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# Potent Lead Identification for the Treatment of Depression: A Computational Approach

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**ABSTRACT**

*Inhibitors of monoamine oxidase-A (MAO-A) are particularly crucial for the treatment of depressive disorders. Current treatment causes hypertension crisis and as a result, newer medications are required with more pharmacological effective and as decreased side effects. Hence, the present study aims to identify new lead compounds to inhibit MAO-A to treat depression. Pharmacophore model was developed from the marketed drugs using Pharmgist webserver. Through the Zincpharmer web server, 1000 most comparable pharmacophoric ligands that are feasible were identified. Using data warrior tool, the compounds were further filtered and used for molecular docking using AutoDock Vina. Based on the binding energy and amino acid interaction four ligands are subsequently evaluated for ADMET properties using PKCSM webserver. ZINC91891618 was found to be the best moiety with good binding affinity and having good interaction good interaction with key amino acid of MAO-A.*

***Key words:*** *Depression,MAO-A inhibitor, Pharmacophore, Molecular docking*

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## INTRODUCTION

According to WHO Depression is a common worldwide illness, The estimated affected population is 3.8%, of which 5.0% of adults and 5.7% of individuals over 60 are affected. There are 280 million depressed people in the globe [1].A psychiatric disorder called depression can have an impact on one's emotions, behaviour, and overall health. Major depression or major depressive disorder are common names for it. Long-lasting sorrow, emptiness, or hopelessness are the outcomes, along with a lack of interest in once-enjoyed activities. Experimental studies say that serotonin is the major cause of the depression, the synapses of serotonin. Tryptophan hydroxylase is an enzyme that converts tryptophan into serotonin. When the neuron has received enough stimulation, serotonin is subsequently discharged from vesicles and into the synaptic cleft. Multiple processes occur when serotonin is discharged into the synaptic cleft from the serotonin neuron. Other neurons' receptors for serotonin bind to them. The signal that initially activated the serotonin cell is transduced as a result of the activation of postsynaptic receptors. In order to offer feedback and control the plasticity of the neuron, Additionally, serotonin binds to postsynaptic serotonin receptors on the cell that produced it. The presynaptic serotonin cell receives serotonin through the serotonin transporter. After then, monoamine oxidase either breaks down or recycles serotonin for later release and excreted through urine.MAO-A can also degrade norepinephrine and dopamine, the monoamine oxidase (MAOA) enzyme is assumed to play a significant part in the breakdown of serotonin after its reuptake from the synaptic cleft. It thus plays a crucial part in controlling nerve transmission, and changes in its activity brought on by pharmacological treatment or genetic variations are expected to have a significant impact on behaviour. In fact, medications that block its function have long been used to treat behavioural problems, including depression [2].The current treatment for depression involves using of anti-depressants drugs MAO-A inhibitors like moclobemide, befloxatone, clorgyline, toloxatone and cimoxatone. The monoamine oxidase will break or degrade the serotonin in the brain, so that inhibiting the monoamine oxidase results in the increase in the level of serotonin [3,4].

The main adverse of the MAO-A inhibitors is hypertension, MAO-A degrades serotonin and norepinephrine in addition to metabolising dietary tyramine in the intestines and liver. As a result, less tyramine is absorbed into the system during digestion. Tyramine may reach the bloodstream in significant amounts when an MAOI is taken. This might cause norepinephrine to start producing, which would rapidly cause blood pressure to rise. Patients may go through a hypertensive crisis, which can cause a stroke or possibly death from cerebral bleeding [5].Computational approach is a technique to design a drug, discovery, and development are being investigated, adopted, and admired at an extremely quick rate. A new drug's introduction to the market is an extremely difficult, risky, and expensive procedure in terms of resources (time, money, and labour). In general, the process of discovering new drugs and developing them requires 10 to 14 years and a total investment of more than $1 billion [6].
Hence the present study is to identify novel molecules to inhibit MAO-B action through the applications of computational tools.

## MATERIAL AND METHODS

**Drugs are identified form the clinical trial:** The drug like Befloxatone (CHEMBL416578), brofaromine (CHEMBL160347), clorgyline (CHEMBL8706), toloxatone (CHEMBL18116), bazinaprine (CHEMBL150365) and cimoxatone (CHEMBL2104092) are in preclinical trial which are determined for the CHEMBL database. These drugs are downloaded in the SDF format from PubChem [7].

**Pharmacophore modelling:** A pharmacophore is a 3D framework generated by mapping the physiologically powerful chemicals necessary for the ligand to attach to the appropriate target protein and interact with it. Molecule are subjected for pharmacophore modelling by uploading to free online tool called pharmagist in Sybyl Mol 2 format with mail ID. Server considers a variety of ways to combine and submit the compounds to produce the pharmacophore in Jmol format [8].

**Collecting data from zinc database:** Pharmgist produces the number of aligned molecules like 7 aligned molecule one up on another gives a cluster in the JMol format, where the molecule with maximum aligned 7 or 6 molecules with high scoring are selected and downloaded, further these molecules were uploaded in free online tool for pharmacophore modelling I.e., ZINC pharma. Which will screen the zinc database and gives the molecules having same pharmacophoric features by submitting to query. After queries over zinc database give around more than a lakh hits of molecule, further obtained hits are filtered and get total of 950 small molecules [9]. Those above molecules are uploaded to the data warrior, where data warrior is free ware tool for doing pharmacophore modelling, these molecules are screened based on the standard drug physicochemical properties like molecular wight, log P, H donor, H acceptor, polar surface area, rotatable bond and steric centre. The SDF files for each of these compounds were retrieved and used for the molecular docking research [10].

**Molecular Docking studies:** Molecular docking studies was carried out to those molecules selected through Data warrior. The aim of docking studies is to find the best fit and binding affinity of the drug towards targeted protein. First thing is preparation of protein for docking studies, the protein is selected and downloaded in the form pdb format, form the Protein Data Bank with PDB ID 2BXR [11]. The X-ray crystallography of targeted protein Human Monoamine Oxidase A in complex with Clorgyline, Crystal Form A with resolution of 3 angstromUnwanted ligands, water molecules, and hetero groups were removed from the proteinby using “Swiss pdb viewer” and docking is carried out using AutoDock vina, Using AutoDock Vina, all of the ligands were produced, minimised, and optimised. PyMol version 2.4, a molecular visualisation programme by Discovery Studio, was used to further validate the docking methodology. The grid generation process is crucial to the docking process because it establishes the location where the ligands will bind with the protein. The grid is defined by the protein structure from the Protein Data Bank using the co-crystallized ligand that is present with the protein. The top ten structures with the best docking scores were chosen from a screening of the docked output of all the ligands[12].

**ADME-T studies:** The ADMET (absorption, distribution, metabolism, excretion, and toxicity) characteristics play a crucial role in deciding a molecule's fate inside the body. When a molecule is administered orally, a good absorption is a desired property. The distribution and absorption of a molecule throughout the system will be governed by the balance of hydrophilicandlipophilic groups in the structure. From a therapeutic standpoint, effectiveness and toxicity are important. The ADME-T studies is carried out using PKSCM online software [13].

## RESULT AND DISCUSSION

**Ligand-based pharmacophore modelling:** The pharmacophore postulate was developed from MAO-A inhibitors in preclinical by using PharmaGist webserver. Molecule produced from PharmaGist has one aromatic ring, 2 hydrogen bond acceptor at a specified distance. The result obtained from the PharmaGist is uploaded in the ZINCPharmer, it will screen and recover the compounds having same pharmacophoric

features from the ZINC database. The developed pharmacophore model aids in determining the structural prerequisite for MAO-A inhibition. Screened molecules were uploaded to the DataWarrior, further the molecules are filtered based on the physicochemical properties, I.e., the log p value, molecular weight, hydrogen donor, hydrogen acceptor and polar surface area, of the standard MAO-A inhibitors. The SDF files for each of these compounds were retrieved and used for the molecular docking research[14].

**Molecular docking studies**: Clinical trial MAO-A inhibitors underwent molecular docking analysis. The target protein's active pocket with PDB ID: 2BXR was the area where the main binding interactions that would be bioactive conformations were to be found. This procedure was essential in figuring out the relationships between compounds discovered in the ZINC database. Investigations on molecular docking were done using AutoDock Vina[15].Befloxatone (CHEMBL416578), brofaromine (CHEMBL160347), clorgyline (CHEMBL8706), toloxatone (CHEMBL18116), bazinaprine (CHEMBL150365) and cimoxatone (CHEMBL2104092) are currently under the preclinical trial as MAO-A inhibitors.Docking score and binding interaction are given in table 1. Among these inhibitors, cimoxatone was found with the highest docking score of -9.9 kcal/mol, which as conventional hydrogen bonding with THR435, VAL244, ARG45, carbon hydrogen bonding with TYR407, SER24, GLY434, GLU43, Pi-Sigma interaction with ALA44, ILE273, Pi-Pi T shaped interaction with TYR402, Pi-alkyl interaction with ARG51, LUE277. Via hydrogen bonds, these compounds adhere to the protein, Pi-Pi T shaped interaction, Pi-Sigma interaction, Pi-alkyl interaction. Residue tacking part in interaction were THR435, VAL244, ARG45, ALA44, ILE273, LUE277, SER24, TYR402, GLY434 and GLU43. So, the mentioned interaction may be important and provide an explanation for the inhibitory capabilities of molecules acting as MAO-A inhibitors [16].

**Table 1:**Docking score and type of interaction of preclinical trial molecules

| Compound | Docking score | Interacting residues | Type of Interaction |
|---|---|---|---|
| Moclobemide | -7.5 | ILE207<br>TYR69<br>TYR444<br>TYR407 | Carbon hydrogen interaction<br>Pi-Sigma interaction<br>Pi-Pi Stacked interaction<br>Pi-Pi T Shaped interaction |
| Clorgyline | -6.1 | THR204, GLY110<br>TRP128<br>TYR124, TYR121, PHE177 | Carbon hydrogen bonding interaction<br>Pi-Pi Stacked interaction<br>Pi-Alkyl interaction |
| Toloxatone | -7.7 | MET445, ARG51, GLY67<br>TYR407, TYR444 | Conventional hydrogen bond interaction<br>Pi-Pi stacked, Pi-Pi T Shaped, Pi-Alkyl interaction |
| Brofarmine | -7.7 | GLY443<br>TYR407<br>LEU337, ILE335<br>TYR444 | Carbon hydrogen bond interaction<br>Pi-Pi stacked interaction<br>Alkyl interaction<br>Pi-Alkyl interaction |
| Befloxatone | -9 | VAL244, ARG45, ARG51<br>PRO243, TYR402, GLY50<br>LEU277<br>ILE273, ALA44<br>LYS280<br>TYR402 | Conventional hydrogen bond interaction<br>Carbon hydrogen bond interaction<br>Halogen interaction<br>Pi-Sigma interaction<br>Alkyl interaction<br>Pi-Alkyl interaction |
| Bazinaprine | -9.6 | ILE23, GLY443, GLY67, CYS406<br>TYR444<br>TYR407<br>ALA448 | Conventional hydrogen bond interaction<br><br>Pi-donor hydrogen interaction<br>Pi-Pi stacked, Pi-Pi T Shaped interaction<br>Alkyl interaction |
| Cimaxatone | -9.9 | THR435, VAL244, ARG45<br>TYR407, SER24, GLY434, GLU43<br>ARG51, LUE273<br>TYR402<br>ARG51, LEU277 | Conventional hydrogen bond interaction<br>Carbon hydrogen bond interaction<br><br>Pi-Alkyl interaction<br>Pi-Pi T shaped interaction<br>Pi-Alkyl interaction |

The chemical was submitted to docking after being retrieved from the ZINC database using ZINCPharmar based on the pharmacophore. For molecular docking with the target protein PDB ID: 2bxr, 6 chemicals were chosen. To compare the binding interactions of the drugs from preclinical trials with those with good docking scores (mostly negative), the docking was examined. The identification of the hit compound as an MAO-A inhibitor is aided by this comparison. The chemicals are identified based on the binding interaction. A docking score of between -8.2 and -10.7 kcal/mol is possible. A molecule named ZINC91891618 has been discovered by molecular docking. It exhibits Pi-Pi stacking interactions with TYR444, TYR407, Pi-Pi t-shaped interactions with PHE208, and alkyl interactions with ILE335.and

interactions between pi-alkyl and LEU337 and PHE352. Another hot molecule, ZINC55580150, similarly displayed conventional hydrogen bonding interactions with TYR407 and TYR444, carbon hydrogen bonding interactions with GLU216 and GLY443, halogen interactions with PHE208 and GLY443, alkyl interactions with LEU337 and MET350, and Pi-alkyl interactions with PHE352, LEU337, and ILE335.Using AutoDock technologies and the Biovia Discovery Studio Visualizer, binding interactions between docked molecules and the proteins were discovered. The amino acids TYR407, TYR444, GLU216, GLY443, PHE208, LEU337, MET350, PHE352 and ILE335 were involved in the binding interaction. These identified molecules bind similarly to the drugs being tested in clinical trials, according to the molecular docking study [17]. Consequently, MAO-A can be inhibited by these 4 compounds. Figure 4 displays the chemical structures of four docked molecules.

**Table 2:** Docking score of molecules obtained from ZINC database

| Compound | Docking score | Interacting residues | Type of Interaction |
|---|---|---|---|
| **ZINC72279339** | -8.2 | ARG356, ASN179, GLU329, ARG172<br>TYR175<br>LEU176, ARG172<br>LYS158, PRO186, ARG172 | Convention hydrogen bond interaction<br>Pi-Pi Stacked interaction<br>Alkyl interaction<br>Pi-Alkyl interaction |
| **ZINC91891618** | -10.7 | TYR444, TYR407<br>PHE208<br>ILE335<br>LUE337, PHE352 | Pi-Pi stacked interaction<br>Pi-Pi t shaped interaction<br>Alkyl interaction<br>Pi-Pi alkyl interaction |
| **ZINC55580150** | -10.1 | TYR407, TYR444<br><br>GLU216<br>GLY443<br>PHE208<br>LEU337, MET350<br>PHE352, LUE337, ILE335 | Convention hydrogen bond interaction<br>Carbon hydrogen interaction<br>Halogen interaction<br>Pi-Pi Stacked interaction<br>Alkyl interaction<br>Pi-Alkyl interaction |
| **ZINC78905378** | -8.3 | TYR124, TRP128<br>TRP128 | Pi-Pi stacked interaction<br>Pi-Alkyl interaction |

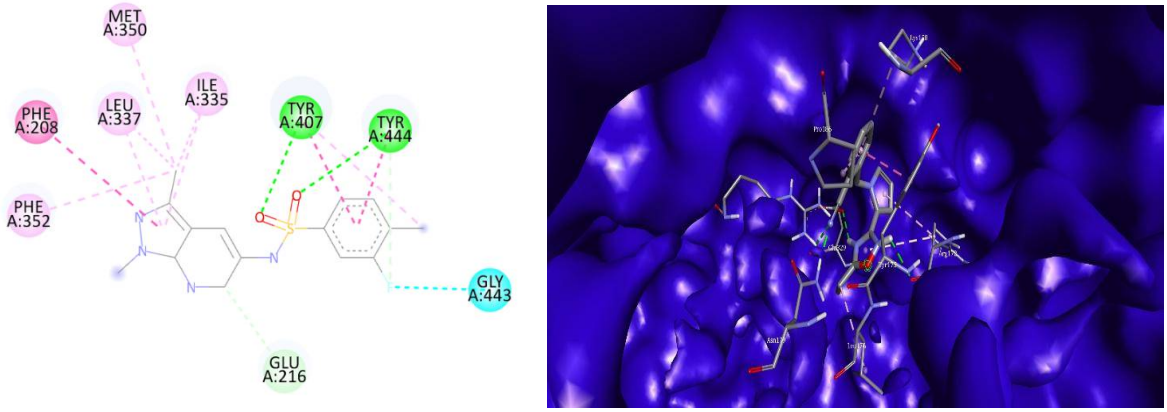


**Fig 1: 2D and 3D interaction of ZINC5580150 with 2BXR**

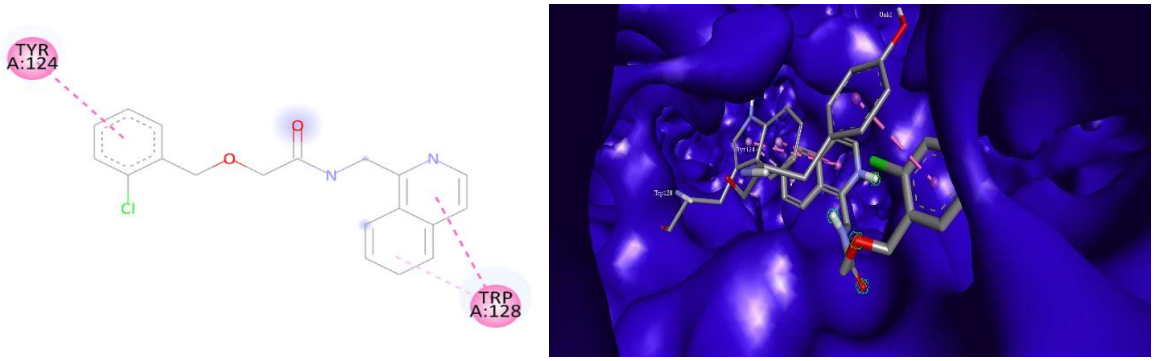


**Fig 2: 2D and 3D interaction of ZINC72279339 with 2BXR**

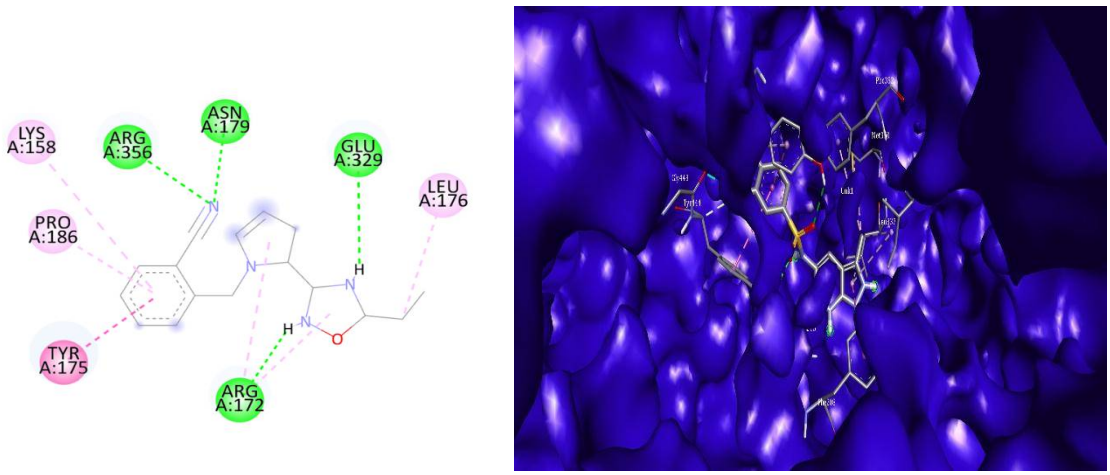


**Fig 3: 2D and 3D interaction of ZINC78905378 with 2BXR**

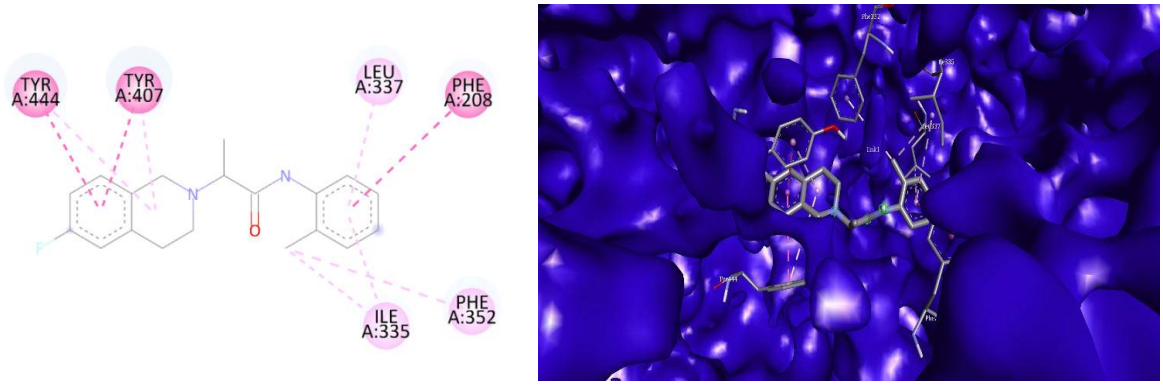


**Fig 4: 2D and 3D interaction of ZINC91891618 with 2BXR**

**ADMET studies:** The ADMET properties with the zincdata base drug i.e., ZINC91891618 has good properties like water solubility, $CaCo_2$ permeability, CNS permeability and it is non hepatotoxic molecule, while other molecules are showing hepatotoxicity. The ADME-T studies is carried out using PKSCM online software [18].

The zincdata base molecule, ZINC91891618 will obey the Lipinski rule of five, by this the molecule can observed well by orally and it pass BBB and CNS to show its activity. The drug-likeness filters based on physicochemical properties speed up the drug development process. The drug-likeness rules/filters based on physicochemical features, however, have drawbacks, as demonstrated by a number of research.

**Table 3:** Drug ability studies of the ligands viz., parameters of Lipinski's rule of 5

| Compound | Physical properties | | | | | | Lipinski's rule |
|---|---|---|---|---|---|---|---|
| | Molecular weight | LOGP | Rotatable bonds | H-bond acceptors | H-bond donors | Surface area | |
| **ZINC72279339** | 282.34 | 2.58 | 4 | 5 | 0 | 65.95 | 0 |
| **ZINC91891618** | 312.38 | 3.56 | 4 | 3 | 1 | 32.34 | 0 |
| **ZINC55580150** | 333.36 | 2.22 | 3 | 6 | 0 | 73.23 | 1 |
| **ZINC78905378** | 340.8 | 3.26 | 7 | 3 | 1 | 51.22 | 0 |

## CONCLUSION

The compounds being tested as MAO-A inhibitors in preclinical studies includeclorgyline, toloxatone, brofarmine, befloxatone, bazinaprine and cimaxtone, used to get ligand-based pharmcophore model. The model gives molecules with similar pharmacophoric feature which is obtained from ZincData base and Datawarrior, Using AutoDock Vina, these molecules were docked based on docking score and binding interaction and then 4 molecules are obtained. Further ADMET studies were done by using PKCSM and Swiss ADME online software. Which predicts the drug-likeness feature and oral rat chronic toxicity and hepatotoxicity. Based on the results molecule ZINC91891618 were predicted as the MAO-A inhibitor. Further *in vitro* and *in vivo* evaluation on the selected compound will lead to identify a potent lead as MAO-A inhibitor.

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**CONFLICT OF INTEREST**
The authors declare that no conflict of interest.

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