONCLUSION

In this work, molecular docking studies were carried out to explore the binding mechanism of substituted thiazole hydrozones inhibitors to the MAO-B enzyme to enable the design of new MAO-B inhibitors. Both the binding conformation of substituted thiazole hydrozones and their binding free energies were predicted by molecular docking. The binding models of the inhibitors demonstrate how the substituted binds to MAO-B enzyme. The molecular docking studies show the potential binding mode of most of the top ranking compounds in substituted thiazole hydrozones to MAO-B catalytic binding site. The binding free energies of these compounds to MAO-B were found to have a good correlation with the experimental inhibitory activities. The most favourable binding mode of substituted

thiazole hydrazones top-ranking compounds will be useful in designing new MAO-B inhibitors.

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