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Docking study of Novel Acetamide Derivatives as Specific MAO A Inhibitors

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ABSTRACT

A Molecular docking study on novel Acetamide derivatives as specific Mono amino oxidase (MAO) A inhibitory agents was performed with a set of 40 compounds to analyze their inhibitory action. For this, compounds were designed on the basis of available literature and used as Ligands for molecular interaction. The structure of molecular target Mono Amino Oxidase A (MAO A) was retrieved from the PDB database (PDB ID 2Z5X). For comparative analysis Clorgyline, a well-known specific MAO A inhibitor was taken as the standard. Computational docking analysis was performed using PyRx, AutoDock Vina option based on scoring functions. Among 40 compounds the top 11 hits were recognized as promising MAO A inhibitors, according to their docking scores and selected for further study of interaction and visualization. Phenyl sulphanyl derivative with chlorobenzyl amino moiety (Code AD31) showed an optimum binding affinity and stable complex with a molecular target MAO A with the binding energy of -8.3 kcal/mol as compared to the standard (-7.6 kcal/mol). These results indicated that proposed modification in Acetamide derivatives may produce potent and specific MAO A inhibitors to treat depression with lesser side effects.

Keywords: Docking, Mono Amino Oxidase, Acetamide derivatives, MAO A inhibitors, PyRx, AD31.

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INTRODUCTION

Monoamine oxidase (MAO) is an iron containing flavoenzyme that occurs within cells, bound to the surface membrane of mitochondria and metabolize neurotransmitter, dietary amines in the brain and peripheral tissues[1]. MAO shows their presence in noradrenergic nerve terminals, liver and intestinal epithelium[2]. MAO enzymes catalyse the α-carbon oxidation of neurotransmitter and dietary amines in the brain and peripheral tissues[3,4]. Functions of synaptic neurotransmission is regulated by MAO mediated degradation of monoamines like serotonin (5-HT), norepinephrine (NE) and dopamine (DA) in the brain[5]. MAO have key role in the regulation of central nervous system activity and contributes to the pathogenesis of human neurodegenerative and depressive disorders[6].

Two types of MAOs are present namely MAO A and MAO B and can be distinguished by their three-dimensional structure[7] and tissue distribution. Imbalance between these enzymes can influence the health of the individual[8,9]**.** MAO-A, the primary type found in fibroblasts and MAO-B found in platelets and brain. Functional deficiency of neurotransmitters like nor epinephrine and serotonin is considered one of the major causes of depression. MAO-A preferentially metabolizes the neurotransmitters like dopamine, adrenaline and nor adrenaline[10,11]. In the central nervous system, serotonin is predominantly metabolised by MAO-A and therefore MAO-A is considered most significant target for the treatment of depression and affective disorders. Selective serotonin reuptake inhibitors (SSRIs) are also used for the treatment of depression but the major drawback behind SSRIs are they can only elevate the extracellular serotonin[12]. Currently MAO-A inhibitors are used as valuable antidepressants. Newer reversible inhibitors of MAO A (RIMA) like Moclobemide do not show hypertensive crisis (Cheese reaction) and are more effective for the treatment of neurological disorders, such as depression and anxiety**.** Because of their reversibility and selectivity, RIMAs are safer than the traditional monoamine oxidase inhibitors (MAOIs) like Phenelzine and Tranylcypromine, have been shown to induce hepatotoxicity and other side effects[13,14]. Therefore it is the challenge to discover the drug with selective MAO A inhibitors without serious side effects. Thus, the rational design of new MAO A inhibitors for the treatment of neurodegenerative disease constitutes a major target. In published literature different substituted acetamide derivatives have revealed strong pharmacological effects in central nervous system[15,16].

A new series of 28 compounds of 2-phenoxyacetamide was synthesized and evaluated for both MAO A and MAO B inhibitory activity and results showed that most of the synthesized compounds were potent and selective MAO-A inhibitors to a certain extent than of MAO-B.[17].

Computational model studies will boost the chances of resulting the required drugs before synthesizing the large number of model compounds. This will not only fasten the time needed to develop a target compound but also will decrease the cost drastically. Several attempts to perform rational design of new inhibitors have been described by means of theoretical calculations, beginning with the crystalline structure of MAO-A[18]. In modern scenario drug discovery mainly depends on target based drug designing. It can be broadly defined as "single compound acting on a single target to a single disease". Single target based drugs are designed such that lead molecules can promisingly bind to its specific target, reducing the off-target side effects[19]. Molecular docking have regularly shown great importance in the field of computer aided drug design, which screens designed molecules by orienting and scoring them in the binding site of a protein. This protein may be an enzyme or receptor. Novel ligands for receptors of known structure were designed and their energies of interaction were calculated using the scoring functions[12]. Docking of designed molecules at the catalytic site of enzymes provides useful structural insight into the binding interaction of the inhibitors with the catalytic residues of enzyme. The present work of docking study on various designed acetamide derivatives[17] attempts to examine the MAO A inhibitory potential in the form of docking score. This study should, therefore, facilitate in designing newer molecules with improved and specific MAO A inhibitory activity.

MATERIALS AND METHODS

Requirement of software

Chemoffice version 7.0 supplied by Cambridge software company, USA, was used for ligand preparation. Docking study was done by PyRx software. PyRx is a graphical user interface for AutoDock 4.2 and AutoDock Vina to perform virtual screening. It provides binding affinities score and RMSD values for each ligand with nine different poses[20]. In present work AutoDock Vina module was used to perform virtual screening. AutoDock Vina is a new open-source program for drug discovery, molecular docking and virtual screening, offering multicore capability, high

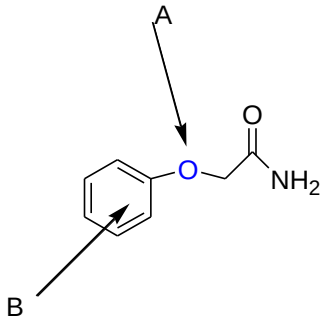


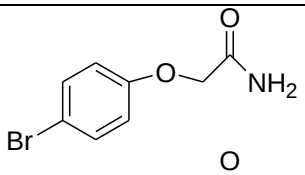
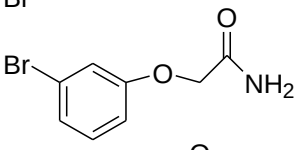
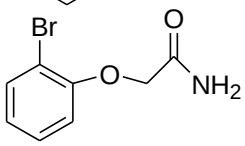
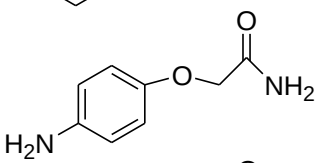
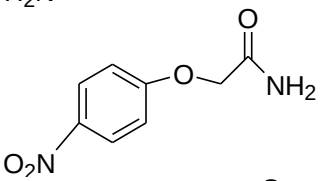
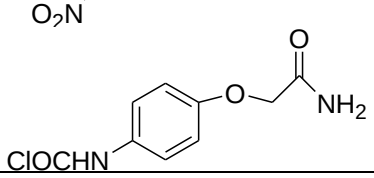
Figure 1: Structure of the lead scaffold and its sites of modification

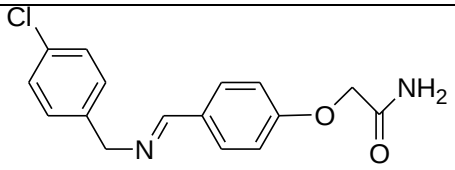
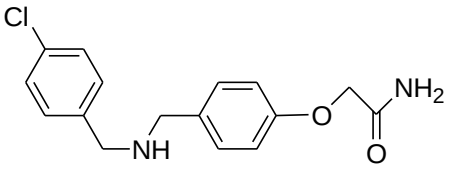
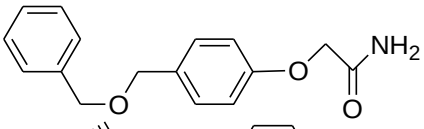
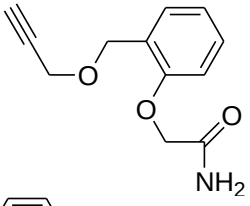
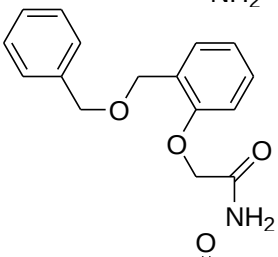
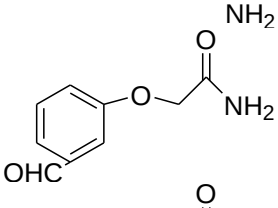
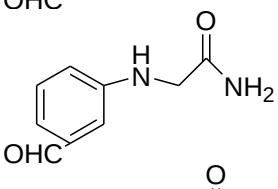
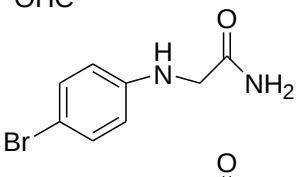
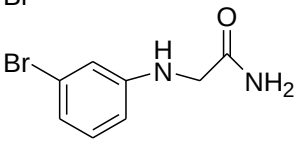
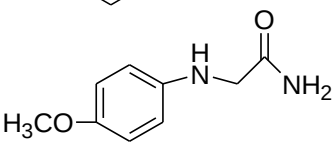
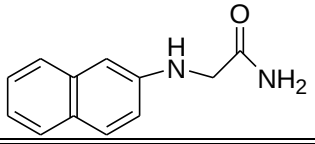
Performance, enhanced accuracy and ease of use[21] and docked poses were analyzed by Discovery studio 4.5 client[22].

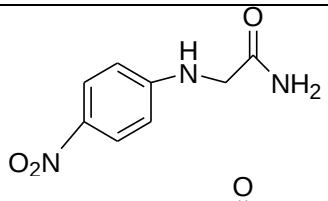
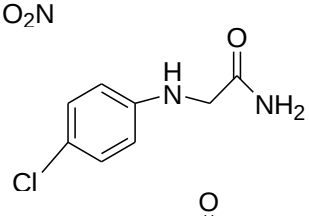
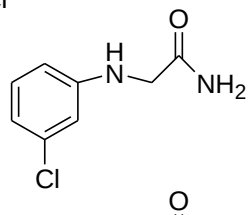
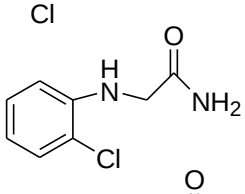
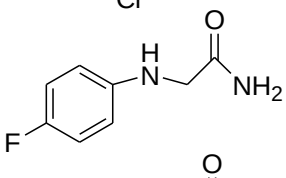
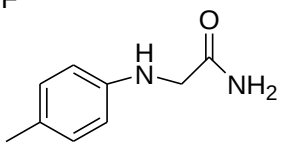
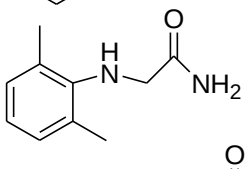
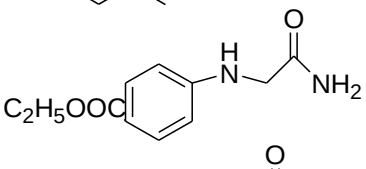
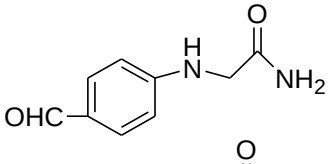
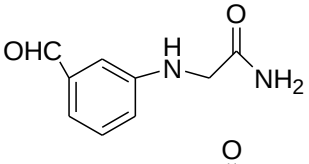
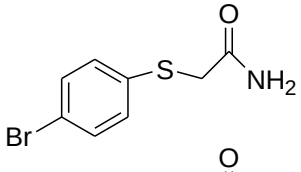
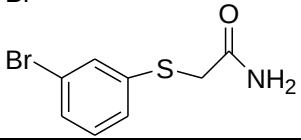
Preparation of ligands

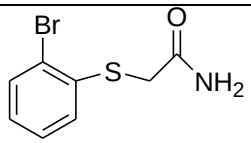
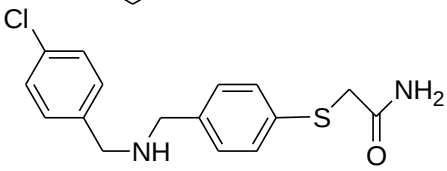
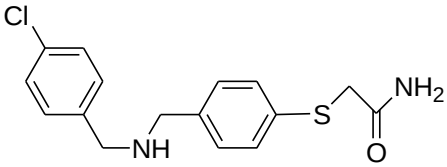
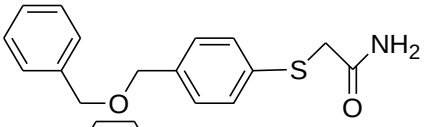
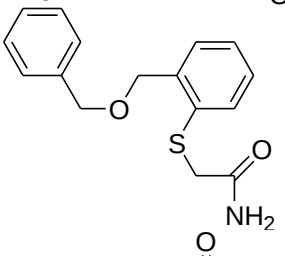
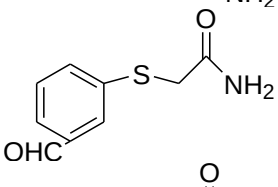
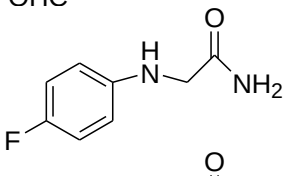
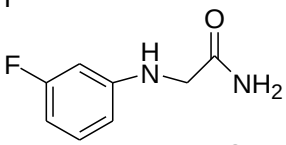
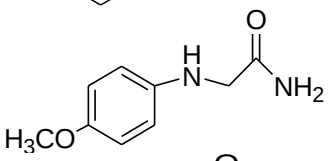
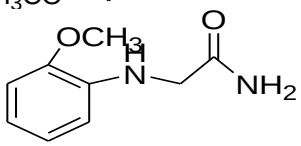
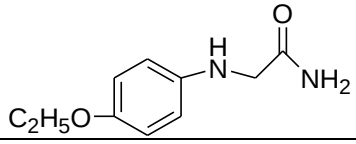
40 Acetamide derivatives were designed based on the findings of published article[17]. A and B sites were selected as modification sites. These acetamide derivatives as ligand molecules were drawn by using Chem Draw Ultra module. Transformation of two-dimensional (2D) structures into three dimensional (3D) structures was done by using the Chem3D Ultra module. Energy-minimization of resulting 3D structures was done by using the molecular mechanics (MM_2) method and then energy minimized molecules were re-optimized using Austin model molecular orbital package (MOPAC)[23]. These three dimensional molecules were saved in protein data bank format (.pdb) for final docking study. Two dimensional structures of all designed molecules were presented in Table 1.

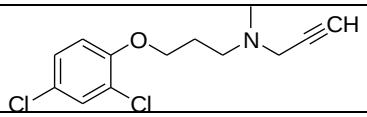
Table 1: Structures of newly designed Ligands from AD1- AD40 for MAO A inhibitory activity.

Sr No	Ligand Code	Structures	IUPAC Name
1.	AD1		2-(4-Bromo-phenoxy)-acetamide
2.	AD2		2-(3-Bromo-phenoxy)-acetamide
3.	AD3		2-(2-Bromo-phenoxy)-acetamide
4.	AD4		2-(4-Amino-phenoxy)-acetamide
5.	AD5		2-(4-Nitro-phenoxy)-acetamide
6.	AD6		2-(4-Chloro carbamoyl-phenoxy)-acetamide

7.	AD7		2-{4-[(4-Chloro-benzylimino)-methyl]-phenoxy}-acetamide
8.	AD8		2-{4-[(4-Chloro-benzylamino)-methyl]-phenoxy}-acetamide
9.	AD9		2-(4-Benzyloxymethyl-phenoxy)-acetamide
10.	AD10		2-(2-Prop-2-ynyloxymethyl-phenoxy)-acetamide
11.	AD11		2-(2-Benzyloxymethyl-phenoxy)-acetamide
12.	AD12		2-(3-Formyl-phenoxy)-acetamide
13.	AD13		2-(3-Formyl-phenylamino)-acetamide
14.	AD14		2-(4-Bromo-phenylamino)-acetamide
15.	AD15		2-(3-Bromo-phenylamino)-acetamide
16.	AD16		2-(4-Methoxy-phenylamino)-acetamide
17.	AD17		2-(Naphthalen-2-ylamino)-acetamide

18.	AD18		2-(4-Nitro-phenylamino)-acetamide
19.	AD19		2-(4-Chloro-phenylamino)-acetamide
20.	AD20		2-(3-Chloro-phenylamino)-acetamide
21.	AD21		2-(2-Chloro-phenylamino)-acetamide
22.	AD22		2-(4-Fluoro-phenylamino)-acetamide
23.	AD23		2-*p*-Tolylamino-acetamide
24.	AD24		2-(2,6-Dimethyl-phenylamino)-acetamide
25.	AD25		4-(Carbamoylmethyl-amino)-benzoic acid ethyl ester
26.	AD26		2-(4-Formyl-phenylamino)-acetamide
27.	AD27		2-(3-Formyl-phenylamino)-acetamide
28.	AD28		2-(4-Bromo-phenylsulfanyl)-acetamide
29.	AD29		2-(3-Bromo-phenylsulfanyl)-acetamide

30.	AD30		2-(2-Bromo-phenylsulfanyl)-acetamide
31.	AD31		2-{4-[(4-Chloro-benzylamino)-methyl]-phenylsulfanyl}-acetamide
32.	AD32		2-{4-[(4-Chloro-benzylamino)-methyl]-phenylsulfanyl}-acetamide
33.	AD33		2-(4-Benzyloxymethyl-phenylsulfanyl)-acetamide
34.	AD34		2-(2-Benzyloxymethyl-phenylsulfanyl)-acetamide
35.	AD35		2-(3-Formyl-phenylsulfanyl)-acetamide
36.	AD36		2-(4-Fluoro-phenylamino)-acetamide
37.	AD37		2-(3-Fluoro-phenylamino)-acetamide
38.	AD38		2-(4-Methoxy-phenylamino)-acetamide
39.	AD39		2-(2-Methoxy-phenylamino)-acetamide
40.	AD40		2-(4-Ethoxy-phenylamino)-acetamide

41.	Clorgyline		[3-(2,4-Dichloro-phenoxy)-propyl]-methyl-prop-2-ynyl-amine

Protein preparation

The target protein for docking study human monoamine oxidase A (PDB Code: 2Z5X), was downloaded from Protein Data Bank (www.rcsb.org) and crystallographic water molecules were removed from the protein by using Discovery studio client 4.5.

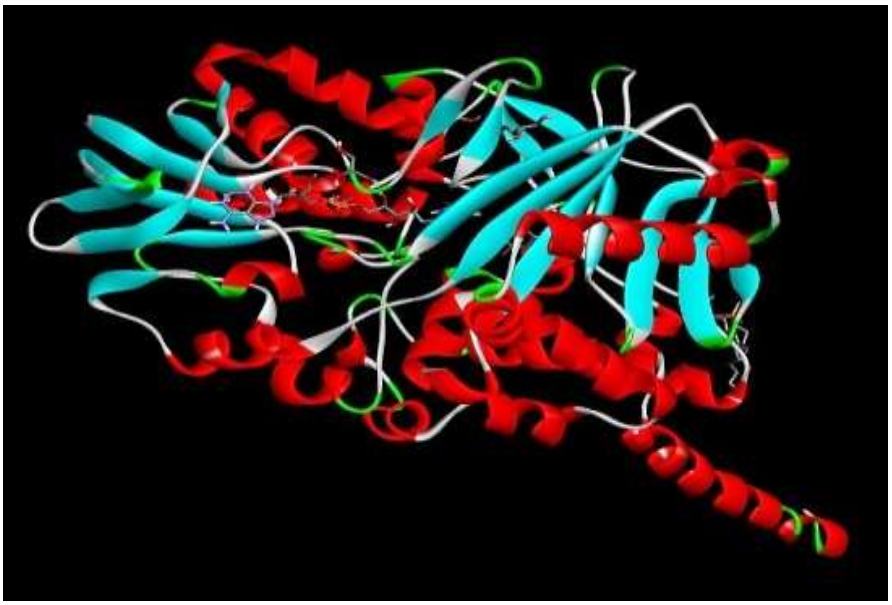


Figure 2: 3D representation of protein MAO A (PDB code 2Z5X)

Virtual screening

A library of generated ligands was subjected for virtual screening against identified potential drug targets using PyRx. The grid for docking calculations was centred on MAO A (2Z5X). During virtual screening ligands and proteins were selected and converted in to PDBQT format for Autodock Vina program. The default parameters of Vina were used for docking simulation. However, docking grid was set of 49.24, 42.83 and 25.00 points (1 point = 1 Å) in the *x*, *y* and *z* directions. In other words, a cube of these arm length was created around FAD of MAO A and the run Vina vizard forward for docking study. Finally the lowest energy binding conformation and root mean square deviation (RMSD) for Ligand binding was analyzed for each protein Ligand interactions in 9 different poses. Low value of RMSD (<2) indicate good interaction between ligand and protein. Efficiency of all the ligands was analyzed using binding energy value predicted by software. Binding energy is the sum of the intermolecular energy and the torsional free-energy penalty, with a more negative binding energy representing a stronger inhibition[24]. From the results

of docking, ligands with best docking score (free energy of ligand binding, Δ*G* binding, kcal/mol), and low value of RMSD were considered as "HIT" and selected for visualization.

Visualization

At the end of docking, the best poses were analyzed for hydrogen bonding, π- π interactions, estimation of ligand binding site. All the visualization of the structure files were done using Discovery studio client 4.5. Visualization was done in both form two dimensionally and three dimensionally to demonstrate protein ligand interaction.

Prediction of crossing blood brain barrier

A drug should show sufficient lipid solubility to cross blood brain barrier (BBB) and to show its effect in brain. To predict the potential of crossing blood brain, the molecules with good docking score and low value of RMSD were screened online by using BBB predictor. Molecules which have the capability to crosses BBB measured as BBB (+) and BBB (-) shows the inability of molecules to cross BBB.

RESULT AND DISCUSSION

Docking scores

To identify the molecular binding interaction of proposed inhibitors set of 40 ligands (AD1-AD40) and one standard Clorgyline were docked in to MAO A (PDB ID: 2Z5X) by using Autodock Vina program of PyRx. Binding energies in the protein –ligand interactions explain how fit the ligand binds with target protein. The low (negative) energy indicates a stable system and therefore a likely binding interaction. The compound with least binding energy against target protein is measured as 'hit compound'. The score as binding free energy values represented in **Table 2**

The results showed that all the designed ligands showed binding free energy ranging between -8.3 kcal/mol to -4.2 kcal/mol while standard Clorgyline showed -7.6 kcal/mol binding free energy. According to literature survey the successful scoring function is one in which the root mean square deviation (RMSD) of best docked confirmation is $\leq$ 2 A^{o25}. All the proposed compounds contributed significant monoamine oxidase-A inhibitory activity because of their structural parameters.

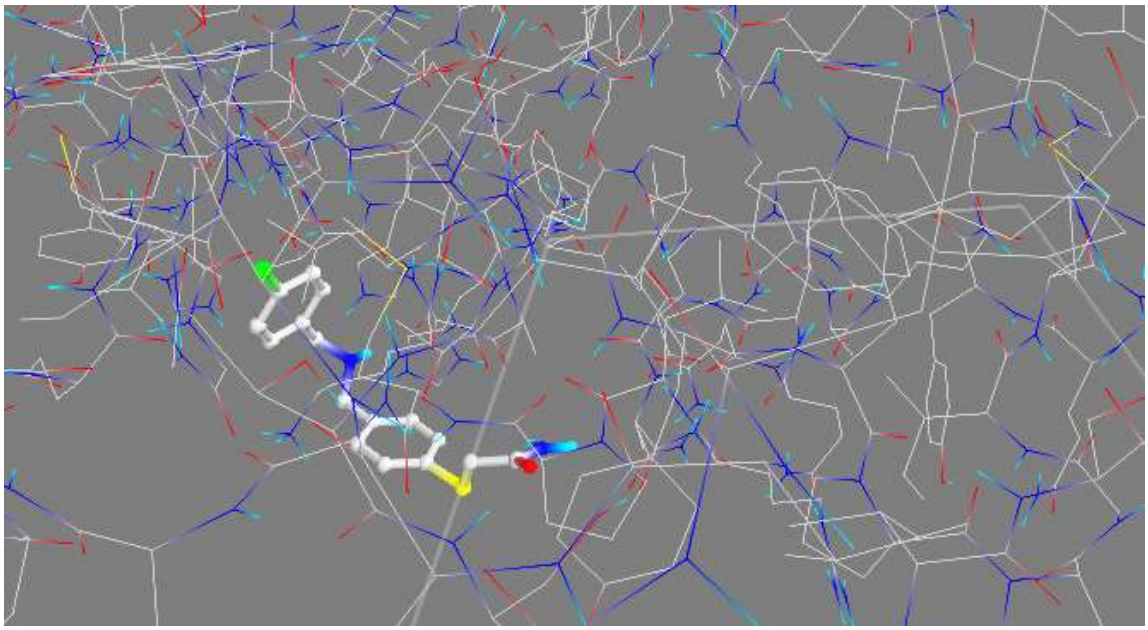


Figure 3: Molecular docking view of ligand AD31 with protein MAO A (PDB code 2Z5X)

Table 2: Free energy of binding of designed ligands with MAO A enzyme estimated by Autodock Vina

SoNo	Ligand Code	Docking score Free (Binding energy Kcal/mol)	RMSD (A^o)
1.	AD1	-5.1	2.138
2.	AD2	-6.5	2.163
3.	AD3	-4.1	3.643
4.	AD4	-5.9	14.941
5.	AD5	-7.0	5.954
6.	AD6	-5.7	2.226
7.	AD7	-7.0	2.413
8.	AD8	-6.6	2.155
9.	AD9	-6.5	2.165
10.	AD10	-6.6	1.958
11.	AD11	-5.8	38.697
12.	AD12	-5.8	4.053
13.	AD13	-6.1	20.712
14.	AD14	-7.2	1.404
15.	AD15	-5.4	2.223
16.	AD16	-7.0	1.738
17.	AD17	-8.1	1.974
18.	AD18	-7.1	1.054
19.	AD19	-7.6	1.096
20.	AD20	-7.2	1.708

21.	AD21	-6.0	4.956
22.	AD22	-7.0	2.971
23.	AD23	-7.3	2.006
24.	AD24	-5.5	2.165
25.	AD25	-7.1	1.947
26.	AD26	-7.2	1.98
27.	AD27	-5.9	23.63
28.	AD28	-6.6	1.52
29.	AD29	-5.5	2.093
30.	AD30	-5.7	4.126
31.	AD31	-8.3	0.715
32.	AD32	-5.7	18.679
33.	AD33	-5.2	19.729
34.	AD34	-5.2	4.628
35.	AD35	-5.5	2.34
36.	AD36	-7.0	0.911
37.	AD37	-5.1	4.988
38.	AD38	-5.2	2.725
39.	AD39	-5.9	3.03
40.	AD40	-6.1	2.271
41.	*Clorgyline	-7.6	1.943

***Standard (reversible inhibitors of MAO A)**

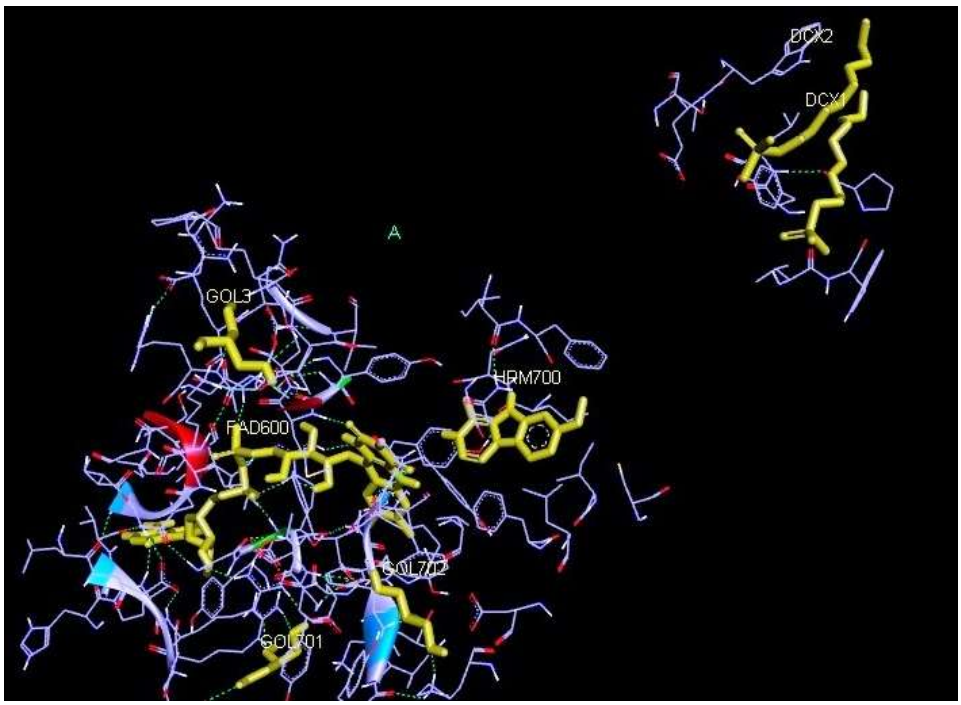


Figure 4: Binding site characterization of protein MAO A (PDB code 2Z5X)

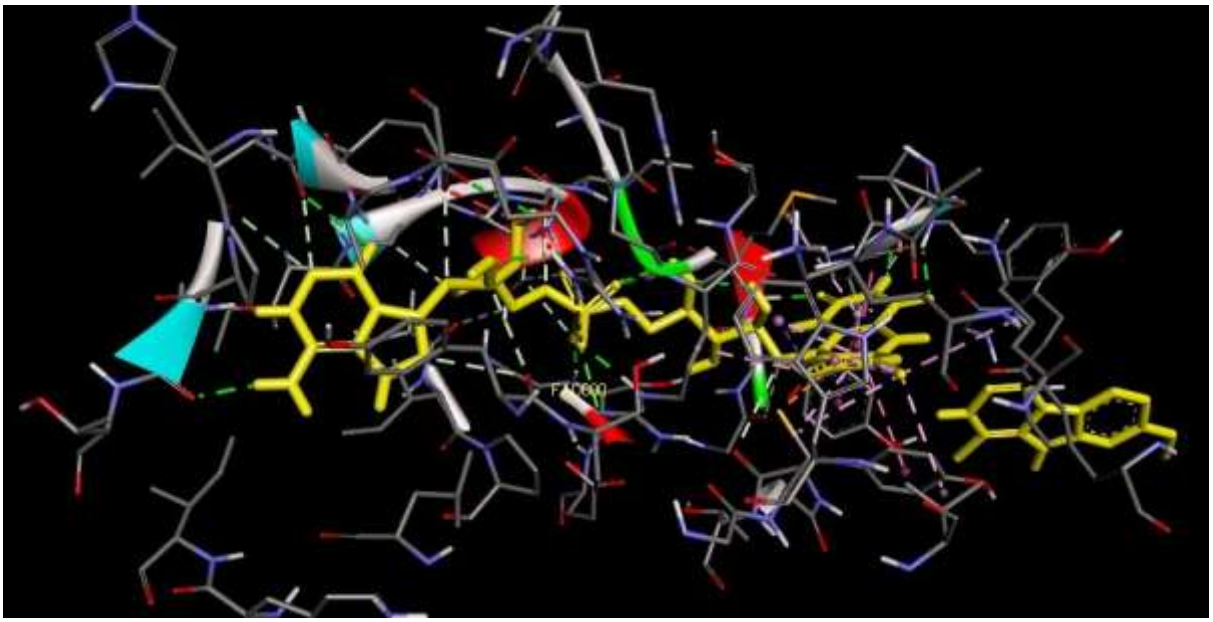


Figure 5: Showing the interactions of the internal ligand

The best score was shown by AD31 (-8.3 kcal/mol) with appropriate low value of RMSD (0.715 A^o) followed by AD17 (-8.1 kcal/mol) with RMSD value (1.974 A^o) and AD19 (-7.6 kcal/mol) with RMSD 1.096 A^o. Following compounds have showed good docking score in decreasing order with enough low value of RMSD.

AD31>AD17>AD19>AD23>AD14>AD20>AD26> AD25>AD18>AD16>AD36

Above mentioned compounds were selected as "HIT" molecules since they showed good docking score and low value of RMSD. These compounds were selected for further study of visualization to find out the target binding site of amino acid residues, other residues and hydrogen bond interaction. The interactions between these compounds and the target protein MAO A was done by using Discovery studio client 4.5. Compounds with tendency to form most stable complex with target protein were selected among these compounds on the basis of hydrogen bond interaction.

Hydrogen bond interaction

The amino acids interacted with set of designed ligands and contribute main role in their binding. The higher affinity of these molecules were primarily due to the formation of hydrogen bonds. Number of hydrogen bonds provides the stability to ligand protein complex. Hydrogen bonding and amino acids involved in bonding between lead compounds and MAO A were given in Table 3. The hydrogen bond between specified ligands and MAO A were highlighted as green colour dotted lines in figure 7, 9, 11 and were also specified in figure 6, 8 and 10 separately in two dimensional forms.

Table 3: Ligands with no of hydrogen bond interaction and interacting residues

Sr No	Ligand Code	No of H-bonds	H-bond interacting residues
1.	AD31	05	VAL 115 ASN 125 PHE 112 PHE 112 GLU 492
2.	AD17	04	ASN 125 GLU 492 ASN 125 ASN 125
3.	AD19	08	GOL 3:03 ASP 480 LEU 78 SER 81:OG ILE86:O ILE86:O THR 88:N THR 88 :OG1
4.	AD23	04	ASN 125 GLU 492 ASN 125 GLU 492
5.	AD14	04	ASN 125 GLU 492 ASN 125 GLU 492
6.	AD20	05	ARG 424 SER 442 THR 408 ALA 409 GLU 436
7.	AD26	04	ASN 125 GLU 492 ASN 125 GLU 492
8.	AD25	05	ASN 125 GLU 492 ASN 125 ASN 125 PHE 112
9.	AD18	07	ARG 356 ARG 356 MET 300 GLY 301 GLY 404

		MET 300
		TYR 410
10.	AD16	06	ASN 125
		GLU 492
		ASN 125
		GLU 492
		PRO 113
		DCX 1:O4
11.	AD36	03	GLU 492
		ASN 125
		GLU 492

ARG: Argenine, ALA: Alanine, ASN: Asparagine, GLN: Glutamine, GLU: Glutamic acid, MET: Methionine, THR: Threonine, DCX: Doublecortin, PHE: Phenylalanine, PRO: Proline, TYR: Tyramine, GLY: Glycine, ASP: Aspartic acid, LEU: Leucine, ILE: Isoleucine, SER: Serine

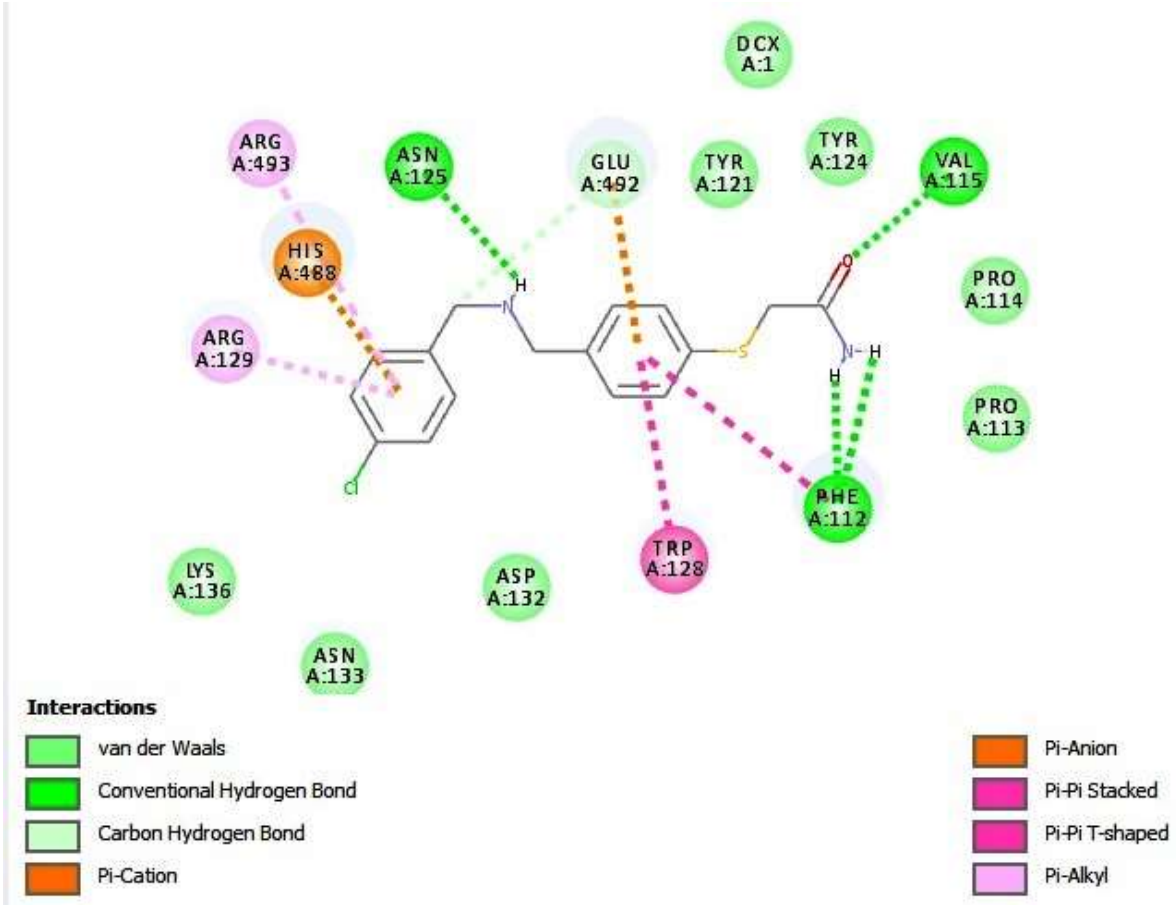


Figure 6: Binding orientation of Ligand AD31with MAO A (PDB code 2Z5X) in 2D

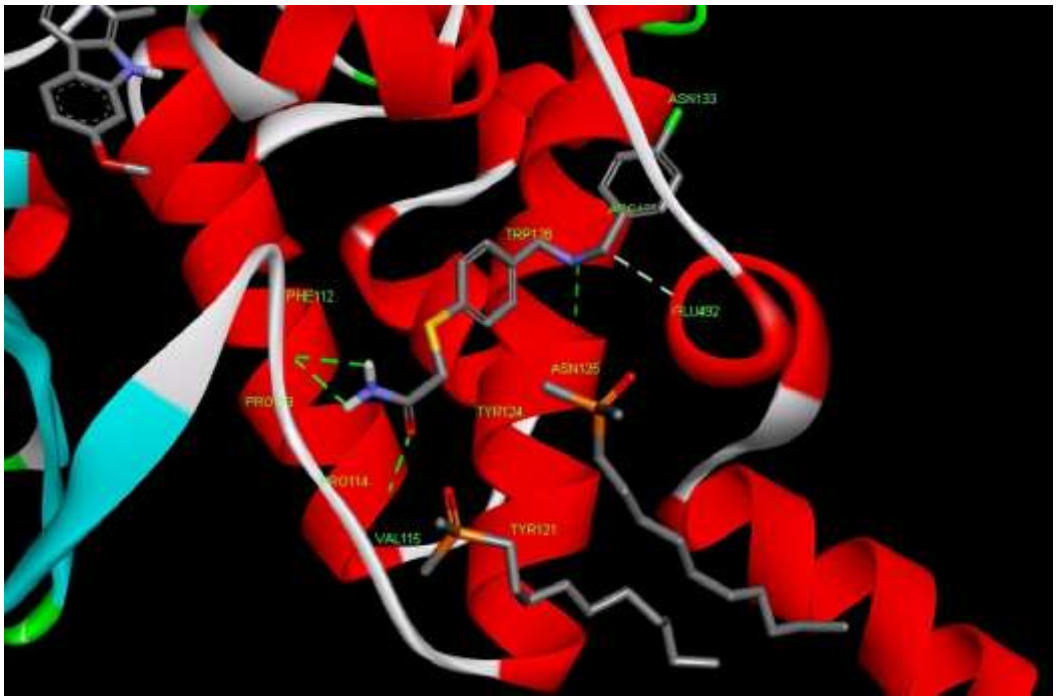


Figure 7: Binding orientation of Ligand AD31with MAO A (PDB code 2Z5X) in 3D

Docking study with AD31 ligand resulted in an Autodock Vina score of -8.3 kcal/mol and a RMSD value of 0.715 A^{o}, showed 5 hydrogen bond interactions with amino acids residues VAL 115, ASN 125, two PHE 112, and GLU 492 within the active binding site region. This was presented in both form 2D and 3 D (Figure 6 and Figure 7). NH group of AD31 shows hydrogen bond formation with ASN 125 (Figure 6) and is a sign of significance in binding with enzyme MAO A. This information can be used for designing new enzyme inhibitors. Carbonyl group show H- bonding interaction with VAL 115 and amino group of amide forms two hydrogen bonds with PHE 112. This interaction yet again revealed the importance of amide group for MAO A inhibitory activity the same as published in different literature [25]. AD31 can be considered most stable binding ligand. Ligand AD17 has not only exhibited 4 hydrogen bond interactions with in the active binding site region with interacting residues ASN 125 (Three), GLU 492 (One) but also has less binding energy i.e. -8.1 kcal/mol respectively. Interestingly AD19 showed 8 hydrogen bond interactions with residues GOL 3:03, ASP 480 LEU 78, SER 81:OG, ILE86:O, ILE86:O, THR 88:N, THR 88 :OG1 (Figure 8 and 9), indicates the stability of ligand protein complex. With good docking score and low RMSD value, it can be considered one of the best designed ligand among AD1- AD40.

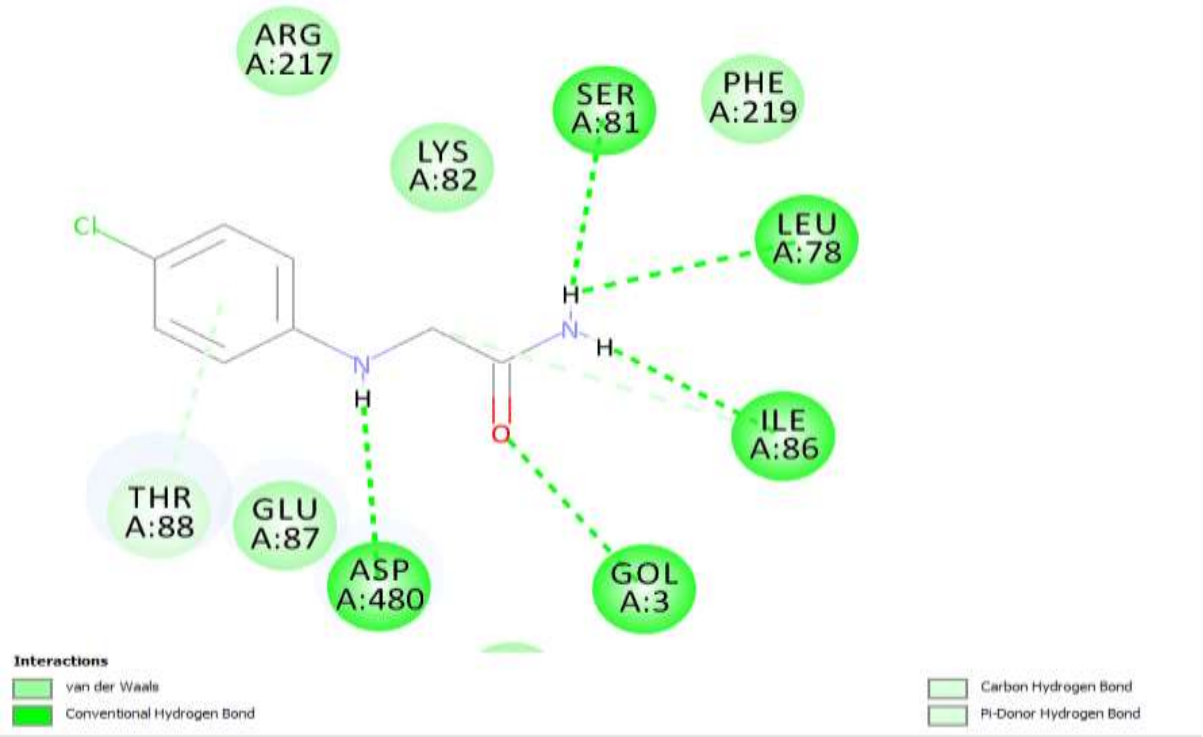


Figure 8: Binding orientation of Ligand AD19with MAO A (PDB code 2Z5X) in 2D

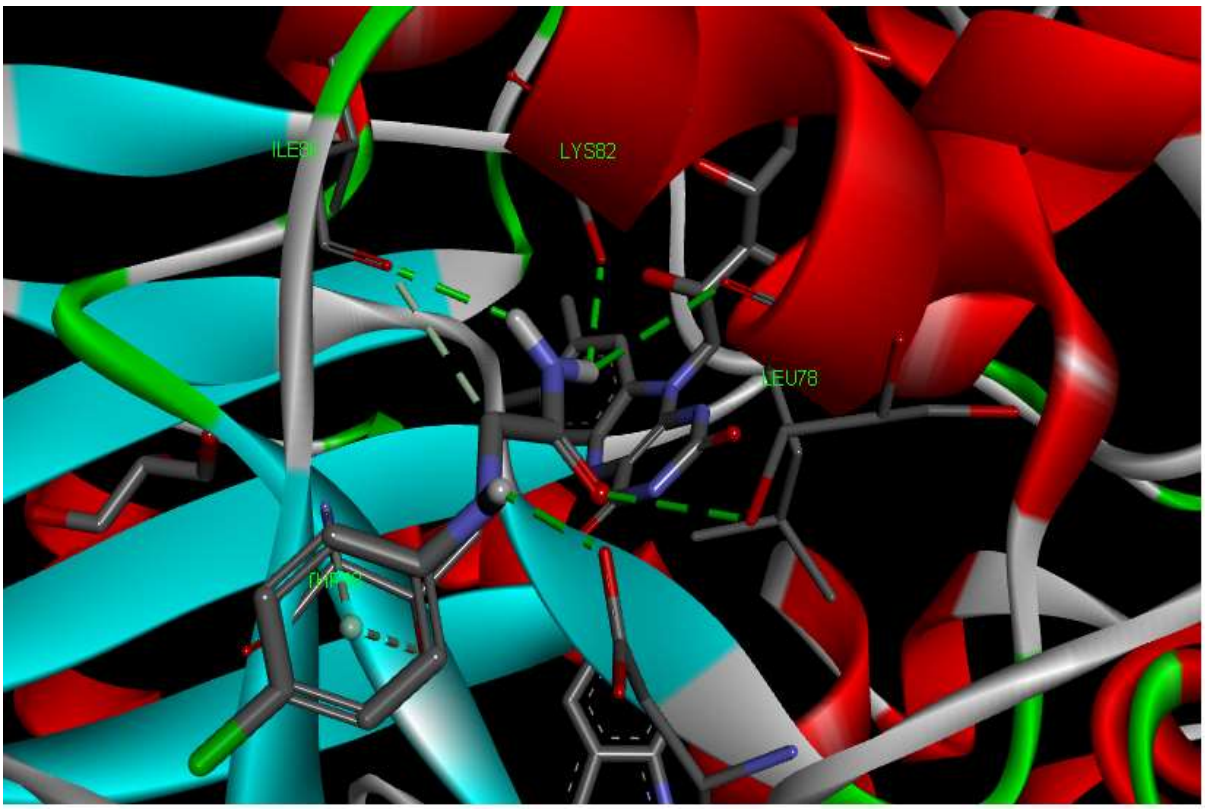


Figure 9: Binding orientation of Ligand AD19 with MAO A (PDB code 2Z5X) in 3D

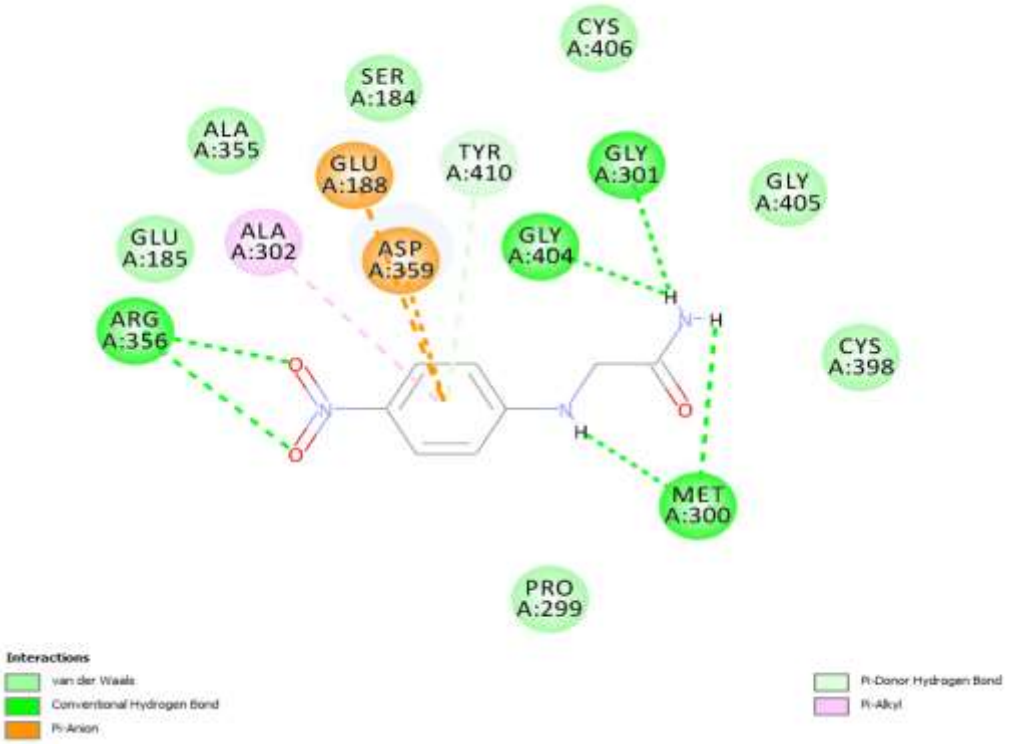


Figure 10: Binding orientation of Ligand AD18 with MAO A (PDB code 2Z5X) in 2D

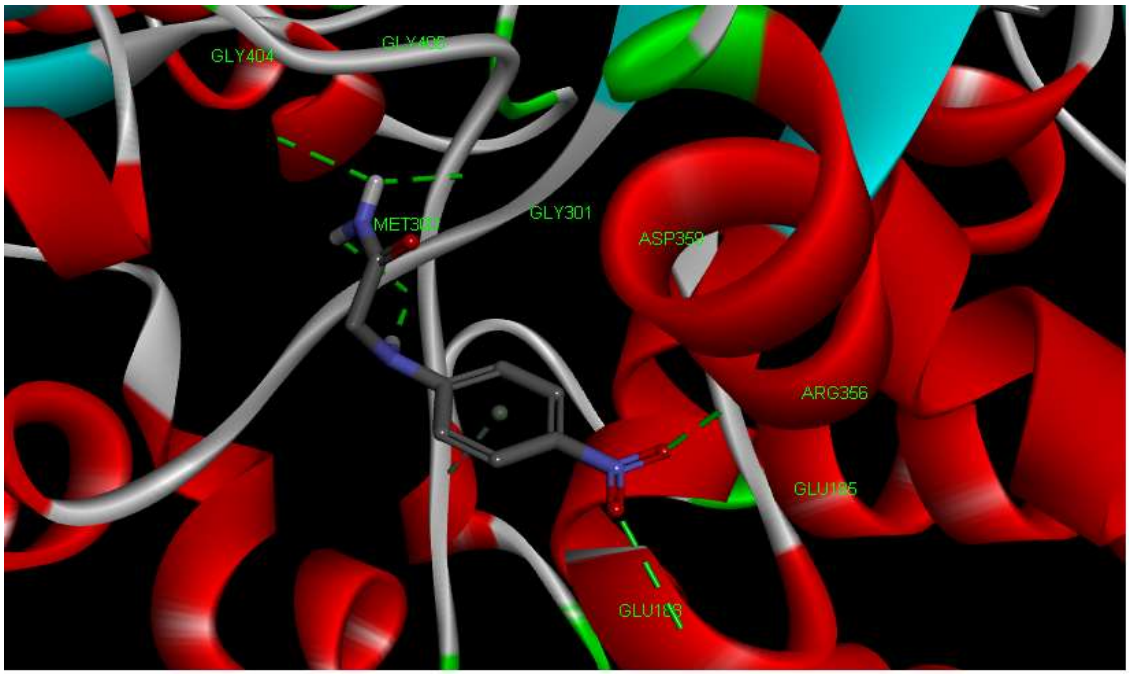


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Figure 11: Binding orientation of Ligand AD18 with MAO A (PDB code 2Z5X) in 3D

Ligand AD18 has shown enormous stability of binding with 7 hydrogen bond interactions with in the active binding site region and the interacting residues were ARG 356, ARG 356, MET 300, GLY 301, GLY 404, MET 300, TYR 410 (Figure 10 and 11). Nitro group at para position showed

vital contribution in binding with target protein showing interaction with argenin residues (Figure 10). This provides significant information concerning nitro group in designing of MAO A inhibitors. ligand AD36 have shown to exhibit three hydrogen bond interaction with amino acid residue and cannot be considered well for enzyme inhibitory activity. Other ligands such as AD25, AD20, AD16, and AD14 have shown satisfactory hydrogen bond interaction with similar amino acid residues and also have shown satisfactory binding energy to provide enough stability to ligand protein complex.

Capability of crossing blood brain barrier

Table 4: Shows prediction about molecules to cross blood brain barrier (BBB)

Name of the Lead	BBB (+) / BBB (--)	BBB Score
AD31	++	**0.114**
AD17	+	**0.081**
AD19	+	**0.041**
AD23	+	**0.044**
AD14	+	**0.052**
AD20	+	**0.041**
AD26	+	**0.067**
AD25	+	**0.011**
AD18	+	**0.070**
AD16	+	**0.021**
AD36	+	**0.052**

All the selected compounds have shown the capability to cross blood brain barrier as indicated by their positive score. Among all the compounds AD31(0.114) have shown maximum BBB score and again strongly reflected their effects in CNS.

CONCLUSION

From this study we have got 11 compounds which showed good MAO A inhibitory activity and results are comparable with standard which already has its potential to treat depression as MAO A inhibitors. All the above mentioned compounds have also shown their capability to cross blood brain barrier and to produce their effects in brain. These findings indicate that this type modification in acetamide derivatives may produce potent and specific MAO A inhibitors to treat depression and affective disorders with lesser side effects. From these results one can also go to synthesis and pharmacological evaluation of these compounds in near future for the development of clinically effective MAO inhibitors.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest in this work.

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