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DESIGN, SYNTHESIS AND BIOLOGICAL EVALUATION OF NEW DRUG CANDIDATE AS A POTENTIAL MEMORY ENHANCER

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■ **Introduction:** Alzheimer's disease (AD) is a neurodegenerative disease of the brain associated with decrease of cognitive function, memory impairment, and behavioral changes. More than 25 million people in the world today are affected by dementia, most suffering from Alzheimer's disease. In both developed and developing nations, Alzheimer's disease has had tremendous impact on the affected individuals, caregivers, and society. The duration of the disease can vary between 5 years and 20 years. 5-hydroxytryptamine (5-HT, serotonin) is an important neurotransmitter in the modulation of the cognitive, behavioral and psychological functions in animals and humans. Among the fourteen subtypes of 5-HT receptor, 5-HT1A receptor has been extensively studied. An azapirone derivative with strong and selective agonist effect on 5-HT1A receptor, has been used for the treatment of anxiety disorders especially generalized Alzheimer's disease for decades. With the advances in studies of the pathogenic mechanisms in AD.The target of new AD drug development has been directed to modifying the pathology.

■ **Aim & Objective:** To design and synthesize the new chemical entity as a new class of azapirone derivative.

■ **Method:** Generated virtual library of compound having structural similarity with available entity then sort out promising compound from the generated library by virtual screening then select specific compounds by performed molecular docking of selected compounds form the library and see the desired interaction then performed molecular dynamics of specific molecules. Sorted final lead molecules showing desired properties and synthesized and characterization of final lead molecule and evaluated the Alzheimer activity.

■ **Results**: azapirone derivative compounds shows significant effect on Alzheimer's disease.

INTRODUCTION

Alzheimer, which has neurobiological, cognitive, and behavioural aspects, is one of the leading mental disorders of the modern world experienced by children and adolescents.[1] Alzheimer disorders affect 3.6 percent of the world's population, or around 264 million people, according to the World Health Organization. Furthermore, Alzheimer affects 4.6 percent of females and 2.6 percent of males worldwide.[2] Alzheimer is a central nervous system (CNS) illness characterized by a negative emotional state that results in unease, fear, and other symptoms in reaction to variables perceived from internal or external sources.[3] The precise process of Alzheimer remains unknown. Several neurotransmitter systems have been linked to one or more of the modulatory stages involved. Alzheimer's disease (AD), a neurodegenerative brain disorder, increasingly affects millions of people and typically presents as cognitive debility and memory loss.[1] The main symptoms of AD include neurodegeneration, the deterioration of brain functions, apathy, anxiety, delusions, and depression.[2,3,4]

The lack of specific treatments for AD highlights the significance of an accurate diagnosis. AD is usually diagnosed with Magnetic Resonance Imaging (MRI) or Positron Emission Tomography (PET). MRI presents images with high-quality contrast of soft tissues and better spatial analysis with no risks for the patient[2], while PET uses radiotr5 HT A1rs to visualize, measure, and record physiological changes in metabolism, neurotransmitters, blood flow, etc.[5]

Currently, there is no effective treatment for AD, which may be associated partially with a lack of a clear underlying mechanism. Based on the fact that AD is characterized by the appearance of extr5 HT A1llular amyloid-beta (Aβ) plaques and neurofibrillary tangles in the intr5 HT A1llular environment, gliosis, loss of synapses, and inflammation, a number of hypotheses have been advanced to explain AD.[6,7,8,9] These include (a) the Aβ-amyloid hypothesis, (b) the Aβ-amyloid oligomer hypothesis, (c) the tau hypothesis, (d) the Ca^{2+} dysregulation hypothesis, (e) the presenilin

hypothesis, and (f) the lysosome hypothesis. According to the hypotheses associated with Aβ-amyloid there is an overproduction of Aβ-amyloid peptide leading to the amyloid plaques synapto- and neurotoxicity and neurodegeneration.[10] According to the tau hypothesis, there is an abnormal tau (tubulin associated unit) phosphorylation, resulting in the formation of abnormal neurofibrillary structures. Tau proteins in normal cells bind to microtubules and promote their stability and polymerization.[11] The Ca^{2+} dysregulation hypothesis is based on the calcium sensing receptor (CaSR), a member of the family C of G protein-coupled receptors (GPCRs), mediating calcium homeostasis and regulating intr5 HT A1llular signals.[12] It has been found that CaSR dysregulation is associated with inflammation and neurodegenerative disorders such as AD.[13,14] The presenilin (PS) hypothesis is based on inherited mutations in the genes encoding presenilin's, the catalytic subunit of γ-secretase, cleaving the amyloid precursor protein (APP) and, thus, contributing to an increased vulnerability of the brain and AD.[15] Finally, the lysosome hypothesis is based on mutations in genes regulating lysosomal pH resulting in impairment of the autophagy–lysosomal pathway.[16]

5-HT1A receptor

The 5-HT1A receptor is the first subtype to be cloned and sequenced among all the serotonin receptors.[7] Analyzing the sequence of this genomic clone showed that 50% of amino acids were homologous with the β2-adrenergic receptor in the transmembrane domain.[8] Furthermore, the 5-HT1A receptor gene is located on human chromosome 5q11.1-q13 and the encoded protein consists of 421 amino acids in human and mice while 422 amino acids in rats.[9, 10] More importantly, it was accessible to visualize the sites of 5-HT1A receptor in various regions of brain at the sub-cellular level by the polyclonal antibodies.[11] The 5-HT1A receptor has been detected in limbic forebrain regions (e.g. hippocampus, raphe nuclei, amygdala) with high density, while in extrapyrimidal areas (e.g. basal ganglia, substantia nigra) with low density.[12] They are present on the soma and dendrites of 5-HT neurons isolated from raphe nuclei as presynaptical autoreceptors to inhibit the firing rate of 5-HT, and on postsynaptic neurons such as hippocampus and amygdala innervated by 5-HT neurons as heteroreceptors, where they also attenuate firing activity.[13]

Since the crystal structures of 5-HT1B and 5-HT2B receptors have been well studied[14], a homology model of 5-HT1A receptor using the crystal structure of the 5-HT1B receptor (PDB ID: 4IAQ) was established to explore the structure basis of the stereoselectivity of a prototypical GPCR.[15] Using molecular interaction fingerprints, it was discovered that the agonist of 5-HT1A receptor could mobilize nearby amino acid residues to form a continuous water channel via molecular switches, while the antagonist of 5-HT1A receptor maintained stabilization in the binding pocket.[16] Although the accurately targeted site of 5-HT1A receptor by tandospirone is still unknown, it is rational to speculate that as a partial agonist of 5-HT1A receptor, tandospirone may act through forming a continuous water channel by mobilizing nearby amino acid residues.

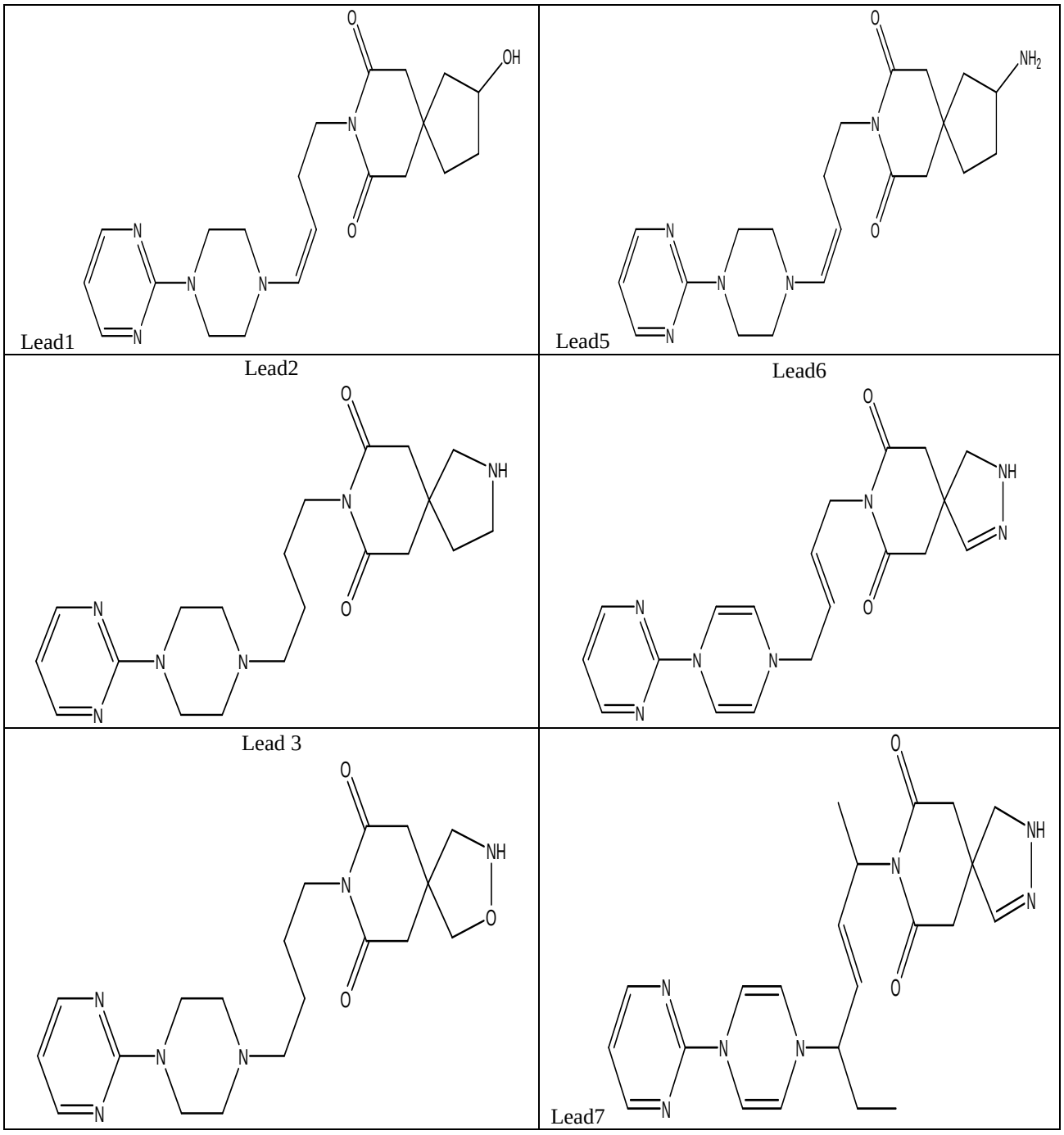
5-HT1A receptor agonists

5-HT1A receptor agonists are one sort of the ligands which is able to activate the 5-HT1A receptors. According to different intrinsic activities, 5-HT1A agonists are clarified in two categories, namely full agonists such as 8-OH-DPAT, F-11440 and flesinoxan, as well as partial agonists such as ipsapirone, gepirone, buspirone and tandospirone.[17–20] Tandospirone is highly potent among partial agonists of 5-HT1A receptor and has a K_i value of 27 ± 5 nM. Moreover, tandospirone is approximately two to three orders of magnitude less potent at 5-HT2, 5-HT1C, α1-adrenergic, α2-adrenergic and dopamine D1 and D2 receptors (K_i values ranging from 1300 to 41000 nM) than at 5-HT1A.[21] Taken together, unlike other azapirones such as buspirone and ipsapirone with moderate-to-high affinity for the dopamine D2 receptor and α1- adrenergic receptors, respectively, tandospirone has a potent and selective agonist effect on 5-HT1A receptor.[22, 23] Specifically, tandospirone is characterized as a full agonist at 5-HT1A autoreceptors in the raphe nuclei as well as a partial agonist at postsynaptic 5-HT1A receptors in the forebrain areas receiving 5-HT input.

Known Azapirone derivatives are a class of drugs, including buspirone, tandospirone, gepirone, and ipsapirone, that act as partial agonists of the 5-HT1A receptor. These compounds are often used as reference compounds for the discovery of novel compounds. Various compound classes have been recently investigated as 5-HT1A agonist, targeting the active site of the enzyme. In the last five years (2018–2022), a number of novel derivatives have been developed and studied for their interaction with 5-HT1A agonist. These novel derivatives and the reference compounds, as well as their inhibitory values and docking results, are briefly presented in the Supplementary Materials. In this review, data from recent literature based on molecular modelling, docking, and simulation techniques have been collected. The results of the novel compounds have been classified based on their molecular structure and mechanism of action.

The molecular docking study is a computational- based research that is used to examine the potency of any generated candidate at the initial stage, targeting any disease-related target.[20] Most researchers now utilized powerful computational algorithms to pick 'hit' or 'lead' candidates. Indeed, natural compounds or phytochemicals have a wide range of biological actions.[21] As a result, assessing individual potencies in a random experimental trial is a difficult and time-consuming task. In this case, molecular docking is a

better method for determining the strength of any desired synthetic drug before doing a randomised experimental trial.[22] Indeed, molecular docking is currently regarded as a sophisticated and cost-effective technology for avoiding the haphazard or 'hit-and-trial' method of drug screening.[23] However, molecular docking is used as an early guiding tool in modern drug development to save time, since medication candidates for human users cannot be suggested in the absence of rigorous experimental and pharmacological research.[24] Overall, molecular docking is simple to utilise and has the potential to be a useful tool in drug development. Scientific data reveals that in silico prediction findings are equivalent to in vitro and in vivo results.[25] In this study, in silico molecular docking examination was carried out on new lead molecule with numerous targets related to Alzheimer in order to design and create a novel medication. The docking investigations on new lead molecule were followed by an estimate of the binding free energy. Furthermore, its physicochemical, drug-likeness, and ADMET profiles were investigated to ensure its safety and efficacy in the treatment of Alzheimer.



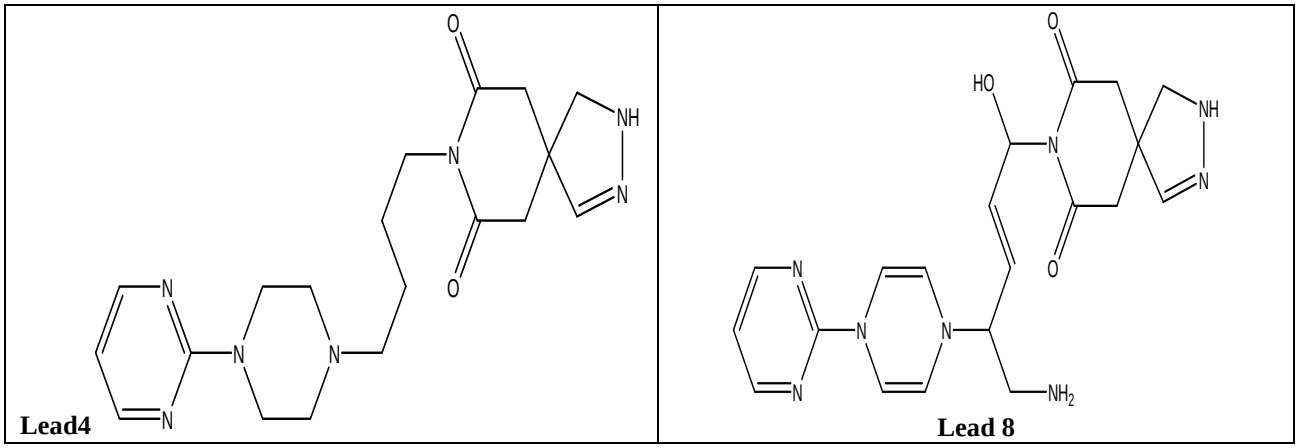


Fig. Lead Molecules.

MATERIALS AND METHODS

Physicochemical and Drug-Likeness Properties

The drug-likeness properties as described in Lipinski's rule of five were calculated using DruLiTo, offline opensource software. DruLiTo is an open-source virtual screening tool in which drug likeliness descriptors such as Molecular weight (MW), log P, Alog P, H-bond acceptor (HBA), H-bond donor (HBD),Total Polar surf5 HT A1 area (TPSA), Atom Molar Refractivity (AMR), number of rotatable bonds (nRB), number of atom, number of acidic groups, rotatable bond count (RC), Number of Rigid bond (nRigidB), nAtom Ring, and Number of Hydrogen Bonds (nHB) parameters can be predicted.[27] The 3D Structure of the ligands was retrieved from the PubChem online database. The generated Ligands were then saved in the Standard Database format (SDF).[28] All the prepared ligands were then tested for drug likeliness properties using the software. The calculations were based on various drug likeliness rules like Lipinski's rule, Veber rule, BBB rule, CMC-50, etc. Overall, compounds that do not violate Lipinski's rule of five are predicted to have superior folding, polarity, and molecular size and to have more potential therapeutic effects.[29] ADME Properties The Swiss ADME web server was used to predict the ADME properties (http://www.swissadme.ch/). This website allows you to compute physicochemical descriptors as well This website allows you to compute physicochemical descriptors as well as to predict ADME Parameters, pharmacokinetic properties, drug like nature and medicinal chemistry friendliness of one or multiple small molecules to support drug discovery.[30] Toxicity Estimation The Toxicity Estimation Software Tool (TEST) was developed to allow users to easily estimate the toxicity of chemicals using Quantitative Structure Activity Relationships (QSARs) methodologies.[31] LC50 threshold was calculated using TEST (https://www.epa.gov/chemical-research/toxicity-estimation-software-tool-test) software based on predictions from each model and the consensus average of the component models.[32] The hierarchical technique, the single-model method, the group contribution method, the consensus method, and the nearest neighbour method are the QSARs methodologies used in this study effort. A compound can be imported into the software using the following methods a) Using the provided molecular structure drawing tool, b) Importing from an MDL mol file, c) Searching by CAS number, SMILES string, or name. T.E.S.T. allows the user to estimate the value for several toxicity endpoints:

- Oral rat LD50 (amount of chemical in mg/kg body weight that is lethal to 50% of rats after oral ingestion).
- Developmental toxicity (binary indication of whether or not a chemical can interview with normal development of humans or animals).
- Ames mutagenicity (a compound is positive for mutagenicity if it induces revertant Colony growth in any strain of Salmonella typhimurium).

In silico studies of anxiolytic compounds In the docking method, ligand structure and orientation inside a specified binding site were predicted. The two main goals of docking research are precise structural modelling and accurate activity prediction. The process of docking is typically represented as a series of steps, each of which adds a new degree (or layers) of complexity.[33] Docking methods are first used to pl5 HT A1 tiny molecules in the active site of a cell. In order to anticipate biological activity, these algorithms are enhanced by scoring functions that assess interactions between molecules and prospective targets.[34] Four human targets associated with Alzheimer were chosen to investigate the new lead molecule anxiolytic effects based on an in silico molecular docking approach.

Table 1: Summarizes the targets and the criteria for selection used in the present investigation. As per the requirements, the retrieved three-dimensional (3D) crystal structure of selected targets was from the protein data bank (PDB) with individual PDB IDs.

Target in Alzheimer			
Disorder	**Targets**	**Reason for Selected Targets**	**References**
Alzheimer	5HT1(5V54)	Activation of the serotonergic system blocks the beta-amyloid (Aβ) oligomer-induced inflammatory response	34

The receptors 5HT1(5V54) which are responsible for Alzheimer and are selected as the targets for anxiolytic action, were chosen as the targets for docking investigations. The target for the disease was first chosen, and then the 3D structures of numerous targets were obtained from the protein data bank in.pdb format (https://www.rcsb.org). It is commonly known that the PDB file format cannot provide bond order information and that PDB files frequently feature incorrect or missing assignments of explicit hydrogen. As a result, the MVD was used to assign the appropriate bonds, bond orders, hybridization, and charges. MVD's integrated cavity detection technique was used to determine the possible binding locations of both targets. A subset zone of 25.0 Å around the active side cleft used as the study area for the search sp5 HT A1 of the simulation used in the docking investigations. The repl5 HT A1ment water molecules received a score of 0.50 when the water molecules are also taken into account.[35] The major 8 synthesize compound are identified from the selected molecular library of azapirone derivative namely Lead 1, Lead3, Lead4, Lead2, Lead7, Lead8, Lead5, and Lead6 the 3D structures of the active constituents are retrieved From PubChem Chemical databases and saved in.mol format. The ligands are imported to the Worksp5 HT A1 and preparation is done for docking studies. The Docking scores of the active Constituents are compared against the Standard drugs such as buspirone, tandospirone obtained from the drug bank in mol format (https://pubchem.ncbi.nlm.nih.gov/). As per docking software, both target and ligand structures were saved in dot PDB (.pdb) file format for a docking study using the software (Molegro virtual Docker 6.0 offline open-source software).[40] The molecular docking investigation was conducted using Molegro Virtual Docker 6.0, and the findings were compared (http://molexus.io/molegro-virtual-docker/, accessed on 26 September 2022), MVD 2013.6.0.1– 2013-12-13 academic license). Analysis Pose Organizer was used to see the returned postures from the docking engine. Pose organiser has the ability to dynamically load postures from a docking run, allowing users to explore thousands of ligands. More sophisticated re-raking calculations combined with binding affinity measurements were made while many energy terms and interactions were simultaneously examined.[41] When changing positions, electrostatic interactions and hydrogen bonds were dynamically updated. Selected ligands' SPDVP scores were compared to those of the reference drug. The ligands with the highest binding affinity to the target protein are those with the lowest binding energy. The top ligands and potential lead molecules for a treatment for Alzheimer were those whose ligands displayed the highest SPDVP scores.[42]

RESULTS

Physicochemical, Drug-Likeness Properties and ADME properties.

All the new lead molecule from azapirone derivative that are Lead1, Lead2, Lead3, Lead4, Lead5, Lead6, Lead7 and Lead8 appears to follow all the five rules of Lipinski's drug-likeness criteria (Table 2). According to the data acquired from DruLiTo and Swiss ADME software, Lead1, Lead2, Lead3, Lead4, Lead5, Lead6, Lead7 and Lead8 also passed Veber's rule, the blood-brain barrier (BBB) likeness rule was passed by all except Lead1and Lead4, the constituents also passed the Ghose filter except the new lead molecule Lead1, Lead4 and Lead6 as shown in table 2. The GI absorption was high in all the constituents except Lead4 which showed low GI absorption. Only Lead7 cannot cross the Blood Brain Barrier (BBB). Lead5, Lead6, Lead2 and Lead3 may produce suppressing serotonergic activity while enhancing dopaminergic and noradrenergic cell firing as showed in table 2.

Table 2: Physicochemical, drug-likeness and ADME properties of anxiolytic compounds.

Property	**Lead1**	**Lead2**	**Lead 3**	**Lead4**	**Lead5**	**Lead6**	**Lead7**	**Lead8**
Molecular weight (g/mol)	399.49 g/mol	386.49 g/mol	388.46 g/mol	385.46 g/mol	398.50 g/mol	379.42 g/mol	421.50 g/mol	424.46 g/mol
Hydrogen bond donors	2	1	1	1	6	4	0	2
Hydrogen bond acceptors	3	1	2	2	7	6	1	3
Hydrogen bond donar	4	1	3	2	1	1	0	2
Rotatable bonds	2.78	2.24	2.37	1.90	-2.79	1.70	4.55	0.95
Log P (Partition coefficient, Predicted value)	74.01	48.01	49.06	45.37	78.20	76.01	133.92	45.13
Molar refractivity	41.13	20.23	29.46	29.10	134.52	111.13	17.07	57.53
Topological polar surf5 HT A1 area in Å²	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Lipinski's rule of five	Yes	No	Yes	Yes	Yes	Yes	No	Yes
Ghose filter								

Veber's rule	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
BBB likeness rule	Yes	Yes	Yes	Yes	Yes	Yes	No	No
GI absorption	High	High	High	High	High	High	Low	High
BBB Permeability	YES	YES	YES	YES	YES	YES	NO	YES
Bioavailability score	0.55	0.55	0.55	0.55	0.55	0.55	0.55	0.85

All of the above findings indicate that all have a good potential drug-like molecule and a useful therapeutic agent against a variety of disorders including Alzheimer.

Toxicity Estimation The endpoint of the oral rodent LD50 is the measure of the compound (chemical mass per rodent body weight) that destroys half of the rodents when administered orally. The oral rodent LD50 directed in four methods for the selected compound and the discoveries were relatively assessed. All new lead molecule have been shown to have an acceptable toxicity limit as shown in Table no 3 for drug production and preclinical and clinical appraisal. Developmental toxicity was performed in four approaches with all of the chosen compounds and the findings were comparatively analysed. Toxicity is indicated by a predicted value greater than 0.5. Except Lead7 all the other new lead molecule shows developmental toxicity. Ames Mutagenicity was conducted in four methods for all of the chosen compounds and the findings were comparatively analysed in Table 3.

Table 3: Predicted value for Oral rat LD50 - Log10 (mol/kg), Developmental toxicity, Ames Mutagenicity.

Method	End point	Lead 1	Lead 2	Lead 3	Lead 4	Lead 5	Lead 6	Lead 7	Lead 8
Consensus	Oral rat *LD50*	2.95	2.18	-	1.85	1.77	2.15	1.67	2.30
	Developmental toxicity	0.35	0.77	-	0.82	0.60	0.75	0.63	0.83
	mutagenicity	-0.14	0.41	-	0.25	0.32	0.62	0.43	0.10
Hierarchical clustering	Oral rat *LD50*	2.78	2.21	_	1.94	1.78	2.24	1.86	2.73
	Developmental toxicity	0.28	0.9	_	0.87	0.56	0.98	0.82	0.78
	mutagenicity	-0.26	0.48	_	0.16	0.3	0.58	0.53	0.21
Single model	Oral rat *LD50*	2.95	2.18	_	-	1.77	2.15	1.67	2.30
	Developmental toxicity	0.35	0.77	_	0.60	0.60	0.76	0.63	0.83
	mutagenicity	-0.14	0.41	_	-	0.32	0.62	0.43	0.10
Group contribution	Oral rat *LD50*	2.95	2.19	_	_	1.77	2.15	1.57	2.30
	Developmental toxicity	0.35	0.77	_	_	0.60	0.76	0.63	0.83
	mutagenicity	-0.14	0.41	_	_	0.32	0.62	0.43	0.10
Nearest neighbor	Oral rat *LD50*	3.13	2.15	-	1.76	1.76	2.07	1.49	1.87
	Developmental toxicity	N/A	1.00	-	1.00	0.67	N/A	0.67	1.00
	mutagenicity	0.00	0.33	_	0.33	0.33	0.67	0.33	0.00

Toxicity is indicated by a predicted value greater than 0.5. All the new lead molecule except Lead 3 are not mutagens based on the results on the Ames mutagenicity as predicted by TEST software as shown in Table 3.

In-silico studies of anxiolytic compounds The ability of the new lead molecule to bind with the targets is given in terms of SPDVP Score. The SPDVP Score is used as the parameter for analysing the docking results. The new lead molecule are ranked according to their SPDVP Score; rank score and hydrogen bond interaction. The pose of the ligand which has least SPDVP score shows a strong affinity towards its enzyme target. The ligand having the most elevated SPDVP and re rank score shows a strong affinity towards its target receptor. In-silico docking analysis was performed for all 8 new lead molecule such as Lead1, Lead2, Lead3, Lead4, Lead5, Lead6, Lead7 and Lead8 and Compared with Marketed drugs using Molegro virtual Docker on 5HT A1 receptors. The pose is represented in ball and stick model along with the molecular weight and the amino acids in protein are represented in stick frame model with the residue numbers. As per the MVD software, the docking score is always expressed in a negative value, where a higher negative value indicates a better potency. The SPDVP score of the ligands Lead5, Lead6, Lead4, Lead8, Lead2, Lead7, Lead3 and Lead 1against 5 HT A1receptor was found to be -53.0226, -47.3339, -76.5405, -46.6556, -71.9564, -57.4265, -58.7002, -65.6419 and -37.7307 respectively shown in Table 4. For 5 HT A1SPDVP score of Lead4, shows -76.5405 followed by Lead2 shows -71.9564 which is higher than the other ligands and marketed drug -37.7307,

Name	Ligand	MolDock Score	Rerank Score	HBond
Lead1	3314	-53.0226	-45.9211	-6.58917
Lead 2	10364	-47.3339	-41.1804	-4.479
Lead3	92785	-76.5405	-56.3844	0
Lead 4	92987	-46.6556	-42.0722	-4.02252
Lead 5	128853	-71.9564	-61.329	-12.616
Lead6	5280863	-65.6419	-59.9399	-4.35857
Lead 7	443143	-57.4265	-47.1977	0
Lead 8	637542	-58.7002	-50.2235	-6.84347

The SPDVP score of the ligands Lead5, Lead6, Lead4, Lead8, Lead2, Lead7, Lead1, Lead3 and pramipexole against 5 HT A1 receptor was found to be -29.0959, -41.9634, -76.2877, -30.5221, -58.338, -59.0293, -58.3074, -46.7278 and -35.9252 respectively as shown in Table 5. For 5HT1 SPDVP score of Lead4, shows -76.2877 followed by Lead7 shows -59.0293 which is higher than the score of marketed drug Donepezil shows -35.9252.

The new lead molecule such as Lead5, Lead6, Lead4, Lead8, Lead2, Lead7, Lead3 and buspirone as standard drug, in silico docking analysis was performed against Dopamine D3 receptor was found as -68.999, -57.675, -92.8193, -60.3203, -70.0025, -76.5438, -74.4535, -55.326 and -103.838 respectively as shown in Table 6. For Dopamine D3 SPDVP score of Lead4, shows -92.8193 followed by Lead7 shows -76.5438 when compared to the score of marketed drug buspirone shows - 103.838.

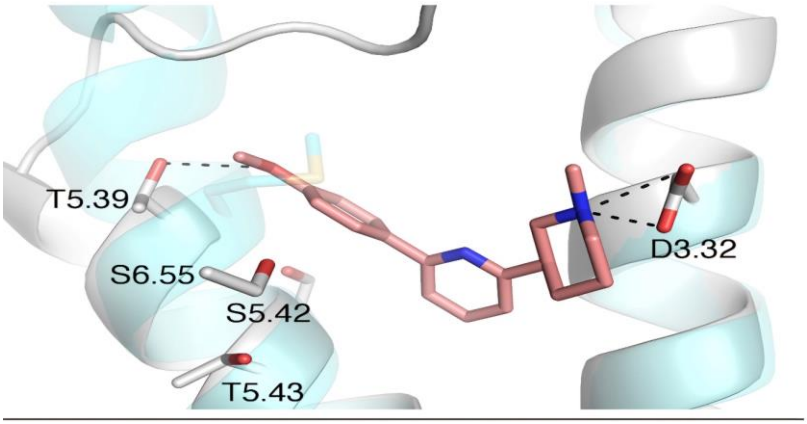


Fig. 1: Docking Image with the Ligands.

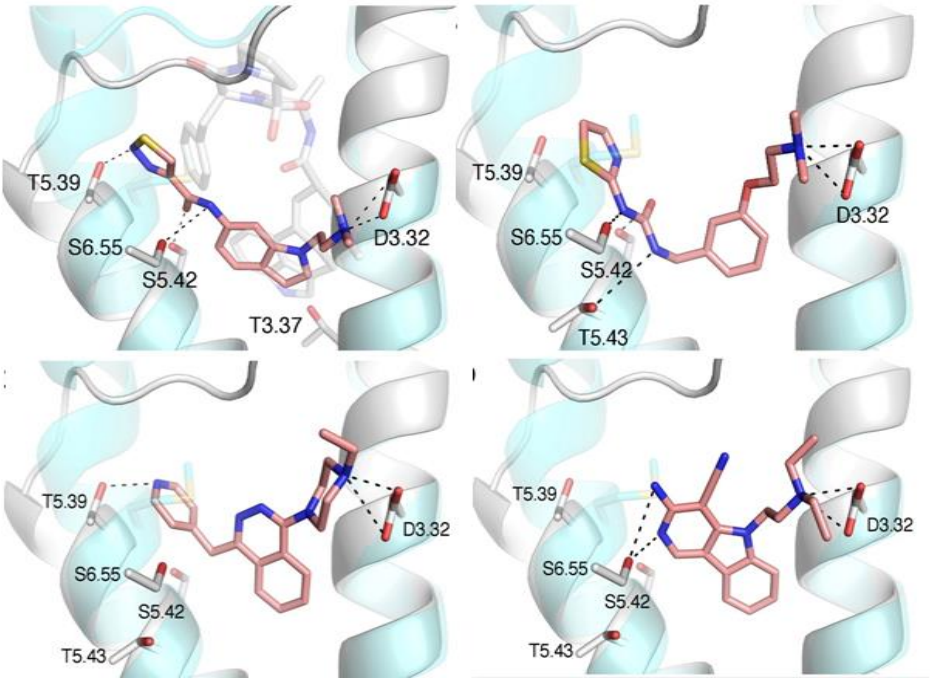


Fig. 2: Docking Image With the Ligands.

DISCUSSION

Azapirone derivative facilitate the agonist actions of 5 HT A1by binding to suppressing serotonergic activity while enhancing dopaminergic and noradrenergic cell firing. Research has shown Azoprione derivative to cause sedation, psychomotor, cognitive impairment, Respiratory arrest, visual disturbances, incontinence and digestive disturbances.[43] In neonates, less than 1% of patients experience laryngospasm and/or bronchospasm, ventricular arrhythmias including ventricular bigeminy or premature ventricular contractions, vasovagal syncope, bradycardia, or tachycardia.[44] Buspirone Hydrochloride is a selective dopaminergic agonist with a minor agonistic activity at D2 receptors also used in treatment of Alzheimer. The adverse effects of Buspirone Hydrochloride are attributed to both peripheral and central dopaminergic stimulation. They also cause Hallucinations and psychotic-like behavior, Dyskinesia and Postural deformity.[45] Buspirone Hydrochloride significantly reduced drinking latency in the novelty-induced hypophagia test in wild-type mice, further confirming its antianhedonic-like effect and showing that it also has anxiolytic-like activity. But also shows some serious side effects that include orthostatic hypotension, Neuroleptic malignant syndrome, Low white blood cell count, High blood sugar and diabetes, Tardive dyskinesia.[46] As an SSRI class drug, paroxetine's mechanism of action is to block the serotonin reuptake transporter (SERT) and thus increase the concentration of synaptic serotonin. It is used to treat depressive disorder, obsessive-compulsive disorder, and social Alzheimer disorder.[47] Many of the side effects of Buspirone Hydrochloride are dose-dependent. The side effects include drowsiness, tachycardia, vasodilation, sleep disturbance, and sexual side effects. The negative side effects of these pharm5 HT A1uticals promote the development of herbal medicines in complementary medicine and advise taking herbs regularly to prevent disorders like Alzheimer and other mental abnormalities that may be prevented by a healthy lifestyle.[48] In silico research has the power to quicken the p5 HT A1 of discovery while lessening the demand for expensive lab work and clinical trials.[49] The benefit of using computational methods is that they can deliver new drug candidates more quickly and for less money which include Drug likeness, Toxicity estimation and Molecular docking to choose the best drug candidate and carried to perform in vitro, in vivo studies easily.[50] The ‘drug likeness properties’ of the new lead molecule was evaluated according to the ‘The Lipinski rule of five’ and to develop them as potential lead compound for anti-Alzheimer activity. All the new lead molecule are Lead5, Lead6, Lead4, Lead8, Lead2, Lead7, Lead1; Lead3 passes the drug likeness properties. All substances have been shown within limit toxicity of Oral LD50 which can be further taken for drug production and preclinical and clinical appraisal. The phytochemical constituents Lead4 which is present in medicinal plant Convolvulus prostratus Frossk (shankhpushpi) shows SPDVP score of -76.5405, -76.2877 and -92.8193 against, 5HT1 which is higher and nearer than to the standard drug Buspirone Hydrochloride -37.7307, gepirone -35.9252 and tandospirone shows -103.838 respectively. Lead4 exhibits a good modulatory effect on the immune system and proves to be a potent drug for the treatment of many allergic disorders. Lead4 is used as anti-parasitic, antifungal, allopathic, antibacterial (which is comparable to the activity of ampicillin against Escherichia coli and other strains), antioxidant, antitumor, and antiviral against herpes simplex viruses.[51] It can prevent catalase and superoxide dismutase, and reduce glutathione concentration. The inhibitory effect of Lead4 on nitric oxide generation was significantly more effective than that of caffeic acid and/or Gallic acid. Lead4 exhibited comparable antioxidant capacities with butylated hydroxyl toluene (BHT) by the DPPH (p=0.117) and FRAP (p= 0.179) assays.[52] Convolvulus prostratus Forssk, one such cognitive booster herb is mainly endowed with neuroprotective, nootropic and neuro modulatory activities.[53] Besides, it also possesses several other therapeutic properties, antidiabetic and cardio protective activities.[54] Therefore, maximum chances of Lead4 to show anti-Alzheimer active since it is active constituent of Convolvulus prostratus Forssk. For serotonin SPDVP score of Lead3, shows -81.0347 which is nearer to the score of marketed drug paroxetine shows -95.7425. Lead3 has therapeutic effects on inflammation associated diseases[55], including allergies, arthritis, diabetes, cardiovascular diseases, cancers and neurological regression by inhibiting protein kinases and transcription factors.[56] If there are chances to work on in vitro and in vivo activity of Lead3 against Alzheimer disorder, more chances to get a good drug candidate without any side effects for the treatment of Alzheimer. The eight new lead molecule were docked against 5 HT, Amyloid, Dopamine D3 and Serotonin receptors. Lead4 showed highest binding affinity when compared with standard drugs against 5 HT A1 inhibitors and 5HT1 agonist can be a good drug candidate and possess potential anxiolytic activity against Alzheimer disorder.

Additional research can be done to determine the Lead4's in-vitro and in-vivo Alzheimer activity as well as the pharmacokinetic characteristics of the new lead molecule to learn about their absorption, distribution, metabolism, and excretion.

CONCLUSION

In our current research, we have chosen eight new lead molecules namely Lead1, Lead2, Lead3, Lead4, Lead5, Lead6, Lead7 and Lead8 to test its affinity towards 5 HT A1and 5HT1 receptors. Synthetic drugs produce side effects and toxicity, as well as various other therapeutic effects, has led to a rise in demand for newly synthesis medicines, which have been approved or are in various stages of clinical trials for a variety of diseases in recent decades. Despite the fact that synthetic chemistry dominates the current drug development and manufacturing field, the importance of newly-derived compounds in the treatment and prevention of various

diseases cannot be neglected. In this study, eight ligands were investigated in order to find out the significant ligand against Alzheimer disorder. The ligand was selected based on its binding affinity against receptors and comparing their activity with the standard drugs available in the market. Findings of this experiment suggested that Lead4 can be administered if the treatment of Alzheimer focuses on inhibiting the 5 HT A1. Further studies can be performed in invitro & in-vivo experimental animal models of Alzheimer disorder to establish the efficacy of promising drug.

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REFERENCES

1. J.M. Palacios et al. The distribution of serotonin receptors in the human brain: high density of [3H]LSD binding sites in the raphe nuclei of the brainstem Brain Res., 1983.
2. N. M. Barnes *et al.* A review of central 5-HT receptors and their function Neuropharmacology, 1999.
3. H. Rollema *et al.* Clozapine increases dopamine release in prefrontal cortex by 5-HT1A receptor activation Eur. J. Pharmacol., 1997.
4. S.-M. Wang *et al.* Vilazodone for the treatment of depression: an update Chonnam Med. J., 2016.
5. M.N. Modica *et al.* Structure-activity relationships and therapeutic potentials of 5-HT(7) receptor ligands: an update J. Med. Chem., 2018.
6. P.B. Hedlund *et al.* Functional, molecular and pharmacological advances in 5-HT7 receptor research Trends Pharmacol. Sci., 2004.
7. D. Hoyer *et al.* Molecular, pharmacological and functional diversity of 5-HT receptors Pharmacol. Biochem. Behav., 2002.
8. K. Peprah *et al.* Multi-receptor drug design: haloperidol as a scaffold for the design and synthesis of atypical antipsychotic agents Bioorg. Med. Chem., 2012.
9. D. Sampson *et al.* Identification of a new selective dopamine D4 receptor ligand Bioorg. Med. Chem., 2014.
10. B.A. Bricker *et al.* Evaluation of SYA16263 as a new potential antipsychotic agent without catalepsy Pharmacol. Biochem. Behav., 2019.
11. The Computer Aided Drug Designing For Anti-Tumor Drug Target Cdk -2 Chinmaya Sadangi, The Computer Aided Drug Designing For Anti-Tumor Drug Target CDK -2. University of Manitoba ResearchGate (July 2010)
12. Melita Salkovic-Petrisic, Ana Knezovic, Siegfried Hoyer, Peter RiedererWhat Have We Learned From The Streptozotocin-Induced Animal Model Of Sporadic Alzheimer's Disease, About The Therapeutic Strategies In Alzheimer's Research, Journal of Neural Transmission, 2013; 120(1): 233-52. ISSN 0300-9564.
13. Zhiyuan Zhu, Jianming Yan, Wei Jiang, Xin-gang Yao, Jing Chen, Lili Chen, Chenjing Li, Lihong Hu, Hualiang Jiang, and Xu Shen12.Arctigenin Effectively Ameliorates Memory Impairment in Alzheimer's Disease Model Mice Targeting Both – Amyloid Production and Clearance, The Journal of Neuroscience, August 7, 2013; 33(32): 13138 –13149.
14. Huahui Zeng a, b, *, Xiang xiang Wu a, *Alzheimer's disease drug development based on Computer-Aided Drug Design* European Journal of Medicinal Chemistry, 2015.
15. ElisaUliassi, Neuroregeneration versus neurodegeneration: toward a paradigm shift in Alzheimer's disease drug discovery, Review Future Med Chem., 2017 Jun; 9.
16. Dubois B., Feldman H.H., Jacova C., Cummings J.L., Dekosky S.T., Barberger-Gateau P. Revising the definition of Alzheimer's disease: a new lexicon. Lancet Neurol., 2010; 9: 1118–1127.
17. Dubois B., Hampel H., Feldman H.H., Scheltens P., Aisen P., Andrieu S. Preclinical Alzheimer's disease: definition, natural history, and diagnostic criteria. Alzheimer's & dementia. J Alzheimer's Assoc., 2016; 12: 292–323.
18. Aisen P.S., Andrieu S., Sampaio C., Carrillo M., Khachaturian Z.S., Dubois B. Report of the task force on designing clinical trials in early (predementia) AD. Neurology, 2011; 76: 280–286.
19. U.S. Food and Drug Administration. 2013. Guidance for Industry Alzheimer's Disease: Developing Drugs for the Treatment of Early Stage Disease. Food and Drug Administration, Washington, D.C.
20. U.S. Food and Drug Administration. U.S. Department of Health and Human Services. Guidance for Industry; Washington, DC: 2018. Early Alzheimer's Disease: Developing Drugs for Treatment.
21. U.S. Food and Drug Administration. U.S. Department of Health and Human Services. Draft Guidance for Industry; Washington, DC: 2018. Adaptive Designs for Clinical Trials of Drugs and Biologics.
22. Jack C.R., Jr., Bennett D.A., Blennow K., Carrillo M.C., Dunn B., Haeberlein S.B. NIA-AA research framework: toward a biological definition of Alzheimer's disease. Alzheimers Dement., 2018; 14: 535–562.
23. Cummings J. The National Institute on Aging-Alzheimer's Association framework on Alzheimer's disease: application to clinical trials. Alzheimers Dement., 2018; 15: 172–178.
24. Egan M.F., Kost J., Tariot P.N., Aisen P.S., Cummings J.L., Vellas B. Randomized trial of verubecestat for mild-to-moderate Alzheimer's disease. N Engl J Med., 2018; 378: 1691–1703.
25. Onesimus Mahdi1,2, Mohamad Taufik Hidayat Baharuldin1, Nurul Huda Mohd Nor1, Samaila

Musa Chiroma1,3, Saravanan Jagadeesan1,4, Mohamad Aris Mohd Moklas1*Chemicals used for the induction of Alzheimer's disease-like cognitive dysfunctions in rodents Biomedical research and therapy, 2019; 6(11): 3460-3484.
26. Xiao S., Zhang Z., Geng M., GV-971 Study Group. 2018. Phase 3 Clinical Trial of a Novel and Multi-targeted Oligosaccharide in Patients with Mild-moderate AD in China. Clinical Trials on Alzheimer's Disease. Barcelona, Spain, October 25.
27. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6617248/
28. Bernstein, F. C.; Koetzle, T. F.; Williams, G. J.; Meyer, E. F.; Brice, M. D.; Rodgers, J. R.; Kennard, O.; Shimanouchi, T.; Tasumi, M. The Protein Data Bank: A Computer-Based Archival File for Macromolecular Structures. J. Mol. Biol., 1977; 112(3): 535–542.
29. Jorgensen, W. L.; Tirado-Rives, J. The OPLS Potential Functions for Proteins.Energy Minimizations for Crystals of Cyclic Peptides and Crambin. J. Am. Chem. Soc., 1988; 110(6): 1657–1666.
30. Martin, Y. C.; Kofron, J. L.; Traphagen, L. M. Do Structurally Similar Molecules Have Similar Biological Activity? J. Med. Chem., 2002; 45(19): 4350–4358.
31. Bajusz, D.; Rácz, A.; Héberger, K. Why Is Tanimoto Index an Appropriate Choice for Fingerprint-Based Similarity Calculations? J. Cheminform., 2015; 7: 20.
32. Hawkins, P. C. D.; Skillman, A. G.; Nicholls, A. Comparison of ShapeMatching and Docking as Virtual Screening Tools. J. Med. Chem., 2007; 50(1): 74–82.
33. Gabriella Marucci a, Michela Buccioni a, Diego Dal Ben a, Catia Lambertucci a, Rosaria Volpini a, Francesco Amenta b,* Efficacy of 5 HT A1tylcholinesterase inhibitors in Alzheimer's disease Neuropharmacology, 1 June 2021; 190: 108352.
34. A Novel 5-HT_{1B} Receptor Agonist of Herbal Compounds and One of the Therapeutic Uses for Alzheimer's Disease Yang Yang†Lijing Zhang†Jiaojiao Yu†Zhaobin MaMoxiang LiJin WangPengcheng HuJia ZouXueying LiuYing LiuSu AnCheng XiangXiaoxi GuoQian HaoTian-Rui Xu*Center for Pharm5 HT A1utical Sciences and Engineering, Faculty of Life Science and Technology, Kunming University of Science and Technology, Kunming, China.
35. https://www.rcsb.org/