MOLECULAR DOCKING STUDIES OF 2-AMINO-4,6-DISUBSTITUTED PYRIDINE-3-CARBONITRILES AGAINST MONOAMINE OXIDASE -B AS POTENTIAL ANTI PARKINSONIAN AGENTS

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Abstract:

Introduction: Parkinson's disease has become one of most worried diseases in the recent days. All the Monoamine oxidase - B inhibitors (MAO-B) were known to exhibit anti Parkinsonian activity. In the present study various 2-Amino-4,6-Disubstituted Pyridine-3-Carbonitriles or 2-amino 3-cyano pyridines were designed and docked against MAO-B enzyme for antiparkinsonian activity. The ligands were compared with that of the standard MAO-B inhibitors like Safinamide, Selegiline and Rasagiline.

Materials and methods: Ligands were drawn initially with Chemsketch software in .mol format and then converted to .pdb format using Avogadro software. Molecular docking studies were carried out by using iGEMDOCK software and finally visualized by using Discovery Studio Visualizer.

Results and discussion: Almost all the compounds have shown better binding affinity towards MAO-B enzyme. Most of the ligands have shown better binding energies than that of the standard MAO-B inhibitor like Safinamide **(**-107.62 kcal/mol), Selegiline (-79.69 kcal/mol) and Rasagiline **(**-76.03 kcal/mol). Compounds C38 (-126.21 kcal/mol) and C94 (-124.75 kcal/mol) were the top compounds which has better binding energies than that of the standard MAO-B inhibitors and selected for visualization.

C**onclusion:** 2-Amino-4,6-Disubstituted Pyridine-3-Carbonitriles were having better binding affinity to MAO-B enzyme than that of the standard inhibitors and can become potential drugs for the treatment of Parkinson's disease.

Keywords:2-amino 3-cyano pyridines, 2-Amino-4,6-Disubstituted Pyridine-3-Carbonitriles, Parkinson's Disease, Monoamine Oxidase – B inhibitor, Molecular Docking, iGEMDOCK Software, Discovery studio visualizer.

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DOI: 10.31838/ecb/2023.12.6.236

Introduction:

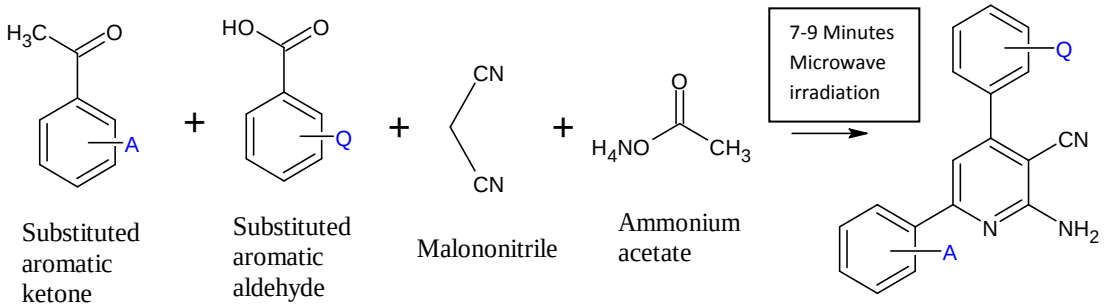
Pyridine containing heterocyclic rings are very important class of drugs for the treatment of many life threatening diseases.[1-4] Pyridine ring is present in over huge number of the existing drugs used for the treatment of various diseases.[5,6]

2-Amino 3-cyano pyridines were reported of having different activities like antiviral, anti-bacterial and fungicidal activities [7,8] Novel IKK-β inhibitors[9],inhibitors of HIV-1 integrase.[10], cardiotonic activity[11],antitumor properties[12],anti-inflammatory, analgesic and antipyretic properties[13,14]

Present study is based on the fact that 2-Amino-4,6-Disubstituted Pyridine-3-Carbonitriles were A2a adenosine receptor antagonists which can show antiparkinsonian activity[15]. MAO B inhibitors also are useful in treating parkinsons disease by elevating the levels of Dopamine. MAO–B inhibitors can help nerve cells make better use of the dopamine that they have. Inhibition of this enzyme reduces dopamine turnover and oxidative stress. MAO-B inhibitors helps more dopamine becomes available to treat the symptoms of Parkinson's disease [16-22] .The present study aims at Insilco evaluation of various designed 2-Amino-4,6-Disubstituted Pyridine-3-Carbonitriles against MAO-B enzyme.

Materials and Methods:

General scheme for the synthesis of 2-Amino-4,6-Disubstituted Pyridine-3-Carbonitriles[23]



Substituted aromatic ketone

Substituted aromatic aldehyde

Malononitrile

Ammonium acetate

2-amino-6,4 Disubstituted Pyridine-3-carbonitrile

The other methods of synthesis of 2-Amino-4,6-Disubstituted Pyridine-3-Carbonitrile or 2-amino-3-cyano pyridines were also reported[24,25] .From the above mentioned scheme[23] various aromatic aldehydes and various aromatic ketones were selected and final products were designed according to the scheme. A huge library of compounds were obtained and they were screened for the Insilco toxicity by using TopKat software[26] and then their ADME properties were predicted using SwissADME software[27].The designed compounds which were predicted as non-toxic, non-carcinogenic, safe and which has good ADME properties were selected for molecular docking studies.

Molecular Docking:

From the library of designed compounds according to the scheme mentioned above [23] .The target was chosen based on the SWISS target prediction software [28] .All the pool of non toxic, non-carcinogenic and safe compounds were predicted for the target for docking through Swiss target prediction software. Most of the compounds have shown adenosine A2a receptor as potential target. So as adenosine A2a receptor antagonists are used for the treatment of parkinsons disease. So the present study aims at evaluating whether MAO-B enzyme inhibition can be done or not for antiparkinsonian activity. The compounds were screened for MAO-B inhibition and they are compared with that of the standard MAO-B inhibitors like **Safinamide, Selegiline and Rasagiline.** The 2D structure of the ligands were drawn through chemsketch software and saved in .mol format. The ligand structures in .pdb format were optimized through the Avogadro tool[29].Docking studies for the assessment of binding poses and interactions were done for the designed compounds which were noncarcinogenic, safe and which has good ADME properties. It was done through the iGEMDOCK version 2.1 software [30] .Docking studies for the assessment of binding poses and interactions were done for the designed compounds which were noncarcinogenic, safe and which has good ADME properties. It was done through the iGEMDOCK version2.1software.

GEMDOCK stands for **G**enetic **E**volutionary **M**ethod for molecular **D**ocking. iGEMDOCK is a graphical–automatic drug design system for docking, screening and analysis. It is a program for computing ligand conformation and orientation relative to the active site of the protein. *In silico* docking simulation studies were performed to evaluate the molecular interactions of the selected safe compounds with the MAO B enzyme (**PDB ID**: **2BYB** with a co-crystallized ligand inhibitor **selegeline**) downloaded from protein data bank.

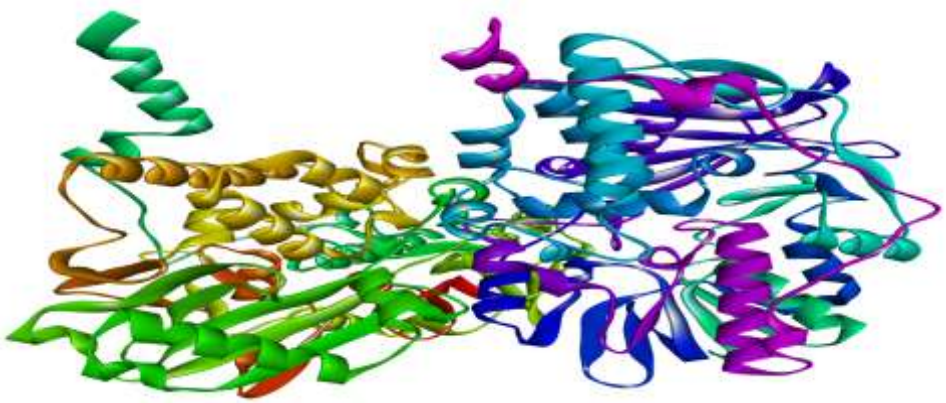


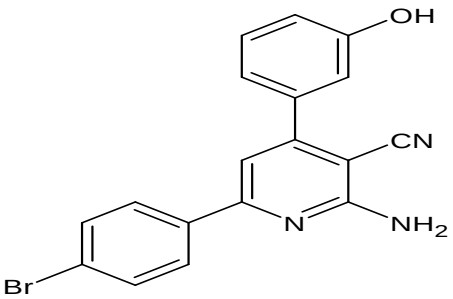
Fig.1 - Cleaned MAO B enzyme –PDB ID: 2BYB

The Ligand interactions were visualized and analyzed through the Discovery Studio Visualizer (Biovia). Standard docking protocol was followed and accurate docking method was selected. Based on the scoring function the best docking solutions were analyzed. The scoring function estimates the fitness by combining van der waals, hydrogen bonding and electro statistic energies. Post docking interaction profile analysis of best poses was conducted to determine the interactions between the ligand and the target protein.

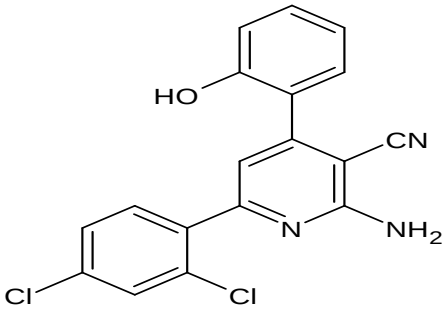
A total of 97 non-carcinogenic and safe compounds were identified by Insilco toxicity prediction and were selected for molecular docking along with standard MAO-B inhibitors like Selegiline[31-34], Rasagiline[35-41] and safinamide[42-48] .Docking simulations for the evaluation of binding affinities and molecular interactions were done. Out of them the top ten compounds with better binding energies were selected and the top two compounds with better binding energies and molecular interaction profile were chosen for post docking analysis of interactions.

Results and Discussion:

Structures of the top two ligands with better binding energies selected for visualization.



C-38:2-amino-6-(4-bromophenyl)-4-(3-hydroxyphenyl) pyridine-3-carbonitrile



C94: 2-amino-6-(2,4-dichlorophenyl)-4-(2-hydroxyphenyl) pyridine-3-carbonitrile

Table 1: Binding energy and interaction summary of compounds with MAO-B

Compound	Binding energy K.cal/mol	Interacting active site residues
C38	**-126.21**	**A:TYR:188, A:CYS:172**, A:VAL:173, A:ILE;198, A-ILE:199, A:PHE:168, A:LEU:171, A:TYR:326, A:GLN:206, A:LEU:328, A:PHE:343, A:MET:341, A:TYR;60, A:LYS;296,A:TYR:398, A:TYR:435, A:GYL:434
C94	**-124.75**	**A:CYS:172**, A:TYR:435, A:GLN:206, A:TYR:398, A:LEU:171, A:TYR:326, A:ILE:199
C67	-123.29	**A:ILE:199, A:TYR:435, A:CYS:172**, A:TYR:60, A:PHE:343, A:TYR:326, A:TYR:398, A:ILE:198, A:LEU:171
C63	-122.16	**A:TYR:188**, A:TYR:435, A:TYR:398, A:LEU:171, A:ILE:199 , A:CYS:172, A:TYR:326
C2	-121.71	A:TYR:326, A:ILE:199, A:CYS:172, A:LEU:171, A:TYR:398, A:TYR:435
C51	-120.40	A:ILE:199, A:LEU:171, A:TYR:326, A;CYS:172, A;PHE:168, A;TYR:435, A:TYR:398
C41	-119.91	A:CYS:172, A:TYR:398, A:TYR:435, A:LEU:171, A:TYR:326, A:PHE:168, A;ILE:199
C54	-118.26	**A:TYR:188**, A:GLY:434, A:TYR:435, A:TYR:398, A:TYR:326, A:LEU:171, A:ILE:199, A:ILE:198, A:PHE:168, **A:CYS:172**
C74	-117.42	**A:TYR:435,** A:ILE:199, A:ILE:198, A:ILE:316, A:LEU:171, A:TYR:326, A:MET:341, A:PHE:343, A:TYR:398, A:LEU:328, A:TYR:60, **A:CYS:172**
C89	-116.08	A:PRO:102, A:ILE:316, A:ILE:199, A:PHE:168, A:TYR:435, A:CYS:172, A:LEU:171, A:TYR:326
Safinamide	**-107.62**	**A:LEU:164**, A:TYR:435, A:TYR:326, A:ILE:199, A:LEU:171, A:CYS:172
Selegiline	-79.69	A:CYS:172, A:ILE:198, A:TYR:398, A:TYR:435, A:GLY:434, A:LEU:171
Rasagiline	-76.03	**A:TYR:435**, A:TYR:60, A:MET:341, A:TYR:326, A:GLN:206, A:LEU:171, A:TYR:398, A:PHE:343, A:ILE:199, A:ILE:198, A:CYS:172

H-bond interacting residues represented in green color and unfavorable interaction are in red color

Table 2 - Docking and visualization data of SAFINAMIDE against MAO-B enzyme

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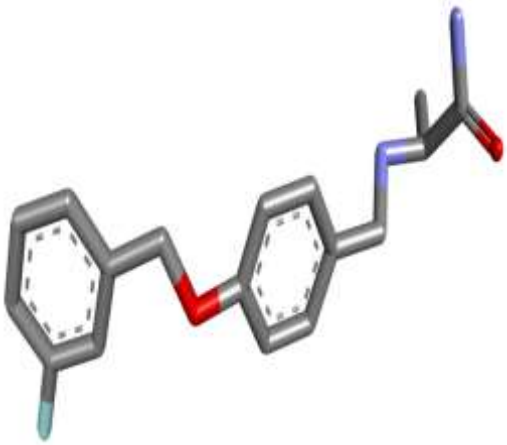
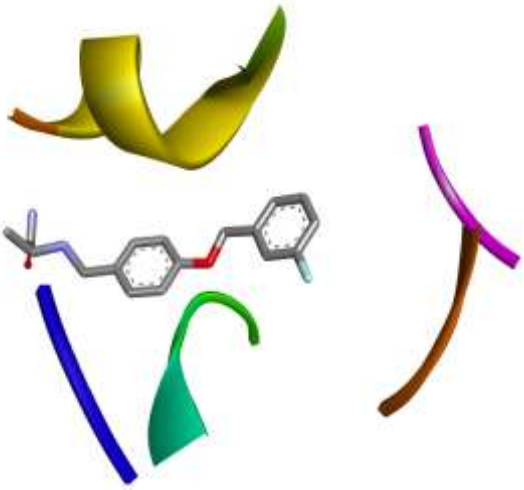
<tr><td>  </td><td>  </td></tr>
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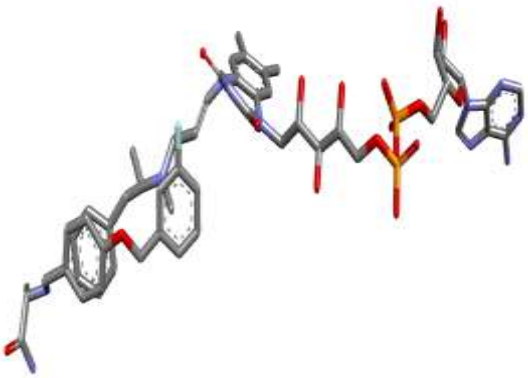
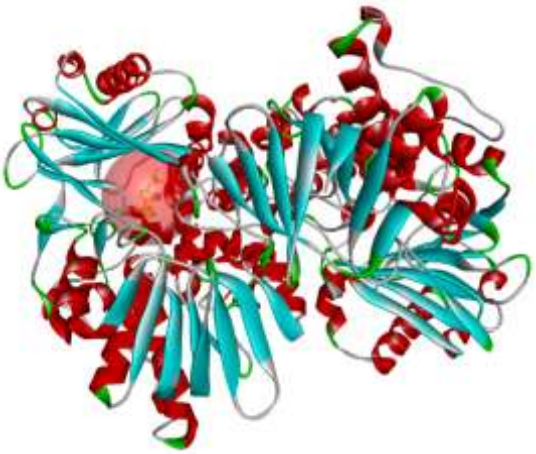
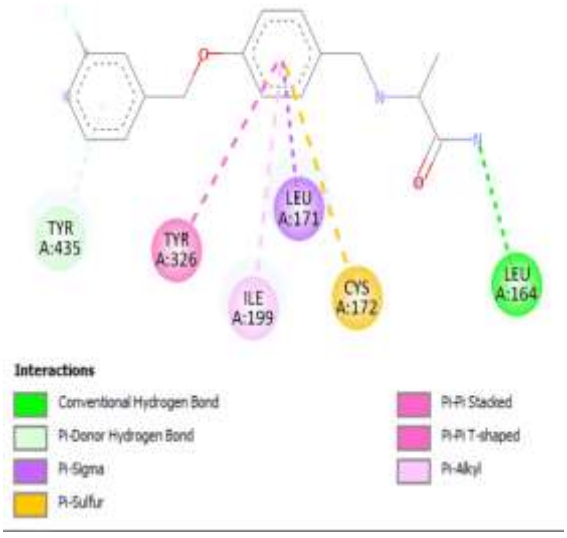
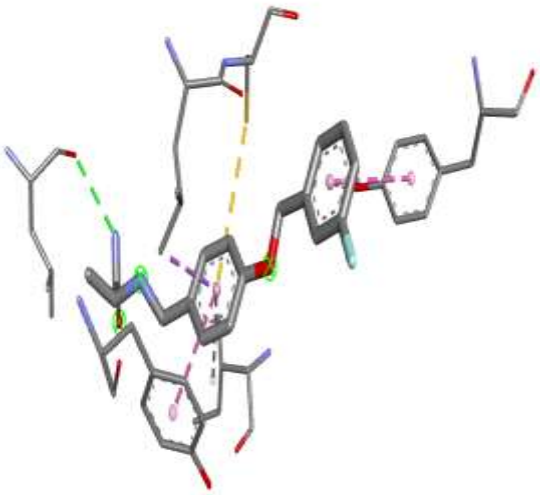
<tr><td>  </td><td>  </td></tr>
<tr><td>3. SAFINAMIDE LIGAND + STANDARD LIGAND SELEGILINE COMPLEX</td><td>4. SAFINAMIDE LIGAND + WHOLE MAO-B ENZYME COMPLEX</td></tr>
<tr><td> 
</td><td>  </td></tr>
<tr><td>5. SAFINAMIDE 2D INTERACTION WITH MAO-B ENZYME</td><td>6. SAFINAMIDE 3D INTERACTION WITH MAO-B ENZYME</td></tr>
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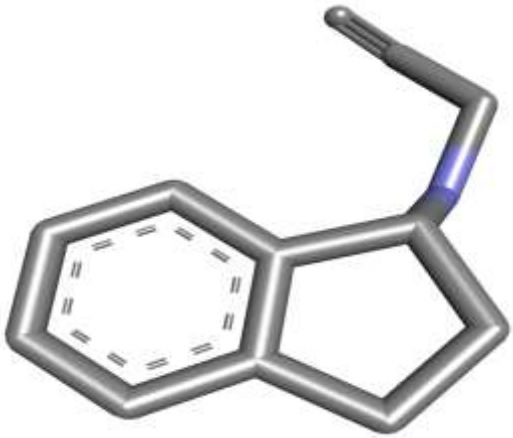
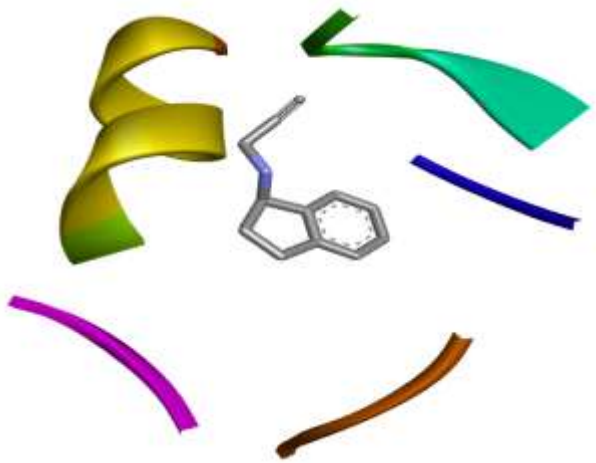
Table 3 - Docking and visualization data of RASAGILINE against MAO-B enzyme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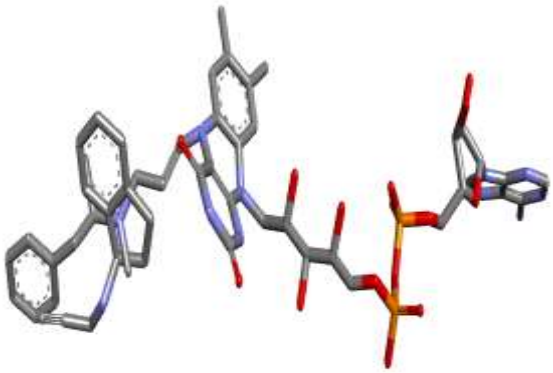
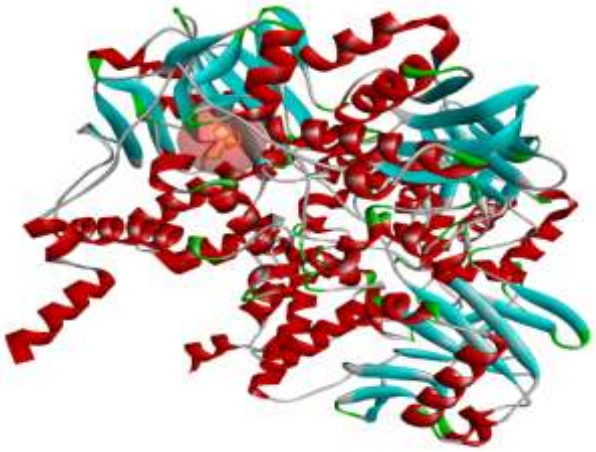
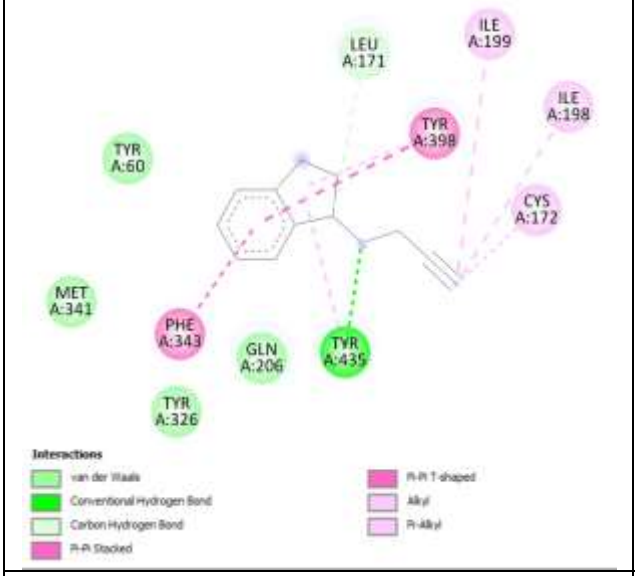
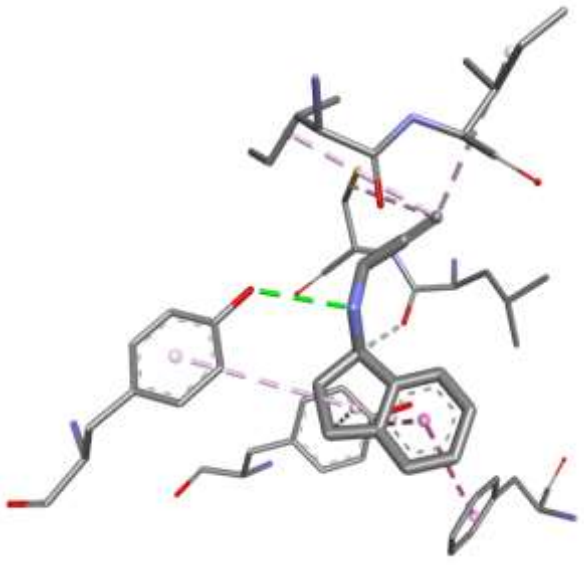
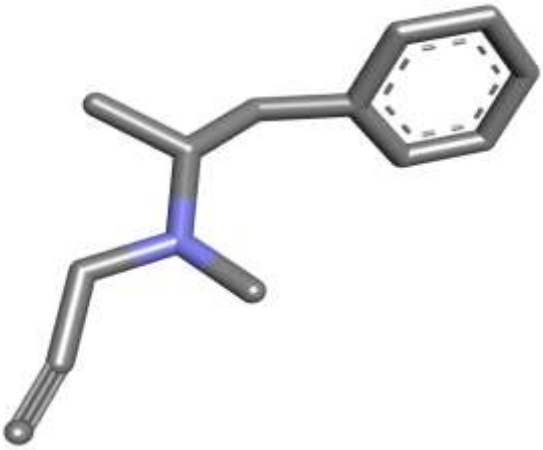
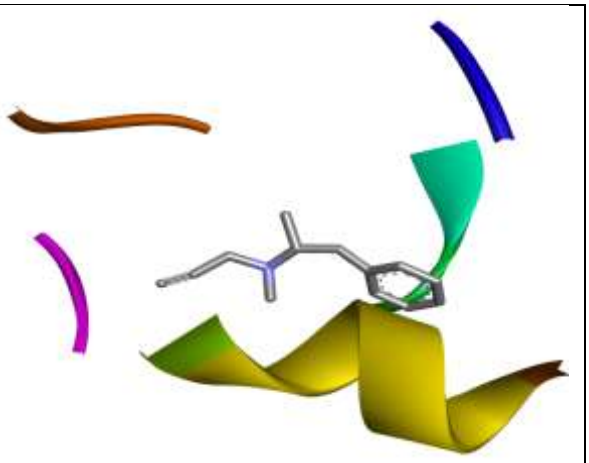
	
3. RASAGILINE LIGAND + STANDARD LIGAND SELEGILINE COMPLEX	4. RASAGILINE LIGAND + WHOLE MAO-B ENZYME COMPLEX
	
5. RASAGILINE 2D INTERACTION WITH MAO-B ENZYME	6. RASAGILINE 3D INTERACTION WITH MAO-B ENZYME

Table 4 - Docking and visualization data of SELEGILINE against MAO-B enzyme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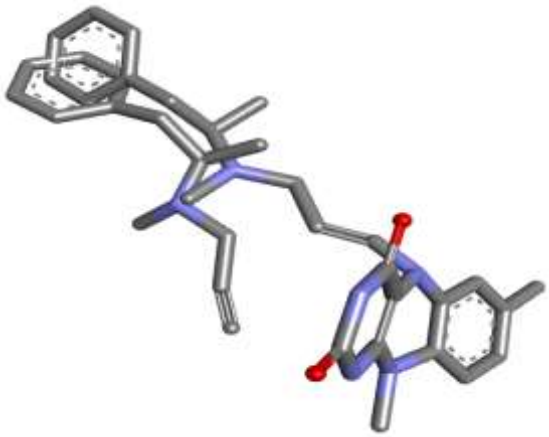
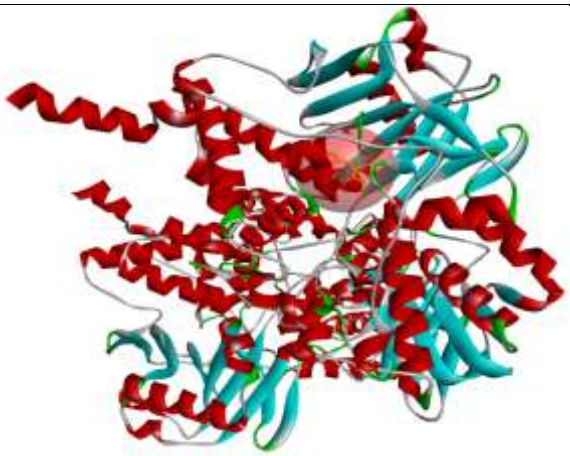
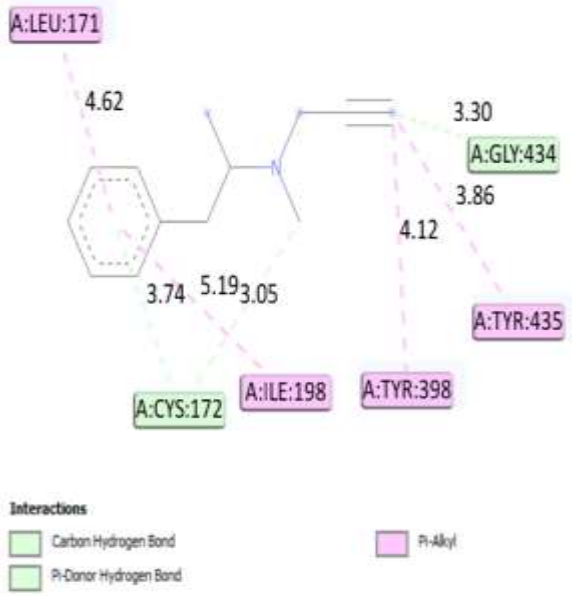
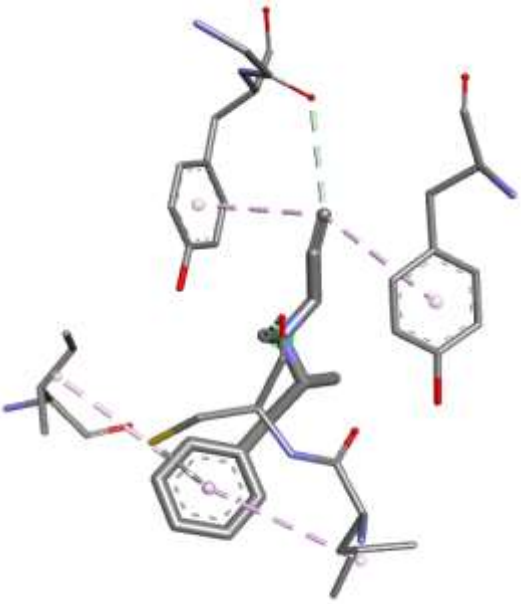
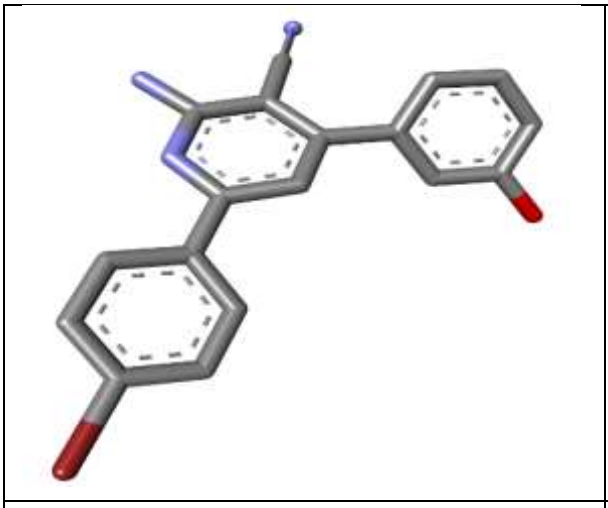
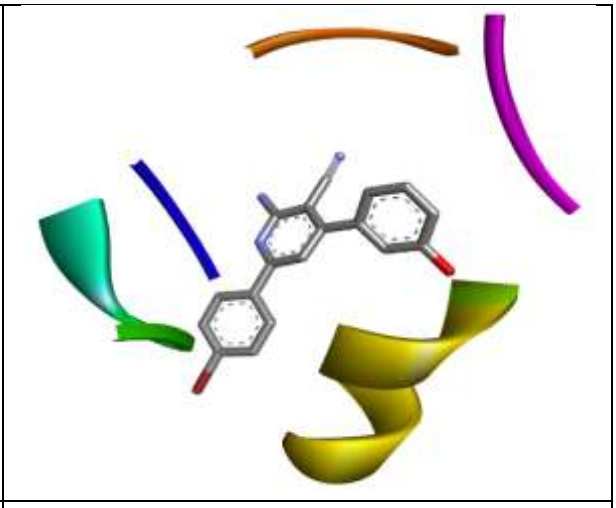
	
3. SELEGILINE LIGAND + STANDARD LIGAND SELEGILINE COMPLEX	4. SELEGILINE LIGAND + WHOLE MAO-B ENZYME COMPLEX
	
5. SELEGILINE 2D INTERACTION WITH MAO-B ENZYME	6. SELEGILINE 3D INTERACTION WITH MAO-B ENZYME

Table 5 - Docking and visualization data of C38 against MAO-B enzyme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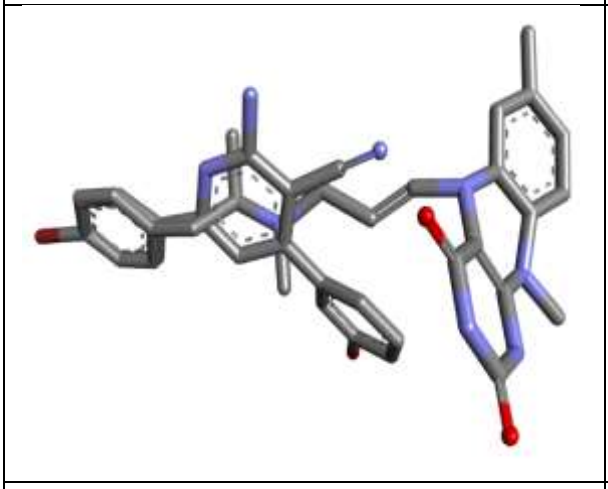
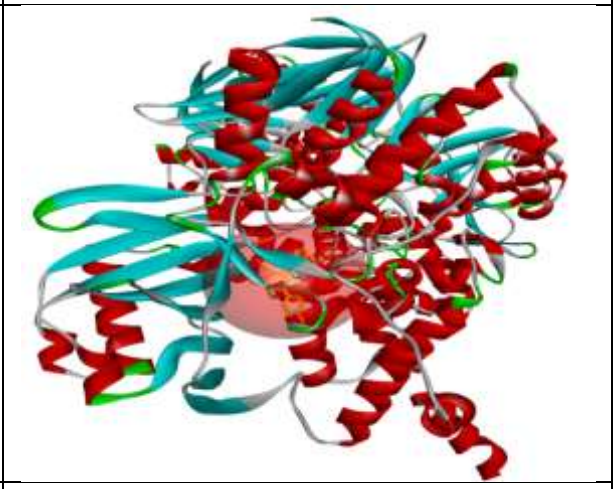
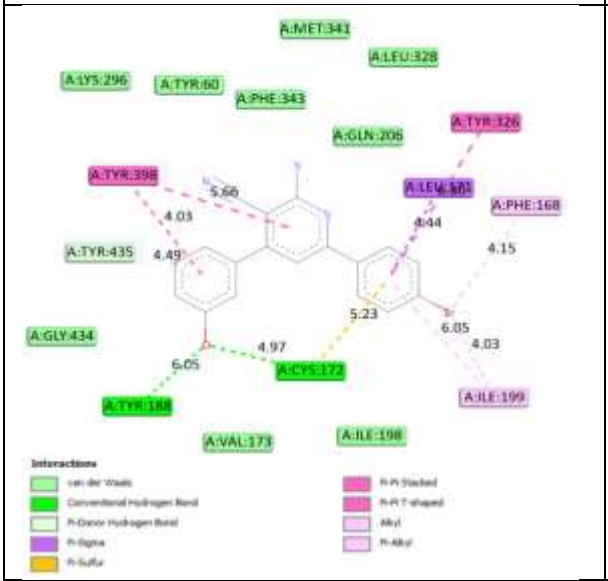
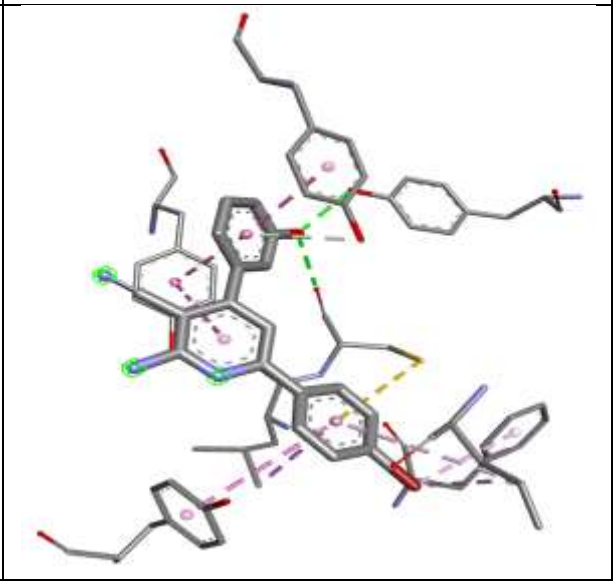
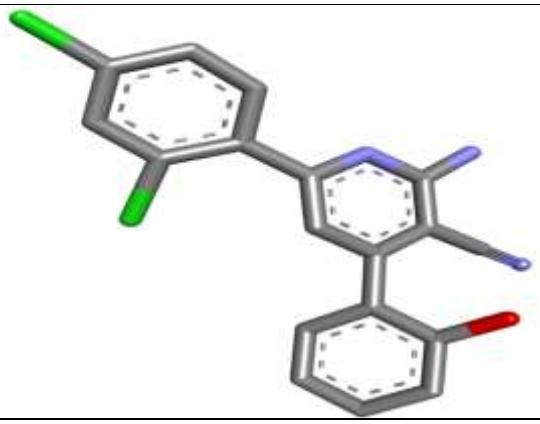
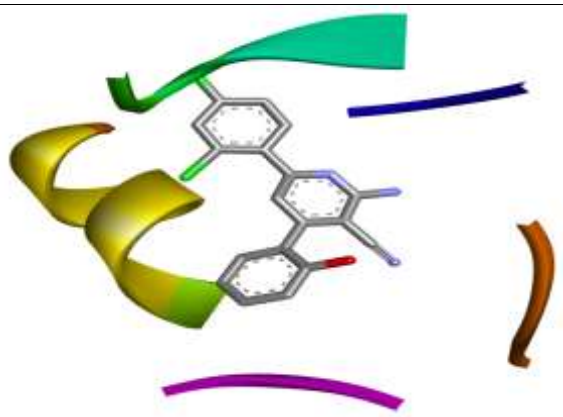
	
3. C38 LIGAND + STANDARD LIGAND OVERLAP	4. C38 LIGAND + WHOLE MAO-B ENZYME COMPLEX
	
5. C38 2D INTERACTION WITH MAO-B ENZYME	6. C38 3D INTERACTION WITH MAO-B ENZYME

Table 6- Docking and visualization data of C94 against MAO B enzyme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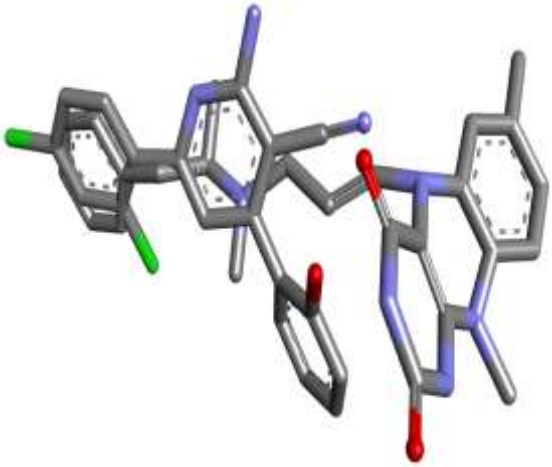
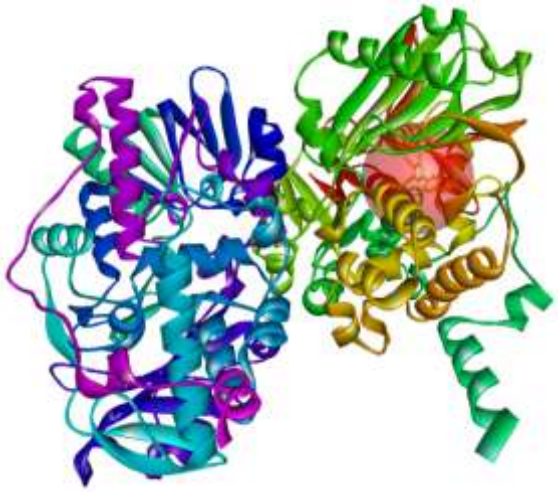
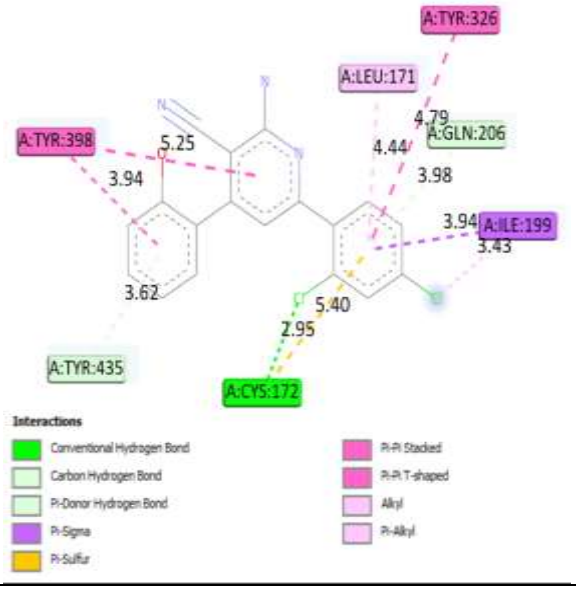
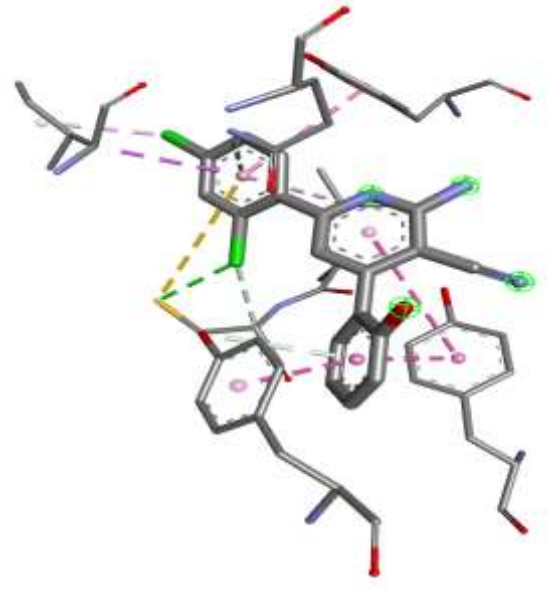
	
3. C94 LIGAND + STANDARD LIGAND SELEGILINE OVERLAP	4. C94 LIGAND + WHOLE MAO-B ENZYME COMPLEX
	
5. C94 2D INTERACTION WITH MAO-B ENZYME	6. 94 3D INTERACTION WITH MAO-B ENZYME

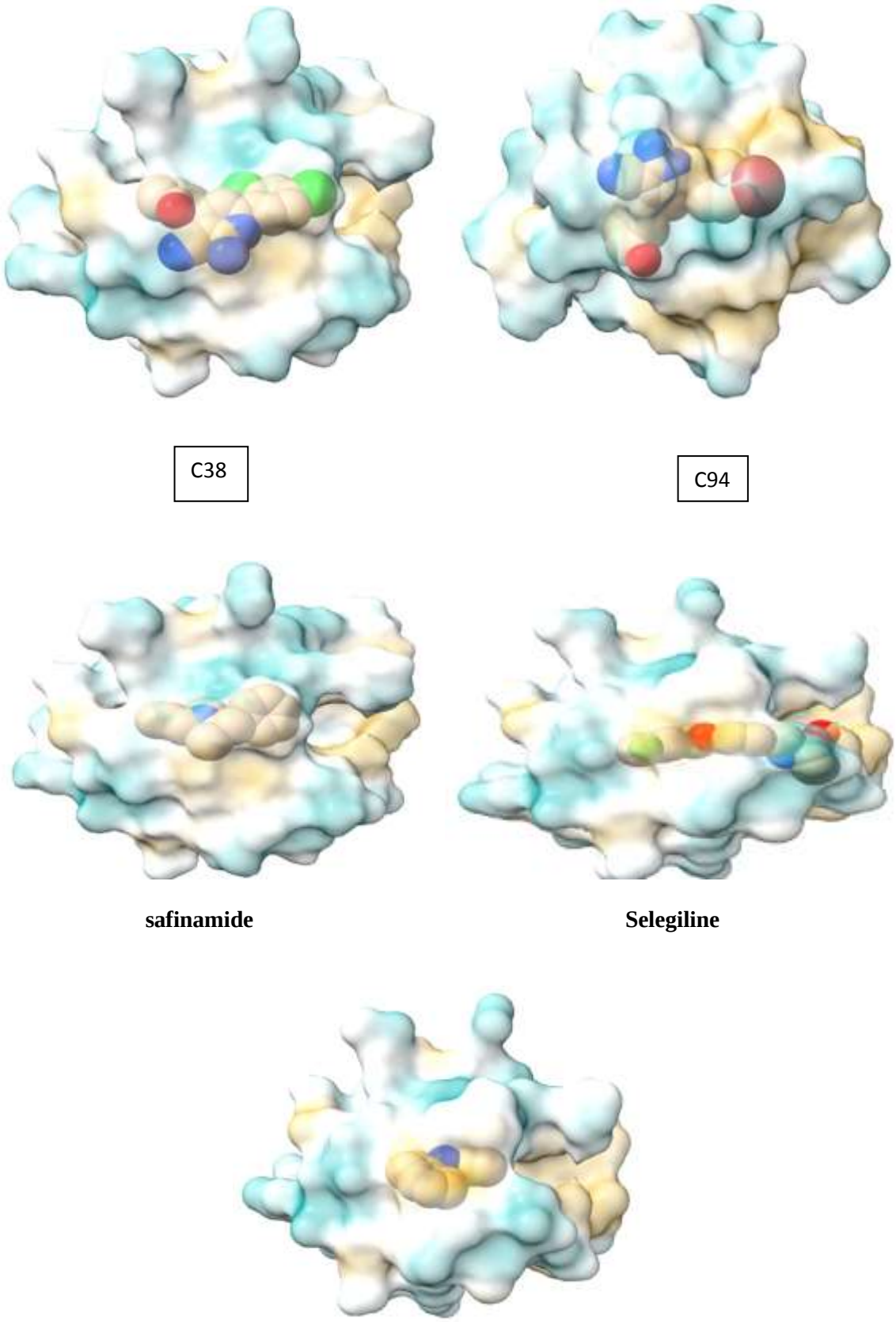


Fig.2- Active site pocket surface and binding modes of C38, C94 along with standard MAO B inhibitor Safinamide, Selegiline and Rasagiline.

Molecular interaction analysis of compounds with MAO B enzyme:

Conclusion:

Almost all the top ten compounds have better binding energies than that of the standard MAO-B inhibitors. The top two compounds C38 and C94 have better binding energy than that of the standard MAO-B inhibitors like Safinamide, Selegiline and Rasagiline. Compound C38 has a binding energy of **-126.21 k.cal/mol** and compound C94 has a binding energy - **124.75k.cal/mol**, which is very good when compared to that of the standard MAO-B inhibitors like Safinamide with a binding energy of -107.62 K.cal/mol**,** Selegiline with a binding energy of -79.69K.cal/mol and Rasagiline with a binding energy of -76.03k.cal/mol.

C38 compound had two H-bond interaction with the **TYR188 (6.05 A^o) and CYS172 (4.97 A^o)** residues. CYS172 also had a pi-sulfur interaction. Pi-pi stacked and pi-pi T shaped interaction with TYR398, TYR435 and TYR326 residues, p-alkyl and alkyl interactions with ILE199, PHE168 and LEU171 and van der waal's interactions with the remaining active site residues.

In C94 compound most of the interactions are hydrophobic interactions such as pi-sigma interaction with ILE199, CYS172 had a pi-sulfur interaction, pi-pi stacked and pi-pi T shaped interactions with TYR435, TYR398, TYR326, pi-alkyl and alkyl interactions with LEU171 and then most of the other residues in the active had a van der waal's interactions.

C38 and C94 have better orientations compared to that of the standard MAO-B inhibitors like Safinamide, Selegiline and Rasagiline due to their positioning inside the active site pocket.The better binding affinity of Compound C38 might be due to the presence of one electron donating group OH and one electron withdrawing group Br. Compound C94 has less binding energy when compared to C38.It might be because of the presence of one OH which is electron donating and two Cl which are electron withdrawing.

Compounds C38 and C94 can be further synthesized and in vivo activities could be performed as they have better binding affinities and energies than that of the standard Mao-B inhibitors like **Safinamide, Selegiline and Rasagiline.**

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