ORIGINAL ARTICLE

Molecular Docking Studies of Substituted Aromatic N-(3-chloro-4-fluorophenyl)-1-phenylmethanimine Derivatives against Monoamine Oxidase-B as Potential Anti-parkinsonian Agents

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Abstract

Introduction: In recent times, Parkinson's disease has been considered a major problem in most of the men than women. The monoamine oxidase-B (MAO-B) inhibitors show anti-Parkinsonian activity. This study describes a range of substituted aromatic N-(3-chloro-4-fluorophenyl)-1-phenylmethanimine derivatives that have been designed and docked against the MAO-B enzyme to evaluate their potential anti-Parkinson's agents. Comparison was made between the ligands and common MAO-B inhibitors such as selegiline, rasagiline, and safinamide. **Materials and Methods:** First, with the help of Chemsketch software, the ligands were drawn and saved in.mol format, and they were converted to .pdb format using Avogadro software. iGEMDOCK software was used to perform molecular docking studies and docked compounds were visualized through BIOVIA Discovery Studio Visualizer. **Results and Discussion:** Most of the substances were found to have enhanced MAO-B enzyme binding affinities. The majority of the ligands have demonstrated greater binding energies when compared with the standard MAO-B inhibitors, such as safinamide (−102.64 K.cal/mol), selegiline (−74.38 K.cal/mol), and rasagiline (−72.76 K.cal/mol). Compounds C23 (−120.20 K.cal/mol) and C33 (−116.97 K.cal/mol) were found to have superior binding energies compared to the standard MAO-B inhibitors and so were chosen for visualization. **Conclusion:** Derivatives of substituted aromatic N-(3-chloro-4-fluorophenyl)-1-phenylmethanimine showed a higher binding affinity toward the MAO-B enzyme than standard inhibitors, suggesting that they might be considered for the treatment of Parkinson's disorder.

Key words: BIOVIA discovery studio visualizer, iGEMDOCK software, MAO-B inhibitors, molecular docking, Parkinson's disease, substituted aromatic N-(3-chloro-4-fluorophenyl)-1-phenylmethanimine

INTRODUCTION

In the current study, docking studies were conducted on aromatic compounds, such as benzaldehyde derivatives, which have demonstrated a stronger affinity toward

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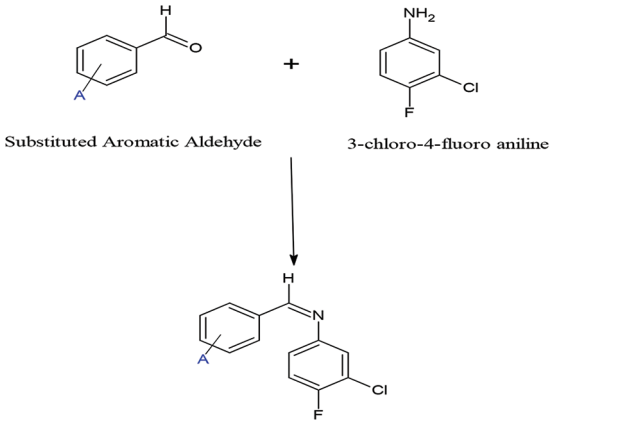
Parkinson's disease. The chemical compound benzaldehyde (C_6H_5CHO) consists of a benzene ring along with a formyl substituent. In industry, it is one of the most often utilized aromatic aldehydes. It is a colorless liquid with a distinct almond-like odor that is frequently used in cherry-flavored sodas.

It was reported that benzaldehyde derivatives exhibit a variety of activities, including antimicrobial, analgesic, anti-inflammatory,[1] antihypertensive,[2] and antitumor effects.[3] The basis for this study is to prove that the substituted aromatic N-(3-chloro-4-fluorophenyl)-1-phenylmethanimine derivatives exhibit antiparkinsonian activity because they increase dopamine levels. Monoamine oxidase-B (MAO-B) inhibitors improve dopamine utilization in nerve cells. Oxidative stress and dopamine turnover are decreased when this enzyme is inhibited. To treat the symptoms of Parkinson's disorder, MOA-B inhibitors increase the amount of dopamine that is available.[4-11] The current work attempts to assess different designed substituted aromatic N-(3-chloro-4-fluorophenyl)-1-phenylmethanimine derivatives against the MAO-B enzyme for anti-Parkinson's disease in an *in silico* manner.

MATERIALS AND METHODS

The General Scheme for Substituted Aromatic N-(3-chloro-4-fluorophenyl)-1-Phenylmethanimine Derivatives: [12,13]



As per the original scheme,[12] the thiophene-2-carboxaldehyde was replaced with various benzaldehyde derivatives and with 3-chloro-4-fluoro aniline to give the final products. A number of benzaldehyde derivatives were chosen from the aforementioned scheme,[12,13] and the final products were designed in accordance with the scheme. Using SwissADME software,[14-19] the ADME properties of the designed vast library of compounds were predicted after they underwent screening using TopKat software[16-20] for *in silico* toxicity. The designed compounds showed excellent ADME properties and exhibited non-carcinogenicity and non-toxicity and later these compounds were chosen for docking studies.

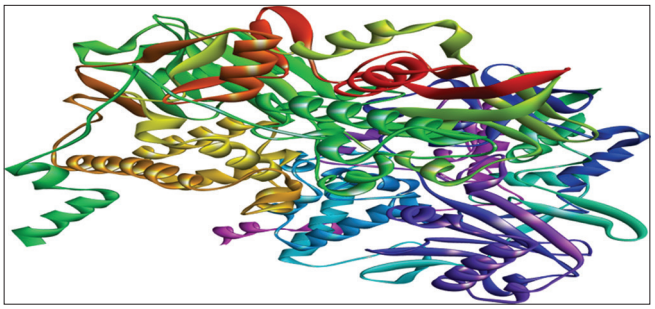


Figure 1: PDB ID: 2BYB

From the above data, it was understood that all the [Table 1] test and standard compounds have better ADME properties.

Molecular Docking

The 2D structure of the ligand was created using Chemsketch software and saved in.mol format. Then these ligands were saved as .pdb format using the Avogadro tool.[16-19,21] The final compounds were designed using previously stated scheme and the targets were predicted with the help of Swiss target prediction software[16-19,22] The majority of the compounds indicate that the MAO-B enzyme was a possible primary target. As Parkinson's disease can be treated with MAO-B inhibitors, the main aim of the current study is to determine whether or not MAO-B enzyme inhibition by the test ligands is possible for antiparkinsonian activity. The compounds were tested for their ability to inhibit the MAO-B enzyme, and their results were contrasted with those of standard inhibitors, namely selegiline, rasagiline, and safinamide. To assess the molecular interactions for chosen safe compounds with MAO-B enzyme [Figure 1] (PDB ID: 2BYB complex with ligand deprenyl), which was acquired through the Protein Data Bank and *in silico* docking studies were performed.

To assess binding positions and interactions for the generated compounds, docking studies were conducted. The software used for it was iGEMDOCK version 2.1.[16-19,23] iGEMDOCK refers to the genetic evolutionary method for molecular docking. A graphical-automated drug design system for docking, screening, and analysis is called iGEMDOCK. This software calculates the orientation and conformation of ligands with respect to the protein's active site. To assess binding affinities and molecular interactions, docking simulations were performed. Using *in silico* toxicity prediction, a total of 39 safe and non-carcinogenic compounds were found. These compounds were chosen for molecular docking in addition to standard MAO-B inhibitors such as safinamide,[24-30] rasagiline,[31-37] and selegiline.[38-41]

Both the standard and accurate docking methods were followed. Regarding the basis of the scoring function, the most effective docking solutions were analyzed. By integrating

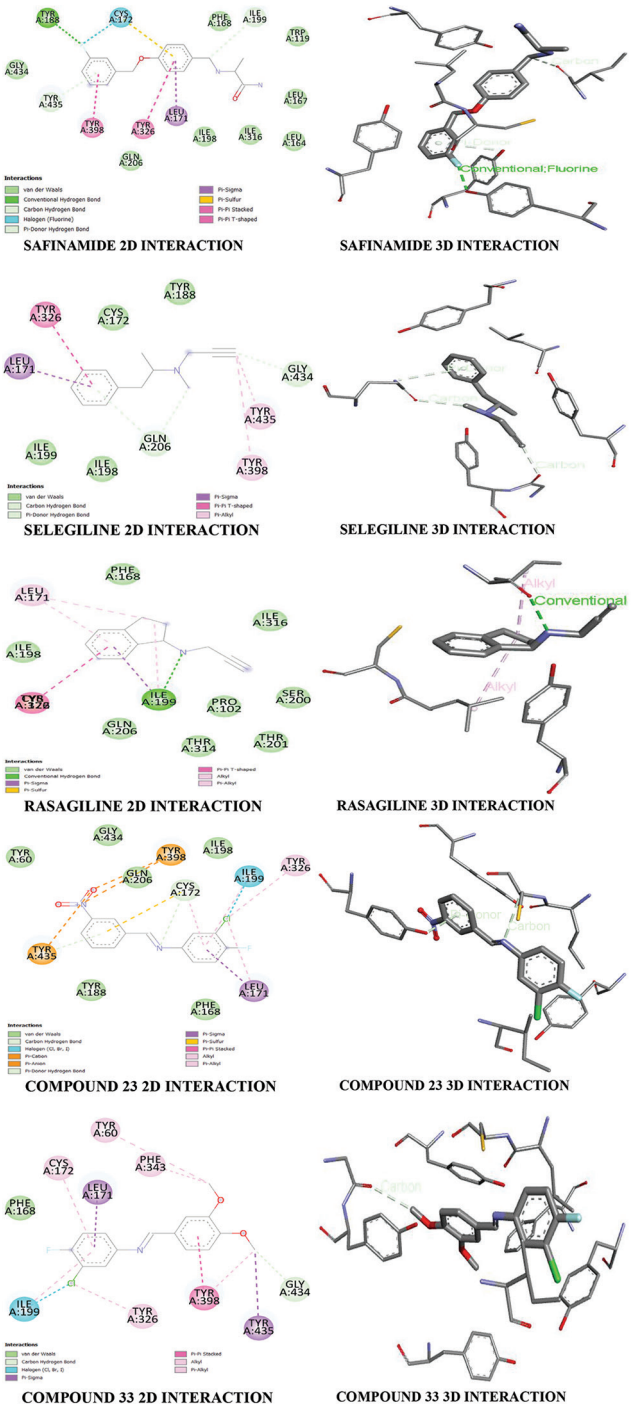


Figure 2: Visualization data of standard MAO-B Inhibitors such as safinamide, selegiline, and rasagiline along with top compounds C23 and C33

hydrogen bonding, Vander Waals, and electrostatic energies, the scoring function was calculated. The interactions between the ligand and target protein were determined by a post-docking interaction profile analysis of the best poses. The top 10 compounds with higher binding energies were chosen, and the top most two compounds with higher binding energies and molecular interaction profiles were taken for post-docking interaction analysis. The ligand interactions were visualized and analyzed using Biovia Discovery Studio Visualizer.

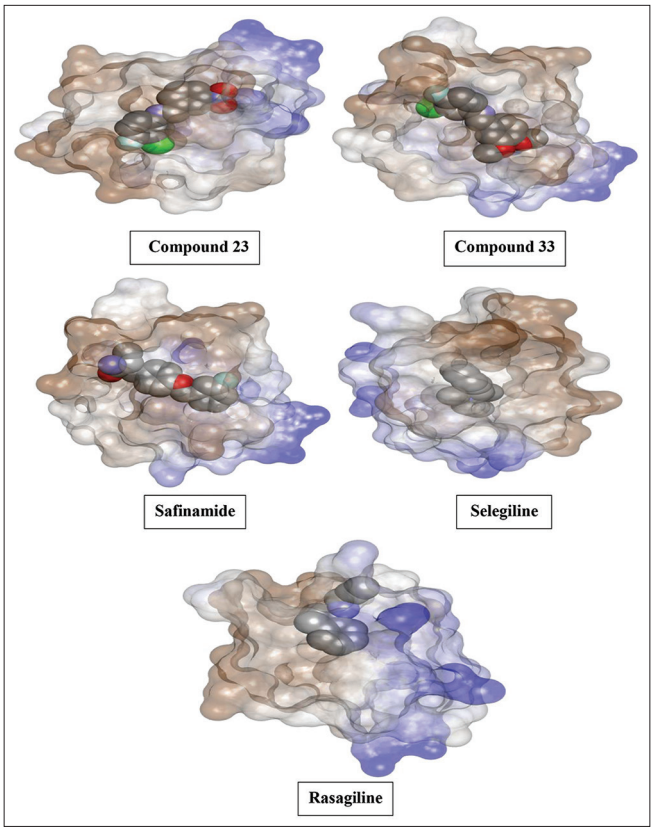
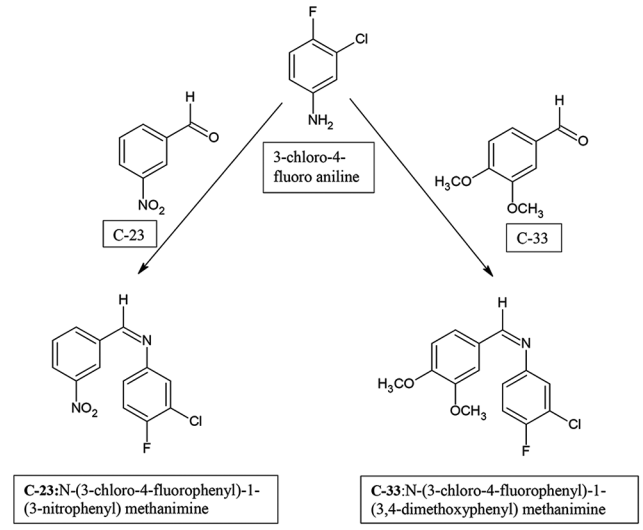


Figure 3: Binding pocket analysis for C23, C33, safinamide, selegiline, and rasagiline

RESULTS AND DISCUSSION

Scheme for the Synthesis of N-(3-chloro-4-fluorophenyl)-1-(3-nitrophenyl) Methenamine and N-(3-chloro-4-fluorophenyl)-1-(3,4-dimethoxyphenyl) methenamine



The green color in the above table represents hydrogen bonding residues and the red color represents unfavorable bumps.

Table 1: ADME data for the top two compounds along with standard MAO-B inhibitors

Parameters	C23	C33	Standard-1 (Safinamide)	Standard-2 (Selegiline)	Standard-3 (Rasagiline)
Molecular weight	278.67 g/mol	293.72 g/mol	302.34 g/mol	187.28 g/mol	171.24 g/mol
Hydrogen bond donors	0	0	2	0	1
Hydrogen bond acceptors	4	4	4	1	1
Lipophilicity	<5	<5	<5	<5	<5

Table 2: Summary of interactions and binding energies of compounds with MAO-B

Compound Code	Binding energy (K.Cal/mol)	Interacting active site residues
C23	−120.205	CYS172, TYR60, GLY434, TYR188, PHE168, GLN206, ILE198, TYR326, LEU171, ILE199, TYR398, TYR435
C33	−116.972	GLY434, PHE168, CYS172, TYR60, PHE343, TYR326, LEU171, TYR435, ILE199, TYR398
C27	−113.622	TYR398, TYR188, GLN206, LYS296, ILE198, GLY434, TYR60, PHE343, ILE199, TYR326, LEU171, TYR435, CYS172, PHE168
C39	−111.267	TYR435, TYR60, TRP119, PHE168, TYR188, GLN206, LEU328, MET341, ILE199, LEU171, TYR326, PHE343, TYR398, CYS172
C07	−111.21	TYR435, PHE168, GLY434, TYR188, GLN206, LEU171, ILE199, TYR326, TYR398, CYS172
C21	−108.372	ILE199, TYR60, TYR188, GLN206, TYR326, GLY434, CYS172, PHE168, LEU171, ILE198, TYR435, TYR398
C38	−107.939	CYS172, PHE168, TYR435, TYR60, ILE198, GLN206, ILE316, PHE343, TYR326, TYR398, ILE199, LEU171
C13	−107.604	CYS172, TYR435, PHE168, ILE198, GLN206, TYR398, LEU171, TYR60, ILE199, ILE316, TYR326
C08	−107.362	CYS172, TYR398, TYR60, PHE343, GLN206, TYR435, PHE168, ILE199, LEU171, TYR326
C04	−106.954	ILE316, TYR60, LEU167, TRP119, LEU164, PHE343, TYR435, ILE198, TYR326, ILE199, PHE168, GLN206, TYR398, LEU171, CYS172
C06	−106.458	TYR60, LEU164, ILE198, ILE316, PHE343, TYR326, TYR435, TRP119, PHE168, ILE199, CYS172, LEU171, GLN206, TYR398
Safinamide	−102.647	TYR188, TYR435, ILE199, CYS172, LEU171, TYR398, TYR326
Selegiline	−74.3821	GLY434, GLN206, TYR398, TYR435, LEU171, TYR326
Rasagiline	−72.7638	ILE199, PHE168, ILE198, GLN206, PRO102, THR314, THR201, SER200, ILE316, CYS326, LEU171

DISCUSSION

The binding energies of nearly all the top most 10 compounds are higher than those of standard MAO-B inhibitors. Among them [Table 2], C23 and C33 have binding energies that are higher than those of standard MAO-B inhibitors such as safinamide, rasagiline, and selegiline. Comparing the binding energies of compound C23 (−120.205 K.Cal/mol) and compound C33 (−116.972 K.Cal/mol) with standard MAO-B inhibitors, such as safinamide (−102.647 K.Cal/mol), selegiline (−74.3821 K.Cal/mol), and rasagiline (−72.7638 K.Cal/mol). It is evident that these compounds performed significantly better in virtual screening and molecular docking.

The Figure 2 shows in the C23 compound exhibits one H-bond interaction with the CYS:172 (4.28 A°) residue. Pi-sigma interaction with the LEU:171. TYR:435 and TYR:398 with pi-sulfur interaction. Pi-alkyl and alkyl interactions with TYR:326 and rest are Vander Waal's interactions.Figure 2 shows in the C33 had one H-bond interaction with GLY:434(3.66A°), pi-sigma interaction with TYR:435, LEU:171, pi-pi stacked interactions with TYR:398, pi-alkyl and alkyl interactions with CYS172, TYR60, PHE343, and TYR326 and then the other had a Vander Waal's interaction with PHE:168.

Previous literature[42] revealed that two amino acids TYR:398 and TYR:435 are responsible for better binding affinity of

the ligands with the MAO-B enzyme. Similarly, in our compounds, these two amino acids have interaction with the MAO-B enzyme. Similarly, standard MAO-B inhibitors safinamide and selegiline also have interaction with TYR:398 and TYR:435 with that of MAO-B active site pocket.

Since [Figure 3] C23 and C33 are positioned inside the active site pocket, their orientations are superior to those of standard MAO-B inhibitors, namely rasagiline, selegiline, and safinamide. C23 might have higher binding affinity because it contains stronger electron-withdrawing groups such as NO_2, Cl, and F. There is better binding energy in compound C33, it might be due to the existence of electron-withdrawing groups such as OCH_3, Cl, and F.

CONCLUSION

Based on all these supportive data, compounds C23 and C33 have higher binding affinities. These compounds also had higher binding energies than standard MAO-B inhibitors such as rasagiline, safinamide, and selegiline. Hence, they can be further synthesized and used for *in vivo* activities.

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