ORIGINAL RESEARCH ARTICLES

EXPLORING THE BINDING MODES OF PIPERAZINE COMPOUNDS ON MAO-A FOR A STEP TOWARDS DEPRESSION THERAPY

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ABSTRACT

Sadness, often referred to as "depression," is a normal emotion. The World Health Organization (WHO) claims that depression is a prevalent psychological condition that affects 264 million people worldwide, involving complex interactions between social and psychological behaviors. Piperazine, a heterocyclic scaffold, has been extensively used in various research studies due to its remarkable pharmacological effects in pharmaceutical chemistry. It has been modified to discover a new reversible neuroactive compound, along with pyrazoline. Early investigations have demonstrated significant inhibition of MAO-A by both compounds. The docking of molecules was performed by employing Autodock Vina programme, an *in silico* approach. Using the docking software AutoDockTools 1.5.6, the molecular docking studies on MAO-A enzyme targeting depression [Protein Data Bank (PDB) ID: 2BXR] was conducted. Compound **C17**, demonstrated significant interactions with specific residues, including Gly25, Arg51, Ser24, Thr435, Lys305, Gly66, Tyr407, Cys406, Gly67, Gly443, Ile23, Thr52, Gly22 and Ala448. This finding suggests that compound **17** could potentially serve as a promising and innovative candidate for the treatment of depression. This study focuses on designing a hybrid molecule combining piperazine and pyrazoline as MAO-A inhibitors. The results of the study indicate that **C17** and **C20** exhibit the greatest affinity, having interaction values of -10.9 kcal mol^{-1} and -10.8 kcal mol^{-1}, respectively. All the chemicals demonstrated similar behavior within the binding pocket of MAO-A. In this study, the *in silico* tool Swiss ADME were used to predict the drug-likeness of all designed compounds. The analysis indicated that all the compounds, except one, comply with Lipinski's rule of five, which defines the drug-like compounds. Further, synthesis and biological evaluations need to be conducted in the future.

Keywords: Depression, MAO-A, piperazine derivatives, pyrazoline, Molecular Docking studies, *in silico*

ABBREVIATIONS

MAO-A, B: Monoamine oxidase enzyme-A, B; OCD: Obsessive-compulsive disorder; SSRI: Selective serotonin reuptake inhibitors; SNRI: Serotonin-norepinephrine reuptake inhibitors; FAD: Flavin adenine dinucleotide; HIV: Human immunodeficiency virus; TPSA: Topological polar surface area

INTRODUCTION

Individuals face substantial obstacles as a result of depression, which creates multi-component and severe disorders[1]. Depression represents an instance of mental health condition characterized by persistent sadness and loss of pleasure. This is an extremely common form of psychological sadness that results in a reduction in the standard of existence among older people[2]. Melancholy is still the greatest cause of psychiatric illness suffering in the world, impacting over three hundred million individuals[3]. One in every 5 females as well as one in every 8 men suffered from serious depressive illness at some time in their life[4]. It appears to be a continuous medical issue that is today regarded internationally as the fourth biggest cause of disease[5]. It additionally serves as a major factor in self-harm behaviors universally. In spite of effective therapy, the possibility of recovery persists, imposing an enormous strain on an individual. When combined with high worry, it may cause more memory loss as well as social isolation[6]. Furthermore, it is a form of mental

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disease highlighted with persistent grief and not having any desire.

There are two varieties of melancholy. The first is unipolar, which implies that mood functions as a single stage, and the second one is bipolar, which acts as strained feeling cycles from mania to sadness in a matter of weeks[7,8,9]. The etiology is influenced by hereditary components, anatomical parameters, and neurological-social aspects. An insufficient level of monoamine neurotransmitters such as serotonin, dopamine and norepinephrine cause depression. Monoamines are produced and accumulated in the pre-synaptic neuron. Depression is caused by a reduction in the amount and functioning of monoamine neurotransmitters found in the brain. As a consequence, synaptic plasticity disturbance has been found in prominent mental diseases including depression, anxiety, schizophrenia, and OCD (obsessive-compulsive disorder). Persistent mental sadness, lack of desire, impaired mental processes, disrupted sleep, psychomotor disturbances or impairment, exhaustion or decreased enthusiasm, and thinking of self-harm or suicide are all indicators of depression[10, 11].

Monoamine oxidase inhibitors, also known as MAOIs seem to be the very first category of medications to be approved for the treatment of symptoms of depression. Now a days, selective serotonin reuptake inhibitors (SSRIs) and SNRI (serotonin-norepinephrine reuptake inhibitors) tend to be the primary therapies for severe depressive illnesses because they impede the reuptake of 5-HT (serotonin) and norepinephrine (NE) produced by brain nerve cells. MAOIs and tricyclic antidepressants (TCAs) are two more types of antidepressants that are commonly utilized as second-line treatments[12,13]. The oxidative breakdown of ingested amines and brain chemicals called monoamine is catalyzed by MAOs (monoamine oxidases) which carry a cofactor, namely, flavin adenine dinucleotide (FAD). Mammals have two distinct forms of MAO enzymes; MAO-A and MAO-B. MAO-A contains Cys406 amino acid while MAO-B contains Cys397, which are distinguished by their covalently attached cysteine amino acids with the FAD. MAOs share roughly 70% of their amino acid sequences, and they additionally possess 3-D arrangements with extremely well-defined sites for activity. The primary distinctions between MAO-A and MAO-B, which include information about the pertinent active areas as well as clarify why they vary in substrates and antagonist specificity, serve as a means of differentiation[14,15]. MAO-A breakdowns 5-HT and is hindered by clorgiline, whereas MAO-B breakdowns 2-phenylethylamine and benzylamine and is blocked by (R)-deprenyl. Identifying such structural variations has opened the way towards iso-form-specific MAO antagonist's rationalized pharmacological development. Although minimal MAO-B inhibitors are employed to treat Parkinson's disease, the enzyme MAO-A targeting exerts an anti-depressant effect[16, 17].

Compounds derived from piperazines and pyrazolines have previously demonstrated their capability as MAO inhibitors. Among them, the derivative combining piperazine and pyrazoline has emerged as a significant player in drug research, showcasing a diverse range of biological activities, including antioxidant properties, inhibition of MAO-A, and inhibition of MAO-B. A heterocyclic scaffold, piperazine has been utilized in several research because of its miraculous pharmacological impacts in pharmaceutical chemistry that were modified for the discovery of a novel particular reversible neuroactive compound[18]. The therapeutic value contained in a modest couple of nitrogen-contained leads was explored for decades, and continues to offer undiscovered medicinal potential with minor chemical alterations. Minimal to substantial changes between the two nitrogens produced a range of chemical arrangements with varying pharmacological consequences.

As an outcome, research has highlighted its bio-activities in a variety of illness states. Computational (*in silico*) investigations are increasingly vital for optimizing and generating novel potential drugs in an efficient and affordable way. Computational methods were used to discover the optimal molecular structure in piperazine for the therapeutic management of depressive disorders via the neurotransmitter stage. Compounds that were chosen were docked and evaluated for medicinal use. This collaborative study hypothesized that fluorobenzyl piperazine alterations provide MAO-A a higher affinity for binding in a way that will substantially suppress the selected enzyme. Over the past few years, pyrazoline analogues have drawn a lot of interest due to their use in agrochemistry, dyes, and pharmaceuticals. Different biological effects, including anti-inflammation, MAO-A, MAO-B, and anti-HIV, are displayed by pyrazolone derivatives[19]. MAO functions can be more effectively inhibited by the incorporation of thiourea components that include sulphur and nitrogen. Earlier studies have documented the development of various compounds as MAO inhibitors. Unfortunately, these compounds exhibited notable adverse effects, including nausea, throat irritation, inability to sleep, being overweight, and heart health disorders. Consequently, there is a pressing need to create small-molecule MAO blockers that are more selective and have fewer negative effects than currently existing medications. In this study, a computer simulation

utilizing molecular docking techniques to identify potential and selective MAO-A inhibitors among pyrazoline and piperazine derivatives was conducted.

A series of piperazine-like compounds were reported by Nandi *et al.* in 2023 as MAO-A inhibitors. The synthetic molecule with the highest inhibitory efficacy against MAO-A was compound **1** (IC_{50}: 0.25 μM)[20]. Similar to this, Sahu *et al.* reported a series of MAO-A inhibitors that included hybrids of piperazine and oxadiazole. With a corresponding IC_{50} of 0.81 μM, compound **2**[21] was found to be the most effective. Another team of researchers discovered the high MAO-A inhibitory efficacy of compounds containing pyrazoline and amino-chalcone in 2023. They discovered that compound **3**[22] with a pyrazoline substitution had the highest potency. Pratyush and their coworkers have described a series of 3,5-diphenyl-pyrazoline analogues **(4)** in 2019[23]. Similarly, a series of potent MAO-A inhibitor containing 1,3,5-trisubstituted-2-pyrazoline analogues was discovered in 2019, with compound **5** (IC_{50}: 0.0445 μM)[24]. Based on these series of literature, in this experiment, piperazine conjugated pyrazoline based MAO-A inhibitors were designed as depicted in

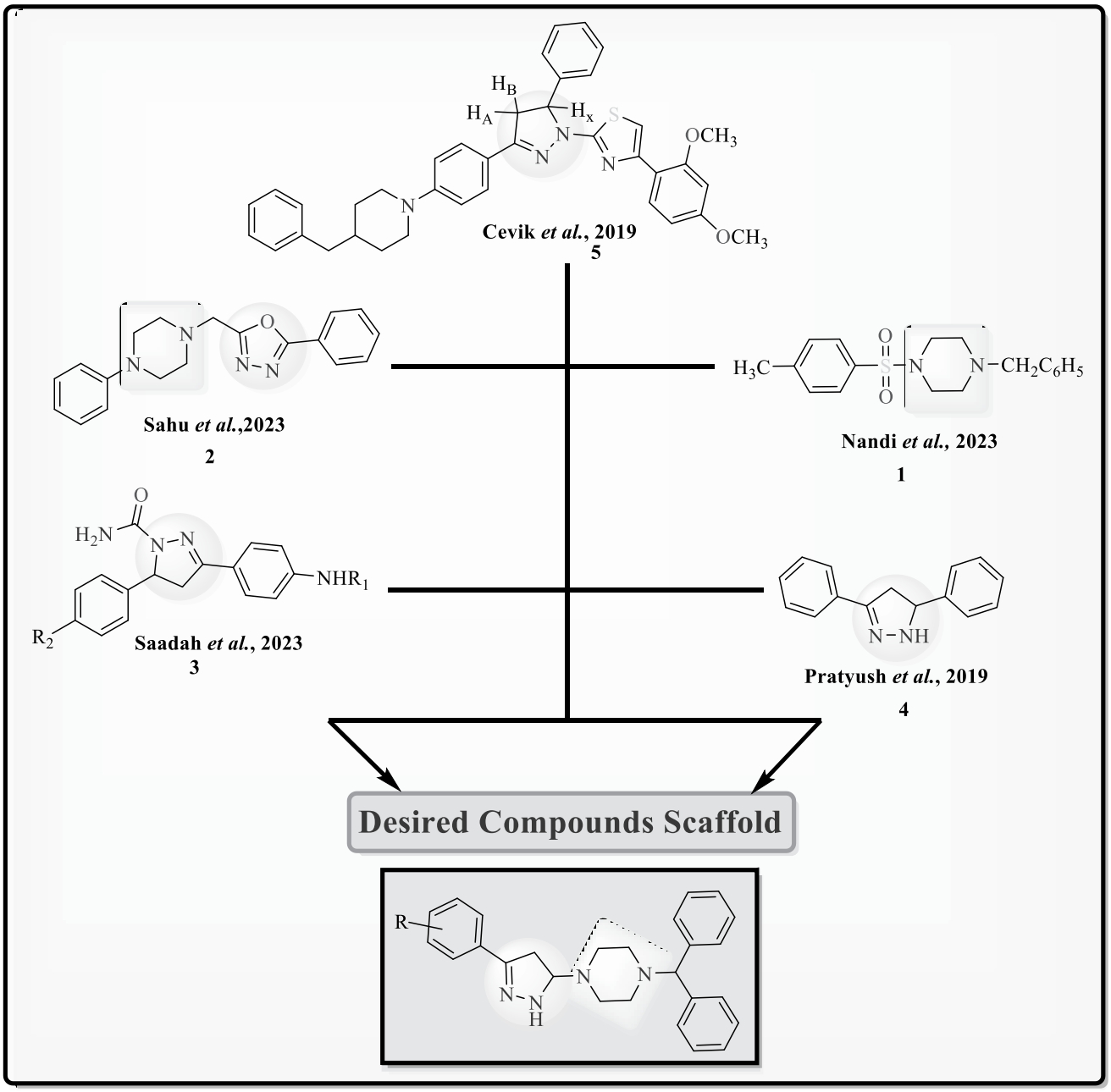

Fig. 1: Literature survey of piperazine and pyrazoline containing MAO-A inhibitors

Fig. 1. The derivatives of newly designed compounds are displayed in Fig. 2.

MATERIALS AND METHODS

Dell Inspiron 15 3000 series, i5 11th Generation Intel processor, 8 GB RAM, 1TB ROM

The crystal structure of MAO-A enzyme (PDB ID: 2BXR) was retrieved from the Protein Data Bank (PDB) to facilitate the computational study, specifically, molecular docking studies. However, the RCSB proteins database library[25] analysis with regard to its resolution, data acquired, and date of availability results in the identification of

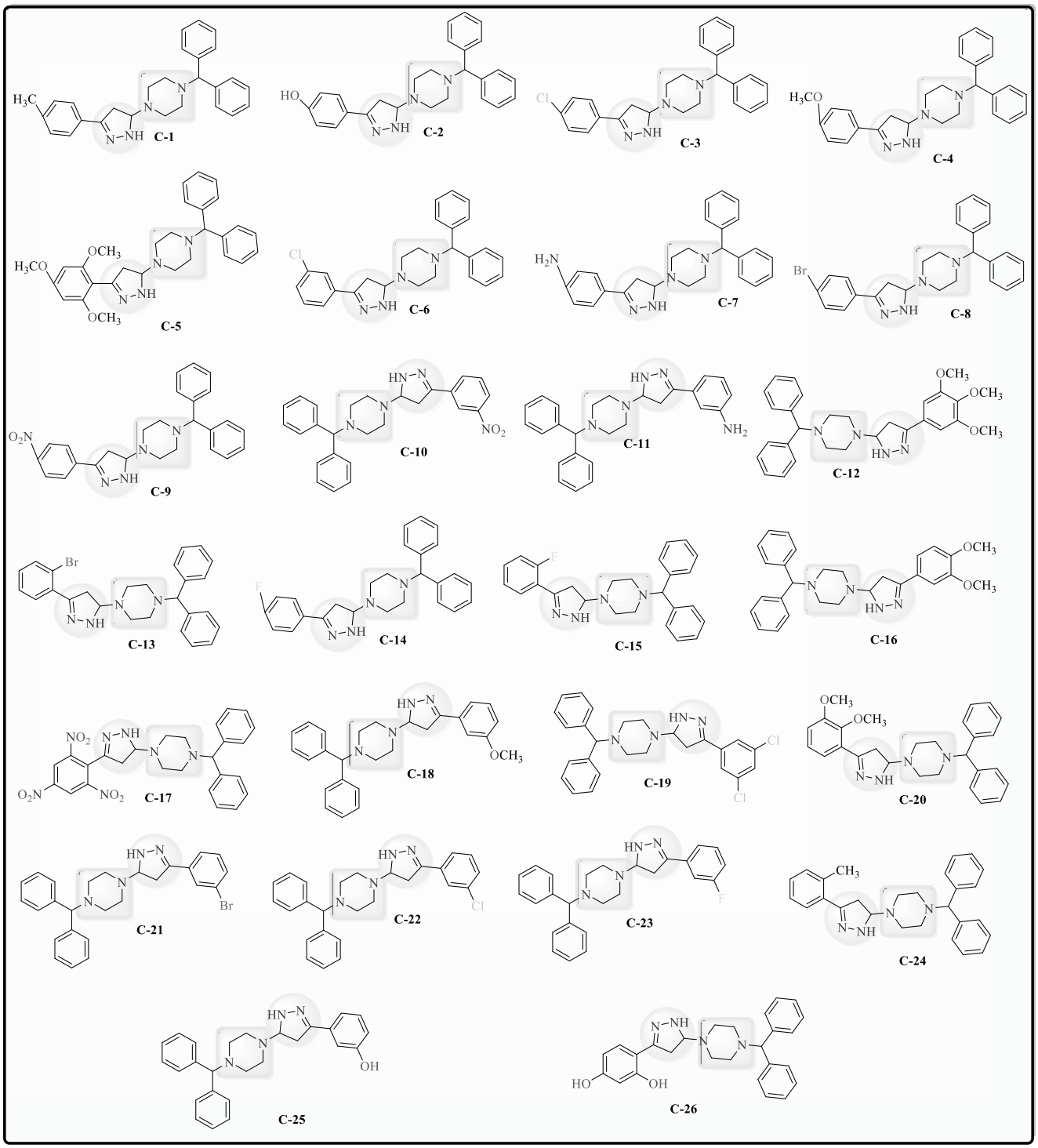

Fig. 2: Derivatives of the designed compounds

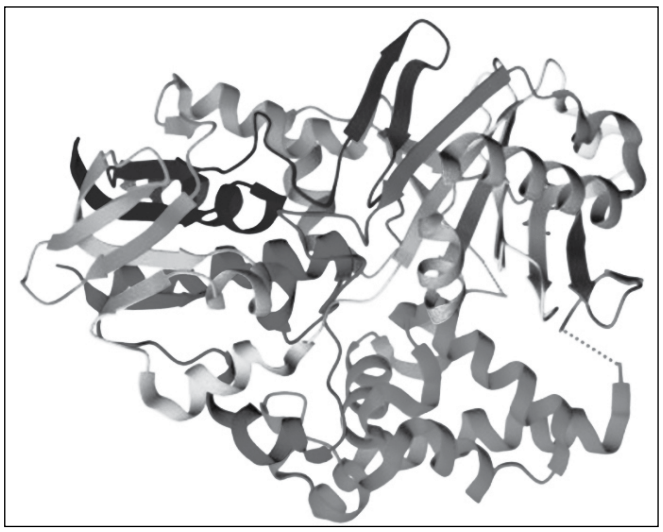

Fig. 3: Structure of the 2BXR protein

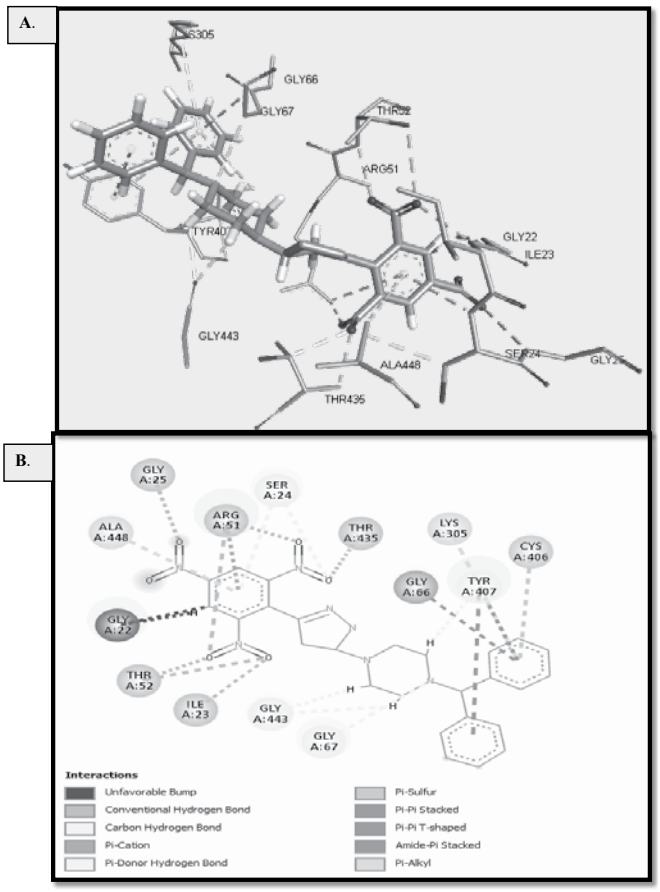

Fig. 4: (A) 3D docking pose of 17, (B) 2D docking poses of 17

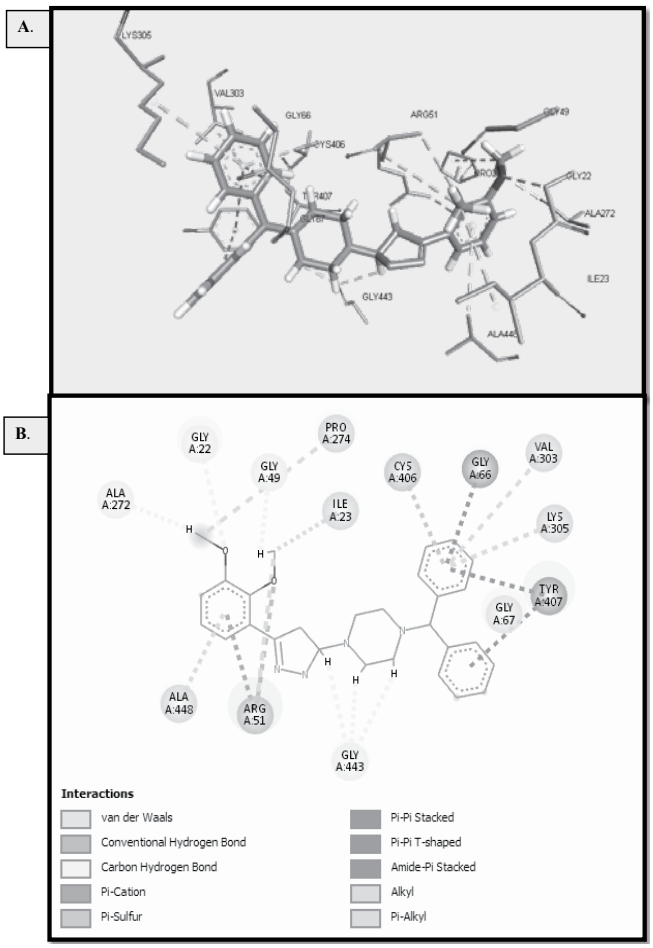

Fig. 5: (A) 3D docking pose of 20, (B) 2D docking pose of 20

2BXR being an approved therapy for depression as shown in Table I. The reason for protein selection is critical in *in silico* research to determine topological significance. 2BXR (Fig. 3) was chosen due to its geometrical features and current research accounting.

MGL Tool 1.5.6 was used to generate the MAO-A protein crystal. The molecules of water with a distance greater than 3Å were removed, partial Kollman charges were applied, and polar hydrogens were added in the initial process. Further, the binding cavity selection was performed via grid generation method. A grid having a grid spacing of about 1Å and the dimensions of 24, 24, 24 in the x, y, and z axis was constructed to demonstrate the clorgiline interaction site. The ChemDraw software was

Table I: PDB ID codes of the selected protein structures analyzed in the study

Enzyme	Disease	PDB ID	Chain	Resolution	Sequence length	Released	Organism
MAO-A	Anti-depressant	2BXR	A	3.00 Å	527	2005-08-09	*Homo sapiens*

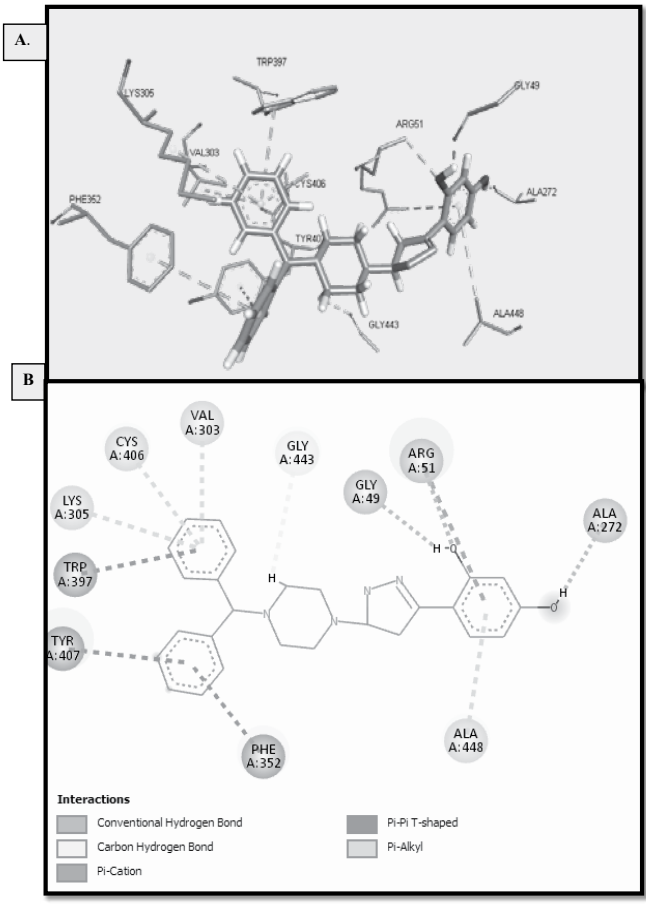

Fig. 6: (A) 3D docking pose of 26, (B) 2D docking pose of compound 26

used to generate the proposed ligands. In the beginning, an energy minimization utilizing the MMFF94 force field with a lesser RMS gradient of 0.001 was done in Chem3D. Then, these structures were stored in PDB format. The ligands were finally prepared in the next phase with MGL Tool 1.5.6.

A site-specific docking molecules investigation was executed in Auto Dock Vina. Using the Lamarckian genetic algorithm, a molecular docking program generates nine docked arrangements for every single ligand. This method is a prominent computational approach and was employed to optimize the supramolecular interaction between a receptor and its ligand for eventual biological functions. Furthermore, docking orientations were observed in Discovery Studio in order to assess the key receptor-ligand interactions for activity.

To assess the druggability of the proposed molecules, ADME and drug-likeness experiments were carried out. The molecular weight (MW) is less than 500 Da (≤500 Da), Log P is less than 5 (Log P<5), the hydrogen bond donor

Table II: Docking score of the designed ligands

Sr. No.	Compound	Docking score (kcal mol^{-1})
1.	**C1**	-10.3
2.	**C2**	-10.3
3.	**C3**	-10.4
4.	**C4**	-10.1
5.	**C5**	-9.0
6.	**C6**	-10.6
7.	**C7**	-10.4
8.	**C8**	-10.5
9.	**C9**	-10.4
10.	**C10**	-10.0
11.	**C11**	-10.5
12.	**C12**	-9.2
13.	**C13**	-9.8
14.	**C14**	-10.5
15.	**C15**	-9.9
16.	**C16**	-10.1
17.	**C17**	**-10.9**
18.	**C18**	-10.0
19.	**C19**	-9.6
20.	**C20**	**-10.8**
21.	**C21**	-10.4
22.	**C22**	-10.5
23.	**C23**	-10.3
24.	**C24**	-9.0
25.	**C25**	-10.5
26.	**C26**	**-10.6**
27.	**Clorgiline**	-6.3

(HBD) is less than 5 (HBD≤5), hydrogen bond acceptor is not more than 10 (HBA≤10) and the topological polar surface area (TPSA) is less than 120(Å)^2 [TPSA≤120 (Å)^2] and number of rotatable bonds (15) are all included during these examinations. The drug-likeness and ADME prediction were carried out using SwissADME, a freeware web server provided by the Swiss Institute of Bioinformatics.

RESULTS AND DISCUSSION

Molecular docking analysis via Auto Dock Vina revealed that the chosen ligands were showing very similar conformational mode to the MAO-A inhibitors,

Table III: Drug-likeness and ADME studies of the designed ligands

Compound	Substitution	MW	HBD	HBA	Log P	TPSA (Å)2	BBB	GI abs	Pains	Rotatable bonds	Lipinski violations
C1	4-CH_3	409.55	0	4	-2.39	18.84	Yes	High	0	5	0
C2	4-OH	411.52	1	5	-2.81	39.07	Yes	High	1	5	0
C3	4-Cl	429.96	0	4	-2.01	18.84	Yes	High	0	5	1
C4	4-OCH_3	425.55	0	5	-1.8	28.07	Yes	High	0	6	0
C5	2,4,6-trimethoxy	485.6	0	7	-1.75	46.53	Yes	High	0	8	0
C6	3-Cl	429.96	0	4	-2.08	18.84	Yes	High	0	5	1
C7	4-NH_2	410.53	1	4	-2.89	44.86	Yes	High	0	5	0
C8	4-Br	474.42	0	4	-1.96	18.84	Yes	High	0	5	1
C9	4-NO_2	440.52	0	6	-2.44	64.66	Yes	High	0	6	0
C10	3-NO_2	440.52	0	6	-2.47	64.66	Yes	High	0	6	0
C11	3-NH_2	410.53	1	4	-3.03	44.86	Yes	High	0	5	0
C12	3,4,5-trimethoxy	485.6	0	7	-1.41	46.53	Yes	High	0	8	0
C13	2-Br	474.42	0	4	-2.43	18.84	Yes	High	0	5	1
C14	4-F	413.51	0	5	-2.2	18.84	Yes	High	0	5	1
C15	2-F	413.51	0	5	-2.81	18.84	Yes	High	0	5	1
C16	3,4-dimethoxy	455.57	0	6	-1.86	37.3	Yes	High	0	7	0
C17	**2,4,6-trinitro**	**530.51**	**0**	**10**	**-3.61**	**156.3**	**No**	**Low**	**0**	**8**	**2**
C18	3-OCH_3	425.55	0	5	-2.1	28.07	Yes	High	0	6	0
C19	3,5-dichloro	464.41	0	4	-1.53	18.84	Yes	High	0	5	1
C20	**2,3-dimethoxy**	**455.57**	**0**	**6**	**-2.46**	**37.3**	**Yes**	**High**	**0**	**7**	**0**
C21	3-Br	474.42	0	4	-2.13	18.84	Yes	High	0	5	1
C22	3-Cl	429.96	0	4	-2.08	18.84	Yes	High	0	5	1
C23	3-F	413.51	0	5	-1.62	18.84	Yes	High	0	5	1
C24	2-CH_3	409.55	0	4	-2.48	18.84	Yes	High	0	5	0
C25	3-OH	411.52	1	5	-2.96	39.07	Yes	High	0	5	0
C26	**2,4-dihydroxy**	**427.52**	**2**	**6**	**-2.17**	**59.3**	**Yes**	**High**	**2**	**5**	**0**
Clorgiline	-	272.17	0	2	3.43	12.47	Yes	High	0	6	0

clorgyline. The primary goal of this docking investigation is to determine the best interactions between proteins and ligands. These are required for the activity. The docking experiment was carried out on MAO-A enzyme (PDB ID: 2BXR). The programme gathered an overall of nine arrangements, which were then visualized in Discovery Studio.

The proposed compounds were shown to interact extensively with the MAO-A binding pockets, and the effects of hydrogen bond donors and acceptors on the binding and the ADME profile were also noticed. Particularly, the permeability of the blood-brain barrier and GI absorption can alter depending on the location of halogen groups like fluorine, bromine, and chlorine

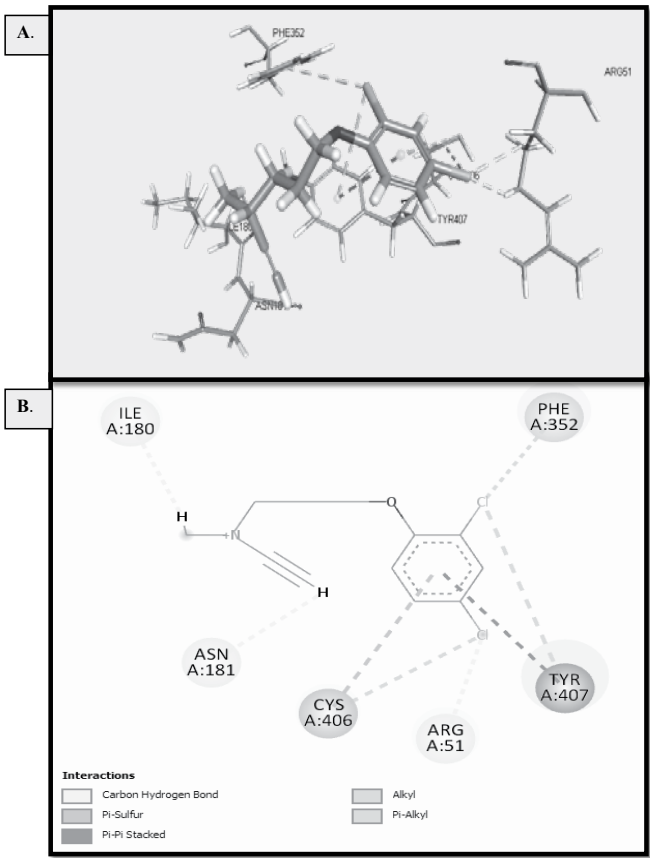

Fig. 7: (A) 3D docking pose Clorgiline, (B) 2D docking pose of Clorgiline

on the ring. Numerous substantial interactions that are comparable to the reference drug have also been reported. In this investigation, Compound **C17** exhibited comparable interactions with several amino acids in the binding pockets, as shown in Fig. 4. These amino acids include Gly25, Arg51, Ser24, Thr435, Lys305, Gly66, Tyr407, Cys406, Gly67, Gly443, Ile23, Thr52, Gly22, and Ala448. When 2,4,6-trinitro substitution occurred, the interactions observed were pi-sulfur, pi-pi stacked, pi-pi T-shaped, amide-pi stacked, and pi-alkyl interactions. Similar results were observed when 2,3-dimethoxy substitution occurred (Fig. 5), despite a lower number of hydrogen bonds. Furthermore, Compound **C20** displayed interactions between cations and the electron cloud of the ring in various regions of its skeleton (Fig. 6). In the investigation, clorgiline was used as the standard, with a binding affinity of -6.3 kcal mol^{-1}. In comparison to clorgiline, Compound **C17** exhibited greater binding potency, with a value of -10.9 kcal mol^{-1}. It was found that all the binding modes of Compound **C17** were comparable to those of clorgiline (Fig. 7). However, this interaction changed to a charge-attractive interaction due to the protonation of the nitrogen in the pyrazoline. It is important to note that the piperazine molecule must be protonated for the inhibitory action to occur.

Detailed information about the docking scores (kcal mol^{-1}) can be found in Table II.

Drug likeness is a crucial factor in the development of new drugs, encompassing various structural features that contribute to stability, oral availability, favorable ADME functions, and minimal addictive potential. Particularly for compounds that affect the central nervous system (CNS), it is of utmost importance to assess their ADME (absorption, distribution, metabolism, and excretion) and target reachability, as these characteristics directly impact their biological efficacy in clinical studies. In our study, we employed the *in silico* tool Swiss ADME to predict the drug-likeness of all designed molecules, indicating that all the compounds (except one) adhere to Lipinski's rule of five, which defines drug-like molecules. Furthermore, the number of hydrogen bond donors (HBD) and acceptors (HBA) fell within the optimal value, enhancing the likelihood of the highest number of connections at the desired site, specifically MAO-A. Regarding the drug-likeness and ADME prediction, only one compound violated the Lipinski rule, while all other compounds conformed to it. Compound **C17** failed to cross the blood-brain barrier (BBB) and exhibited low gastrointestinal (GI) absorption, which can be attributed to the presence of trinitro groups in its ring structure, as shown in Table III. However, among the top-scoring ligands compounds **C20** and **C26** were found to possess good drug-like feature due to their BBB permeation and GI absorption.

A total of 26 ligands were developed and investigated in this *in silico* study using molecular docking, drug likeness, and ADME. All of the compounds have been found to fit well into the MAO-A binding pocket and to interact similarly with clorgiline. Here, the terminal position of piperazine was clubbed with pyrazoline, favoring a particular binding mode for optimum interactions.

CONCLUSION

The study's findings showed that the piperazine molecules exhibited strong binding affinities towards the active site of MAO-A. The binding modes of these compounds were characterized by key interactions with critical residues within the binding pocket of the enzyme. These interactions included hydrogen bonding, hydrophobic interactions, van der Waals interactions and pi-pi stacking interactions, which are essential for stabilizing the ligand-protein complex. Furthermore, the researchers identified specific structural features

of the piperazine compounds that contribute to their binding affinity and potency towards MAO-A. This information can be utilized in the rational design and synthesis of novel piperazine-based antidepressants with improved therapeutic efficacy. Overall, the findings of this study shed light on the potential of piperazine compounds as promising candidates for depression therapy through their interaction with MAO-A. The insights gained from the docking studies provide a solid foundation for further experimental validation and the development of new therapeutic strategies for depression treatment. Compound **C17** has the highest binding affinity, however, due to higher TPSA value due to trinitro group, it reduced the BBB permeation. Compound **C20** with good BBB permeation has been found to be a promising lead towards MAO-A inhibition due to favorable supramolecular interactions. Also, it might show significant biological activity in *in vitro* and *in vivo* evaluation, in future studies.

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