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Research Article

Design, Synthesis and *In Silico* Evaluation of 1,3,4-Oxadiazole Derivatives for Their Nootropic Activity

Suvarna A Katti[1], Namrata Revar[2], Sarvesh Sonawane[3], Shubhangi H Pawar[4], Rupali A Patil[5], Anuja P Bhosale[6] Manisha A Tayde[7]

[1,2,3,4,5,6]Department of Pharmaceutical Chemistry, MGV'S Pharmacy College, Panchavati, Nashik, Maharashtra, India.
[7]Department of Pharmaceutical Chemistry, Panchavati Education Society's Institute of Pharmacy, Panchavati, Nashik, Maharashtra, India.
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I N F O

Corresponding Author:
Suvarna A Katti, Department of Pharmaceutical Chemistry, MGV'S Pharmacy College, Panchavati, Nashik, Maharashtra, India.
E-mail Id:
suvarnakatti@yahoo.co.in
Orcid Id:
https://orcid.org/0000-0001-7243-8229
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A B S T R A C T

Introduction: Computational methods have become indispensable in modern medicinal chemistry research, enabling the rapid screening and evaluation of potential drug candidates. This study leverages *in silico* approaches to investigate the neuroprotective potential of 1,3,4-oxadiazole derivatives. By employing software such as PASS online, SwissADME, ProTox-III, and Autodock Vina, we aimed to predict the biological activity, pharmacological properties, and toxicity profiles of these compounds.

Method: We utilised a combination of *in silico* techniques, including PASS online for predicting biological activity, SwissADME for assessing pharmacokinetic properties, ProTox-III for evaluating toxicity, and Autodock Vina for molecular docking studies. The predicted properties of the 1,3,4-oxadiazole derivatives were then compared with those of donepezil, a well-established neuroprotective drug. Furthermore, compounds exhibiting significant predicted activity were synthesised and subsequently characterised using analytical techniques such as TLC, FTIR, and NMR.

Results: The results from the PASS online analysis revealed that compound NR1 exhibited the highest predicted activity score (0.636) compared to donepezil (0.553). The predicted activity order was determined as NR1>NR7>NR2>NR3>NR5>NR6>NR4. Molecular docking studies further supported these findings, indicating that 2,5 diaryl 1,3,4-oxadiazole derivatives with polar group substitutions at specific positions (3, 4, and 5; 3, 5; or 2, 5) displayed favorable docking scores.

Conclusion: The *in silico* analyses conducted in this study suggest that 1,3,4-oxadiazole derivatives possess promising neuroprotective potential, comparable to the standard drug donepezil. These findings provide a valuable foundation for further experimental investigations and optimization of these compounds as potential therapeutic candidates for neurodegenerative disorders.

Keywords: Nootropic, Alzheimer`s Disease, 1,3,4-oxadiazole

Introduction

Alzheimer's disease (AD) stands out as the predominant progressive neurodegenerative disorder, serving as a primary contributor to dementia. As individuals age, a natural decline ensues in memory retention and task execution capabilities, escalating the susceptibility to neuronal damage.[1] AD exhibits a robust association with the ageing process, emerging as a strongly age-linked malady.[2]

In the pathogenesis of AD, the amyloid-beta peptide (Aβ) assumes a pivotal role, with amyloid plaques serving as crucial hallmarks extensively employed in the diagnostic protocol, particularly in brain tissue analysis.[3] Numerous studies have underscored the toxicity of diverse Aβ species in both *in vitro* and *in vivo* settings, affirming the significance of age-dependent Aβ accumulation in driving AD progression.[4]

Recent investigations have unveiled region-specific vulnerability to Aβ deposition, intricately linked to localised brain metabolism and neuronal activity. This correlation suggests an interplay between Aβ and glucose metabolism in the context of AD.[1]

The aggregation and accumulation of Aβ fibrils and oligomers contribute to disruptions in cell signalling, instigating progressive neurotic injuries, compromised immunity, neuronal shortfalls, and a discernible loss of cognitive function.[5] Furthermore, the deposition of Aβ induces brain damage by generating free radicals within mitochondria, exacerbating the overall impairment.

Alzheimer's disease, a neurodegenerative disorder, poses a formidable challenge to global health, emphasising the urgent need for innovative therapeutic interventions. Amidst this backdrop, the exploration of nootropic agents has gained prominence as a potential avenue to address cognitive decline associated with Alzheimer's.[6]

This research focuses on the design of derivatives of 1,3,4-oxadiazole, *in silico* evaluation, synthesis of compounds and structural elucidation of synthesised derivatives.

The rationale for investigating substituted 1,3,4-oxadiazoles lies in their ability as agents possessing nootropic activity, which could modulate cognitive functions, and highlight their relevance in addressing Alzheimer's disease-related cognitive dysfunction. Building upon this foundation, our research aims to systematically design and synthesise novel derivatives, leveraging *in silico* evaluations to predict their potential nootropic activity.

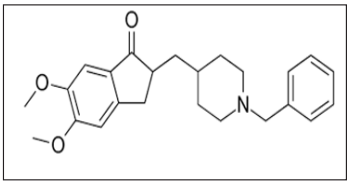
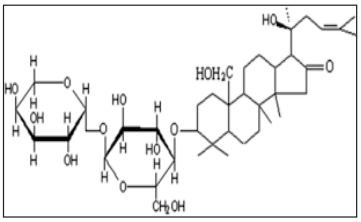
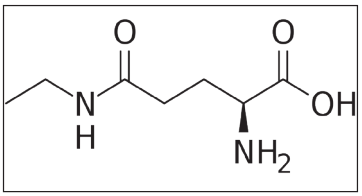
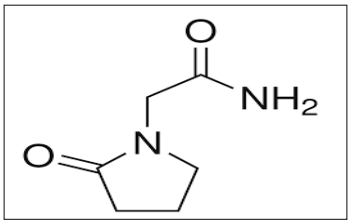
The utilisation of computational methods allows for a rational approach, enhancing our understanding of the interactions between these derivatives and relevant biomolecular targets. Through this multidisciplinary approach, we aspire towards the development of a novel anti-Alzheimer's drug, potentially mitigating cognitive impairments.

Oxadiazole

Oxadiazole is a basic heterocyclic organic compound which plays a key role in drug discovery and design due to its different types of biological properties. Heterocyclic oxadiazole compound with chemical formula $C_2H_2N_2O$. There are possible four isomers of oxadiazole 1,3,4-oxadiazole, 1,2,3-oxadiazole, 1,2,4-oxadiazole, 1,2,5-oxadiazole respectively.[7] 1,3,4-oxadiazole derivative Compounds with this structure have demonstrated significant memory-enhancing effects in animal models.[8] They are believed to act through mechanisms such as cholinergic modulation, antioxidant activity, or by interacting with glutamatergic receptors involved in synaptic plasticity.[9] The drugs having nootropic activity are given in Table 1.

Drugs having Nootropic Activity

Table 1.Drugs having Nootropic Activity

S. No.	Drugs
1.	Donepezil[10] 
2.	Bacopa monneri [11] 
3.	L-Theanine [12] 
4.	Piracetam [13] 

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Mechanism of Action of Donepezil as Nootropics

Donepezil is used globally for treating mild-to-moderate AD. The neuroprotective mechanism of action of donepezil is linked to the BDNF (Brain-derives neurotrophic factor)/ TrkB (Tropomyosin receptor kinase B) pathway.[10] BDNF and its receptor TrkB are biosynthesised in the brain and then distributed in the central nervous system, specifically in the hippocampus and cerebral cortex region. The binding of BDNF to TrkB controls the survival and differentiation of neurons. It also modulates the long-term potentiation and plasticity of neurons. Additionally, the BDNF/ TrkB signalling pathway is also associated with learning and memory function.[14] It is observed that abnormalities in BDNF/ TrkB signalling result in the progression of Alzheimer`s Disease, as it contributes to the production of Aβ and thus cognitive impairment. Brain-derived neurotrophic factor is vital for the growth, development, differentiation, and repair of neurons after the injury. It promotes TrkB dimerisation and autophosphorylation.[15] Donepezil stimulates the BDNF/ TrkB pathway and increases the expression of BDNF mRNA levels and thus it activates the TrkB receptor (p-TrkB) level in the brain of the Aβ1–40-induced TS model of AD. This activation is potentially attributed to the neuroprotective effects of donepezil. These results prove that involving the protection of neurons and cognitive activity enhancement by donepezil might have been the stimulation of the BDNF/ TrkB pathway in cells of neurons.[16, 17]

It is observed that treatment with Bacoppa monnieri, in rats with chronic unpredictable stress activates (BNFD) and enhances the TrkB receptor signalling pathway. These effects activate the cAMP response element binding protein (CREB) and thus result in the synthesis of neurons and neuroprotection.[11]

Designing of Library of Compounds

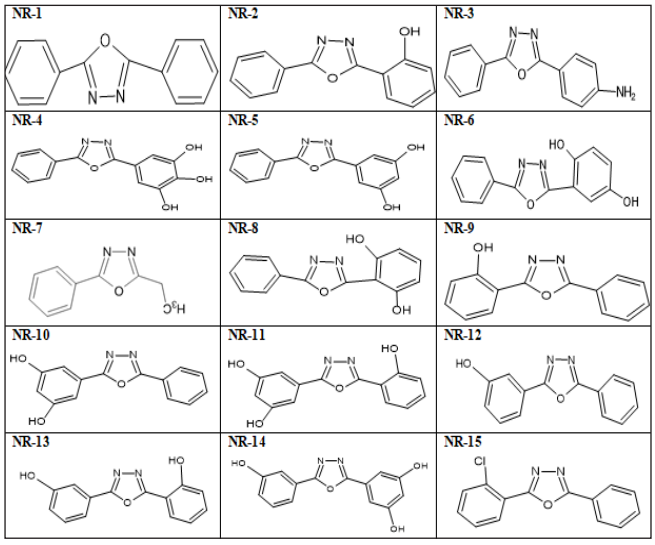

Figure 1.Library of Compounds

Material and Method

All materials were purchased from Modern Science Satpur, Nashik. Melting points were determined using the Thiele tube method with an open glass capillary and are reported without correction. Infrared spectroscopy analysis was carried out on KBr pellets using a Shimadzu 8400S FTIR spectrophotometer. Proton (1H) nuclear magnetic resonance (NMR) spectra of the compound were recorded at 300 MHz using Dimethyl Sulfoxide as a solvent. The recordings took place in the Department of Chemistry at Savitribai Phule Pune University, Pune. Chemical shifts (δ) were expressed in parts per million (δ ppm), downfield from TMS as an internal standard.

Results and Discussion

In Silico Evaluation of Pharmacological Profile of Designed Molecules (PASS Online)

In this study, the nootropic potential of compounds, Pa (probability to be active) and Pi (probability to be inactive) were assessed. Table 2 details the biological activity of compounds (NR-1 to NR-15) and standard drugs (donepezil), indicating their potential nootropic effects through specific biological actions.

Table 2.Biological and Pharmacological Activities Determined using PASS Online

S. No.	Compound Code	Biological Activity	PASS Online	PASS Online
-			Pa	Pi
1	NR-1	Alzheimers disease treatment	0636	0061
2	NR-2	Nootropic	0585	0083
3	NR-3	Nootropic	0584	0083
4	NR-4	Nootropic	0563	0094
5	NR-5	Nootropic	0584	0084
6	NR-6	Nootropic	0572	0089
7	NR-7	Nootropic	0628	0065
8	NR-8	Nootropic	0466	0159
9	NR-9	Nootropic	0553	0079
10	NR-10	Nootropic	0543	0067
11	NR-11	Nootropic	0567	0088
12	NR-12	Nootropic	0546	0065
13	NR-13	Nootropic	0612	0097
14	NR-14	Nootropic	0567	0065
15	NR-15	Nootropic	0544	0034
16	Donepezil	Nootropic	0553	0099

Pa: Probability of being active
Pi: Probability of being inactive

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In Silico Evaluation of Pharmacokinetic Properties of Designed Molecules (SwissADME Software)

Application

The physicochemical features, pharmacokinetic properties, ADME predictions as well as drug-like nature of molecules under examination were calculated by SwissADME software.

In this study, the pharmacokinetic properties of compounds (NR-1 to NR-15) were evaluated and the evaluation of Lipinski's rule of five, water solubility, GI absorption, and affinity to cross the blood-brain barrier, along with bioavailability, was studied. NR-1, NR-2, NR-3, and NR-7 show better crossing of the blood-brain barrier as compared to donepezil.

In Silico Evaluation of Pharmacological Toxicity of Designed Molecules (ProTox-III)

Application

The software operates by analysing the similarity of molecules, fragment propensities, common features, and applying machine learning techniques. It predicts the toxicity profile of molecules, including acute toxicity, hepatotoxicity, cytotoxicity, carcinogenicity, mutagenicity, and immunotoxicity. ProTox-III is used to assess the toxicity profiles of five synthesised derivatives, providing insights into their potential harmful effects.

- NR-1, NR-7, NR-10, and NR-14 are the compounds having LD_{50} 888 mg/kg.
- NR-3 have LD_{50} 2000 mg/kg.
- NR-2, NR-4, NR-5, NR-6, NR-8, NR-9, NR-11, NR-12, NR-13, NR-15 have LD_{50} 2032 mg/kg
- Toxic doses are mentioned as LD_{50} values in mg/kg body weight. LD_{50} is defined as a median lethal dose which is the dose at which 50% of test subjects die upon exposure to a compound.
- According to above results the compound NR-2, NR-4, NR-5, NR-6, NR-8, NR-9, NR-11, NR-12, NR-13, NR-15 shows better LD_{50} than donepezil and cytotoxically inactive.
- A toxicity radar chart was employed to visually represent the confidence levels associated with the predicted toxicity outcomes.

Table 3.Pharmacokinetic Property Determined using SwissADME

Compounds Code	Molecular Weight	Lipophilicity (Consensus Log o/w)	Water Solubility	Gastrointestinal Absorption	Blood Brain Barrier	Bioavailability Score
NR-1	222.24	2.75	-3.76	High	Yes	0.55
NR-2	238.24	2.54	-3.60	High	Yes	0.55
NR-3	237.26	2.37	-3.38	High	Yes	0.55
NR-4	270.24	2.05	-3.28	High	No	0.55
NR-5	254.24	2.11	-3.43	High	No	0.55
NR-6	254.24	2.06	-3.43	High	No	0.55
NR-7	250.30	3.10	-4.29	High	Yes	0.55
NR-8	254.24	2.04	-3.43	High	No	0.55
NR-9	257.54	2.65	-3.56	High	Yes	0.55
NR-10	244.32	2.54	-3.65	High	yes	0.55
NR-11	227.76	2.34	-3.44	High	No	0.55
NR-12	257.87	2.87	-4.76	High	No	0.55
NR-13	209.98	3.65	-3.34	High	Yes	0.55
NR-14	298.77	3.76	-4.70	High	No	0.55
NR-15	288.87	2.88	-3.55	High	No	0.55
Donepezil	379.49	3.92	-4.81	High	Yes	0.55

Table 4.Toxicity Profiles of Synthesised Compound by ProTox-III

Compound Code	Predicted LD_{50} (mg/kg)	Predicted Accuracy	Hepatotoxicity	Carcinogenicity	Immunotoxicity	Mutagenicity	Cytotoxicity
NR-1	888	100	Active	Active	Inactive	Inactive	Inactive
NR-2	2032	100	Active	Active	Inactive	Inactive	Inactive

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NR-3	2000	72.90	Active	Active	Inactive	Inactive	Inactive
NR-4	2023	69.26	Active	Active	Inactive	Inactive	Inactive
NR-5	2032	70.97	Active	Active	Inactive	Inactive	Inactive
NR-6	2032	70.97	Active	Active	Inactive	Inactive	Inactive
NR-7	888	69.26	Active	Active	Inactive	Inactive	Inactive
NR-8	2032	72.90	Active	Active	Inactive	Inactive	Inactive
NR-9	2032	66.76	Active	Active	Inactive	Inactive	Inactive
NR-10	888	87.54	Active	Active	Inactive	Inactive	Inactive
NR-11	2032	77.98	Active	Active	Inactive	Inactive	Inactive
NR-12	2032	87.34	Active	Active	Inactive	Inactive	Inactive
NR-13	2032	66.76	Active	Active	Inactive	Inactive	Inactive
NR-14	888	77.56	Active	Active	Inactive	Inactive	Inactive
NR-15	2032	66.76	Active	Active	Inactive	Inactive	Inactive
Donepezil	505	68.07	Inactive	Active	active	Inactive	Active

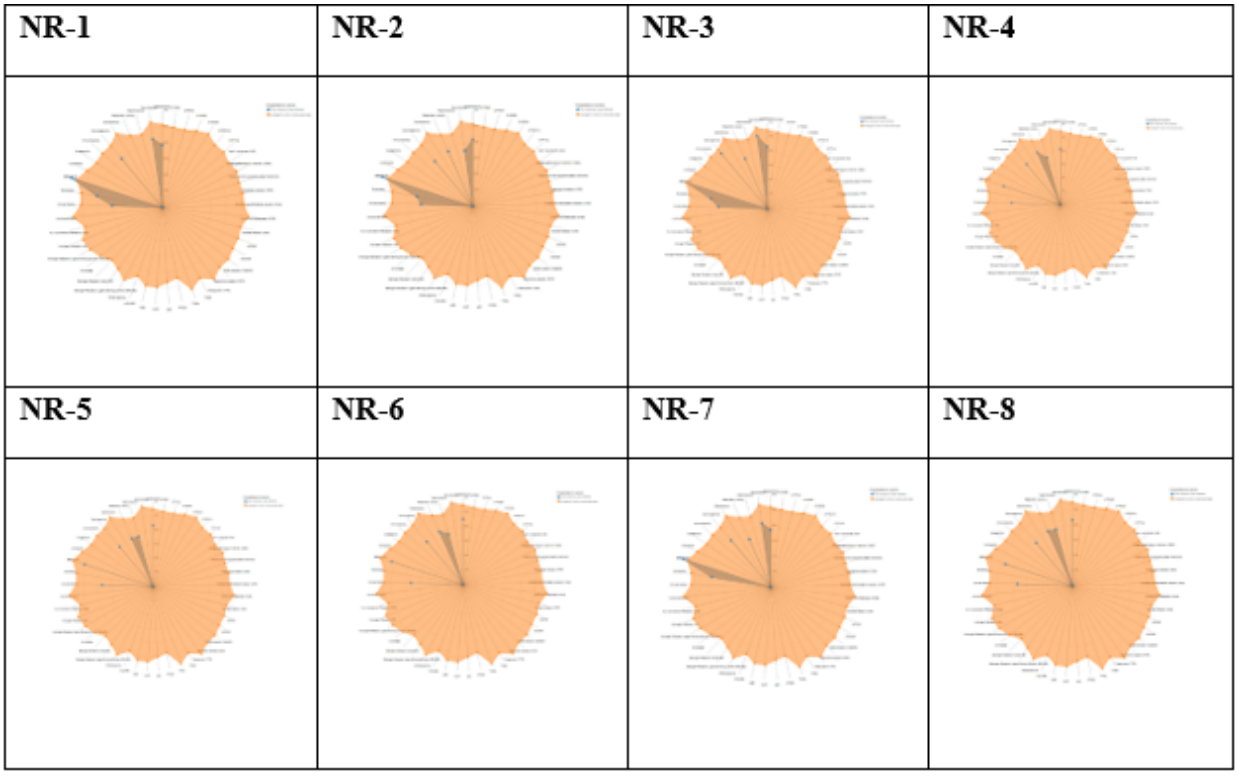

Figure 2.Images of Toxicity Radar Chart using ProTox-III

Molecular Docking using Molecular Docking Software (Autodock Vina)

Computational molecular docking is utilised for the study of interactions between proteins and ligands. It is also helpful in drug discovery and development studies. The process begins with the identification of a target of known structure, which may be the crystallographic structure of an enzyme of medicinal interest or a homology model. The docking is performed to know the bound conformation and the binding free energy of small molecules to the target. The docking study helps for exploring the function of the target, and virtual screening. The library of compounds can be docked and ranked for the identification of new inhibitors for drug development.

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Molecular Docking of Synthesised using Molecular Modeling Software (Autodock Vina)

TProtein Data and Active Site

TrkB-d5: It is found that when neurotrophin ligands bind to their respective TrkB-d5 cellular receptors, they initiate intracellular signals. These play a crucial role in the growth and survival of neurons[18]. Neurotrophin binds to the fifth extracellular domain of the TrkB receptor. The binding at this location regulates the affinity and specificity of the TrkB receptor with neurotrophin.[19] The role of neurotrophin is proven in neurological disorders, like Parkinson's disease and Alzheimer`s disease.[20]

Table 5.Molecular Docking of Ligands Interacting with Surrounding Residues

Ligands	Surrounding Residues	Dock Score
NR-1	PHE A:57, ILE A:115, VAL A:97, ARG A:98, TRP A: 110, VAL A:44, LEU 52, GLN 54	-7.7
NR-2	ILE A:115, VAL A 97, LEU: A52, VAL A:44, MET673	-8.0
NR-3	VAL A:44, PHE A:56 LEU: A52, VAL A:44, MET673	-8.1
NR-4	MET1209D, VAL1213D, GLN 54, ILEA115, ARG A 98, AVR 998, PHE34F	-8.7
NR-5	GLN 54, ILEA115, ARG A 98, AVR 998, PHE34F, LEU: A52, VAL A:44, MET673	-8.4
NR-6	LEU: A52, VAL A:44, MET673, ILEA115, ARG A 98, PHE A:56,	-8.3
NR-7	MET6734, VAL A:44, PHE A:56, TRP A, LEU78, MET 1209C, VAL1213C, THE1206B, VAL1205	-6.7
NR-8	ILEA115, ARG A 98, PHE A:56, GLN 54, THE1206B, LEU78, MET 1209C	-8.2
Donepezil (reference)	MET6734, VAL A:44, PHE A:56, TRP A, LEU78, MET 1209C, GLN 54	-8.1

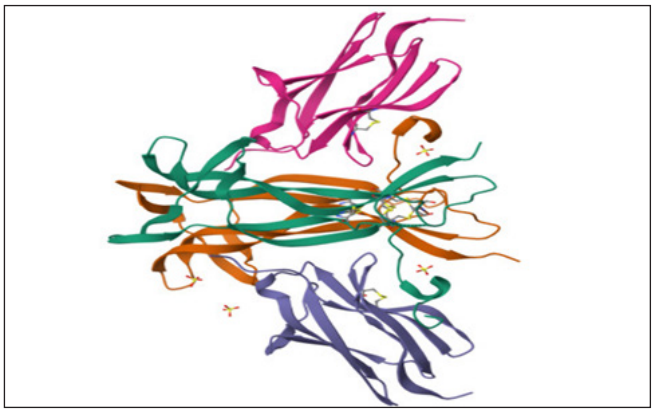

Figure 3.Crystal Structure of –TrkB PDB-1HCF

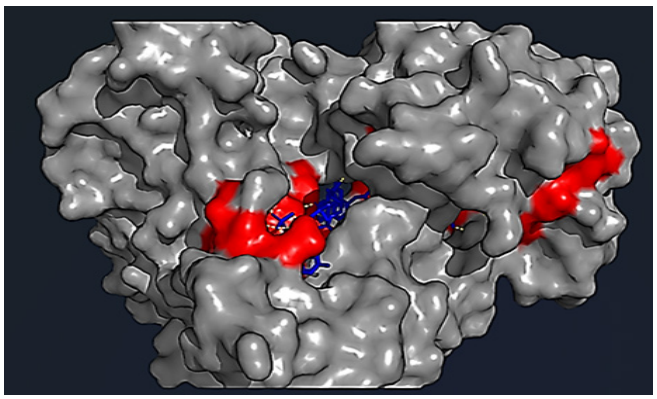

Figure 4.Structural Basis of TrkB 1HCF 3D View

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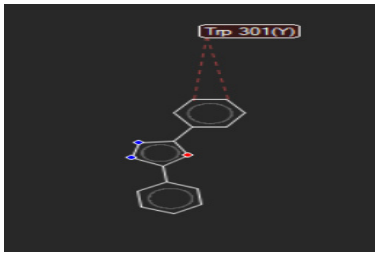
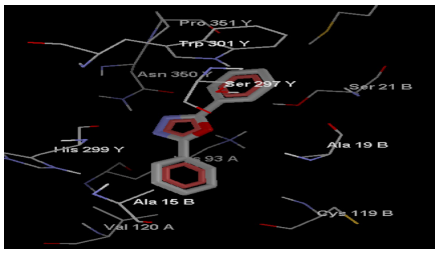
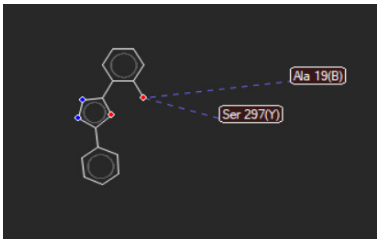
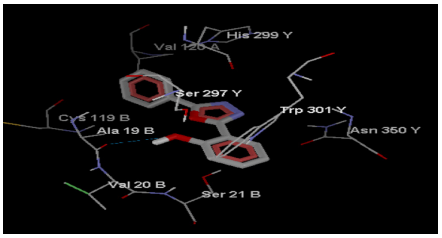
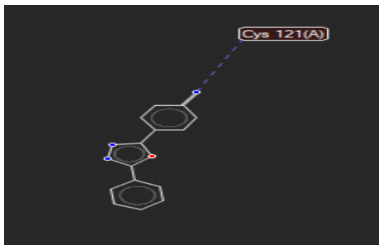
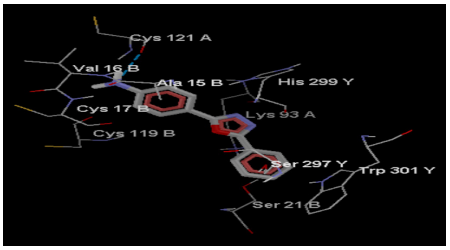
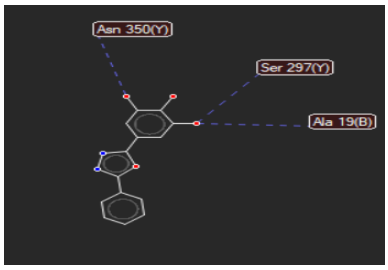
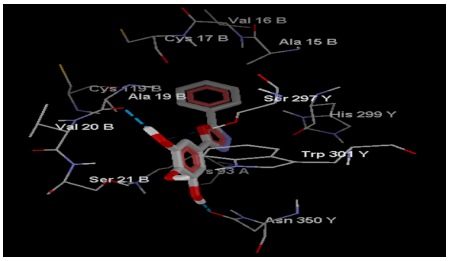
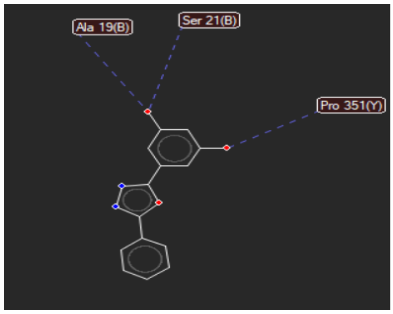
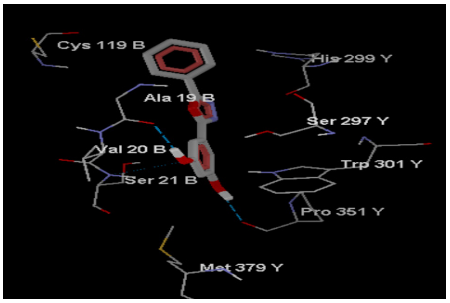
Molecular Docking using Molecular Modelling (Autodock Vina)

Table 6.Results of Molecular Docking and 2D, 3D Images of Interaction

Compound Code	Dock Score (Kcal/mol)	2D Molecular Visualisation	3D Molecular Visualisation
NR-1	-7.7		
NR-2	-8.0		
NR-3	-8.1		
NR-4	-8.7		
NR-5	-8.4		

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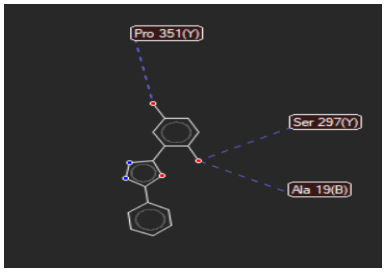
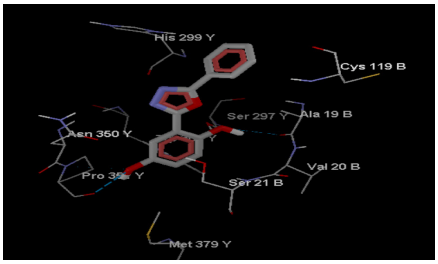
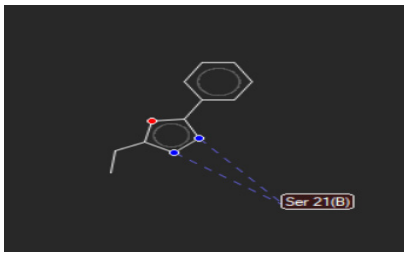
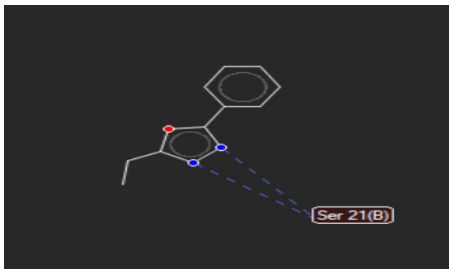
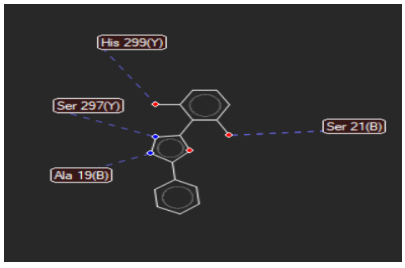
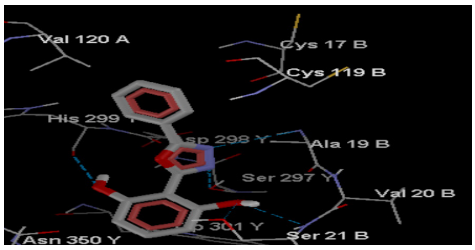
NR-6	-8.3		
NR-7	-6.7		
NR-8	-8.2		

According to the results of molecular docking, compound NR-4 was seen to have a greater docking score of -8.7 surpassing the standard drug donepezil (-8.1). The order of activity was NR-4>NR-5>NR-6>NR-8>NR-3>NR-2>NR-1.

Experiment

The study, designed based on a literature survey, was conducted in the MGV`S Pharmacy College Pharmaceutical Chemistry Lab between October and November 2023 as shown in Figure 1 to evaluate drug properties, specifically ADME/ADMET, using computational tools such as PASS, SwissADME, ProTox-III and molecular docking by Autodock vina.

PASS (Prediction of Activity Spectra for Substances): This tool was utilised to assess the drug-likeness of molecules by exploring their general biological potential. It predicts pharmacological activity on the basis of the chemical structure of molecules, and virtual molecules underwent screening before synthesis and biological testing, achieving an average prediction accuracy of approximately 96%. The biological and pharmacological activities determined using pass online detailed in the Table 2.[21]

SwissADME: It was developed by the Swiss Institute of Bioinformatics. It is found to be useful in predicting the physicochemical, pharmacokinetic (ADME), and drug-likeness abilities of newly synthesised molecules, contributing to the drug discovery and development process. The pharmacokinetic property determined using swissADME presented in the Table 3.[22]

ProTox-III: Functioning as a virtual lab, ProTox-III was employed to predict the toxicities of novel molecules. This computational method offered a faster alternative to preclinical experimentation, reducing the necessity for animal experiments. The tool utilises models to predict various toxicities, including acute toxicity, hepatotoxicity, cytotoxicity, carcinogenicity, mutagenicity, immunotoxicity, adverse outcomes pathways, and toxicity targets.[23]

The classification of toxicity as per the globally harmonised system of classification of labelling of chemicals (GHS) is as follows:

- Class I: Highly toxic ($LD_{50} \leq 5$ mg/kg)
- Class II: Moderately toxic ($5 \text{ mg/kg} < LD_{50} \leq 50$ mg/kg)
- Class III: Slightly toxic ($50 \text{ mg/kg} < LD_{50} \leq 300$ mg/kg)
- Class IV: Harmful ($300 \text{ mg/kg} < LD_{50} \leq 2000$ mg/kg)
- Class V: May be harmful ($2000 \text{ mg/kg} < LD_{50} \leq 5000$ mg/kg)
- Class VI: Relatively harmless ($LD_{50} > 5000$ mg/kg)

The toxicity profiles of synthesised compound by ProTox-III is given in Table 4 and Toxicity Radar Chart shown in Figure 2.

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Molecular Docking using Molecular Docking Software (Autodock Vina)

In the realm of drug discovery, the utilisation of computational molecular docking, particularly through software like Autodock Vina, helps to know the interaction between protein and ligand. This approach, which has evolved over time, has significantly contributed to the development of new drugs.The molecular docking of ligands interacting with surrounding residues provides in the Table 5.[23,24]

The process traditionally commenced with a designated target possessing a known structure, often derived from the crystallographic structure of medically significant enzymes or constructed homology models. Subsequently, molecular docking techniques are applied to predict the conformation and binding free energy of molecules under examination with the specified target. Figure 3 displays the crystal structure of TrkB(PDB-1HCF) and Figure 4 offers a 3D visual representation of the TrkB 1HCF structure.[25]

The results obtained in these molecular docking studies are evident in unravelling the functional aspects of the target. The Table 6 presents comprehensive results from molecular docking studies and 2D,3D images of interaction. Additionally, the incorporation of virtual screening, a method involving the systematic docking and ranking of an extensive compound library, proved instrumental. This strategic approach not only provided insights into the target's behaviour but also held the promise of uncovering novel inhibitors crucial for advancing drug development.[26]

Synthetic Scheme and Procedure

We have selected NR-1 to NR-8 compounds in this study, which were synthesised as per the following scheme (Figure 5).

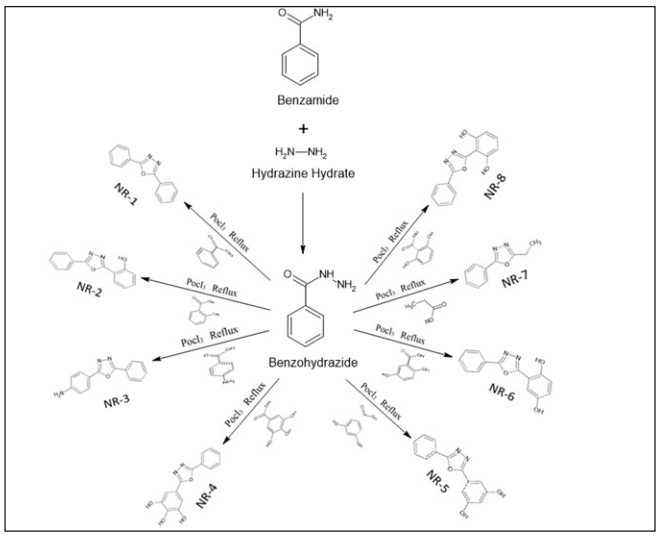
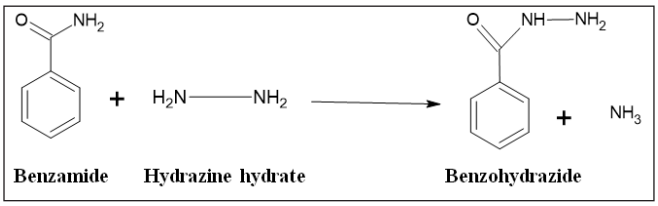


Figure 5.Synthetic Scheme of 1,3,4-oxadiazole Derivatives

Synthesis of Benzohydrazide from Benzamide

1 gm (0.07 mole) benzamide was placed in a round bottom flask, to which, 12 ml (0.30 mole) hydrazine hydrate was added, and the mixture was refluxed for 15 minutes. The content was allowed to cool at room temperature. The product was filtered and washed, and the melting point and yield were noted. The TLC was performed by using ethyl acetate:toluene (7:3).[3]



Synthesis of 1-aryl,5-phenyl-1,3,5-oxadiazole from Benzohydrazide

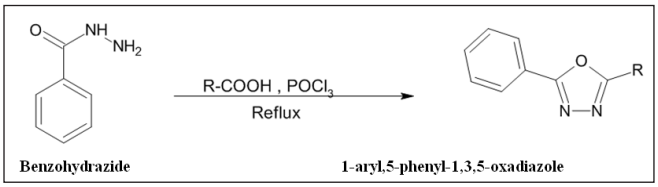
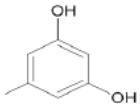
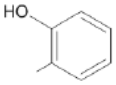
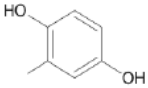
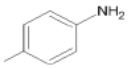
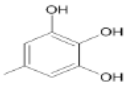
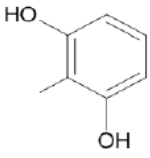


Table 7.Substituted Groups (R) of Different Synthesised Compounds

Compound	R	Compound	R
NR-1		NR-5	
NR-2		NR-6	
NR-3		NR-7	$-CH_2-CH_3$
NR-4		NR-8	

Method for Synthesis of (NR-1):-2,5-diphenyl-1,3,4-oxadiazoles

A mixture of aromatic acid (0.5 mole) and benzohydrazide (0.5 mole) was placed in a round bottom flask, $POCl_3$ (1 mole) was added to it and the mixture was refluxed for 30 min. It was allowed to cool to room temperature. Water was added to it dropwise in a fume hood and the contents were further refluxed for 3–4 hours. The contents were allowed

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to cool to room temperature. It was basified with 0.1M KOH solution. The precipitate obtained was filtered and recrystallised with ethanol. The reaction was monitored by TLC using mobile phase benzene:ethyl acetate (7:3).[3] The substituted groups (R) of different synthesised compounds are presented in the Table 7.

Molecular formula: $C_{14}H_{10}N_2O$

Formula weight: 222.247

It was obtained as a white powder. Melting point: 112 ^{O}C; IR(KBr): 3132.21,2959.04, 841.76 cm^{-1} (Ar-H)1646 cm^{-1} (Ar-bending vibration) 1235.21 cm^{-1} C=N (part of oxadiazole ring)

^{1}H NMR: δ 7.41-7.65 (5H,4d,2t,Ar-H), 7.94 (5H,2d,t,Ar`-H)

Similarly, compounds of NR1, NR2, NR3, NR4, NR5, NR6 and NR8 were synthesised using benzoic acid, salicylic acid, p-amino benzoic acid, gallic acid, 3,5-dihydroxy benzoic acid, 2,5-dihydroxy benzoic acid, propionic acid, 2,6-dihydroxy benzoic acid, respectively.

Method for Synthesis of (NR-2):-2-(5-phenyl-1,3,4-oxadiazol-2-yl)phenol

Molecular formula: $C_{14}H_{10}N_2O_2$

Formula weight: 238.246

It was obtained as a black crystalline solid with melting point: 134 ^{O}C; IR(KBr): 3315 cm^{-1} (O-H stretch) 3132.21, 2959.04, 841.76 cm^{-1} (Ar-H) 1646 cm^{-1} (Ar-bending vibration) 1235.21 cm^{-1} C=N (part of oxadiazole ring).

^{1}H NMR: δ 7.551-8.125 (5H,3t,6d,Ar-H), 7.368-7.967 (4H,t,10d,Ar`-H), 4.530 (s,OH)

Method for Synthesis of (NR-3):-4-(5-phenyl-1,3,4-oxadiazol-2-yl)aniline

Molecular formula: $C_{14}H_{11}N_3O$

Formula weight: 237.262

It was obtained as a red crystalline solid with melting point: 145 ^{O}C; IR(KBr): 1235 cm^{-1} C-O (part of oxadiazole ring), 2919 cm^{-1} (Ar-H), 1646 cm^{-1} (Ar-bending vibration), 1318 cm^{-1} C=N (part of oxadiazole ring).

^{1}H NMR: δ 7.524-7.9615(5H,4t,4d,Ar-H), 6.78-7.7938 (4H,6d,Ar`-H), 3.80 (s,N)

Method for Synthesis of (NR-4):-5-(5-phenyl-1,3,4-oxadiazol-2- yl)benzene-1,2,3-triol

Molecular formula: $C_{14}H_{10}N_2O_4$

Formula weight: 270.244

It was obtained as a yellow crystalline solid with melting point: 129 ^{O}C; IR(KBr): 3305 cm^{-1} (O-H stretch), 2919.25, 800 cm^{-1} (Ar-H), 1646 cm^{-1} (Ar-bending vibration), 1236 cm^{-1} C=N part of oxadiazole, 1180 cm^{-1} C-O (part of oxadiazole).

^{1}H NMR: δ 7.474-7.976 (5H,3t,6d,Ar-H), 7.388 (2H,d,A`r-H), 4.715(s,OH)

Method for Synthesis of (NR-5):-5-(5-phenyl-1,3,4-oxadiazol-2- yl)benzene-1,3-diol

Molecular formula: $C_{14}H_{10}N_2O_3$

Formula weight: 254.245

It was obtained as a green solid with melting point: 118 ^{O}C; IR(KBr): 3317 cm^{-1} (O-H stretch) 3126.2, 3114.9, 3093.3 cm^{-1} (Ar-H) 1648 cm^{-1} (Ar-bending vibration) 1237.30 cm^{-1} C=N (part of oxadiazole ring).

^{1}H NMR: δ 7.523-8.0433 (5H,4t,6d,Ar-H),6.60-7.5625 (3H,4d,Ar`-H), 4.580(s,OH)

Method for Synthesis of (NR-6):-2-(5-phenyl-1,3,4-oxadiazol-2- yl)benzene-1,4-diol

Molecular formula: $C_{14}H_{10}N_2O_3$

Formula weight: 254.245

It was obtained as a brown solid with melting point: 155; IR(KBr): 3318 cm^{-1} (O-H stretch) 3118.0, 3098.6, 820.5 cm^{-1} (Ar-H) 1618 cm^{-1} (Ar-bending vibration) 1241.15 cm^{-1} C=N (part of oxadiazole ring).

^{1}H NMR: δ 7.49-8.0525 (5H,4t,4d,Ar-H),6.92-7.427 (3H,6d,Ar`-H), 4.43(s,OH)

Method for Synthesis of (NR-7):-2-(3-ethylphenyl)-5-phenyl-1,3,4- oxadiazole

Molecular formula: $C_{16}H_{14}N_2O$

Formula weight: 250.301

It was obtained as a white solid with melting point: 162; IR(KBr): 3117.7, 3084.9, 841.76 cm^{-1} (Ar-H) 1646 cm^{-1} (Ar-bending vibration) 1235.21 cm^{-1} C=N (part of oxadiazole ring), 2869.05 cm^{-1} (C-H stretch).

^{1}H NMR: δ 7.28-7.765 (5H,6d,3t,Ar-H), 1.21 (3H,t,Ar`-H), 3.02 (2H,q,Ar`-H),

Method for Synthesis of (NR-8):-2-(5-phenyl-1,3,4-oxadiazol-2- yl)benzene-1,3-diol

Molecular formula: $C_{14}H_{10}N_2O_3$

Formula weight: 254.245

It was obtained as a brown solid with melting point: 158 ℃ IR(KBr): 3315 cm^{-1} (O-H stretch) 3120.05, 3100.10, 818.15 cm^{-1} (Ar-H) 1637 cm^{-1} (Ar-bending vibration) 1242.21 cm^{-1} C=N (part of oxadiazole ring).

^{1}H NMR: δ 7.52-7.967 (5H,4d,2t,Ar-H),6.759-7.544 (3H,2d,t,Ar`-H), 4.67 (s,OH)

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Conclusion

Exploring Nootropic Potential of Designed 2,5-Substituted Diaryl 1,3,4-Oxadiazole Derivatives

In this study, a library of 2,5-substituted diaryl 1,3,4-oxadiazole derivatives was systematically designed and evaluated for its pharmacological, physicochemical, and toxicological properties.

- ***In Silico* Assessment:** Utilising PASS online and SwissADME software, compounds were screened for nootropic potential, GI absorption, and blood-brain barrier penetration. NR1 exhibited the highest nootropic activity (score: 0.636), surpassing donepezil (0.553), and all compounds demonstrated favourable physicochemical parameters.
- **Toxicity Prediction:** ProTox-III predicted LD_{50} values exceeding 2032 mg/kg for NR2, NR4, NR5, NR6, and NR8, ensuring their safety.
- **Synthesis and Conformation of Compounds by Spectral Data:** Eight compounds were successfully synthesised, purified and validated through TLC, MP, IR, and NMR techniques.
- **Molecular Docking Analysis:** Autodock Vina 1.5.7 revealed NR-4 as a standout nootropic candidate (dock score: -8.7) compared to donepezil (dock score: -8.1). The order of activity was NR4>NR5>NR6>NR8>NR3>NR2>NR1.Polar group substitutions at positions 3,4,5 on 2,5 diaryl 1,3,4-oxadiazole (NR-4) resulted in the highest dock score. Additionally, substitutions at positions 3,5 (NR-5) or 2,5 (NR-6) also showed good dock scores (Figure 6). In summary, our comprehensive approach combines *in silico* evaluations, experimental synthesis, and molecular docking to provide the prediction and conformation of the nootropic potential of these designed derivatives, which would contribute to further research in cognitive enhancement.

Molecules without aryl group substitution (NR-1) exhibited a dock score of -7.7, while those substituted with an alkyl group at the second position on the aryl ring (NR-7) had the lowest dock score of -6.7 (Figure 7).

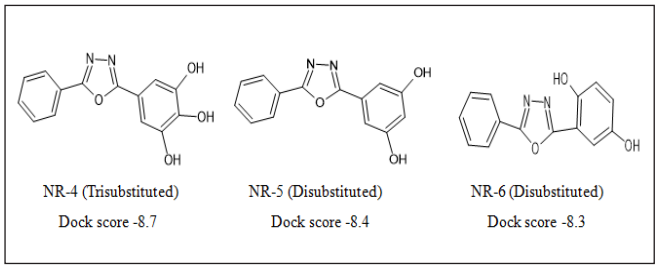

Figure 6.Structure and Dock Score of NR-4, NR-5 and NR-6

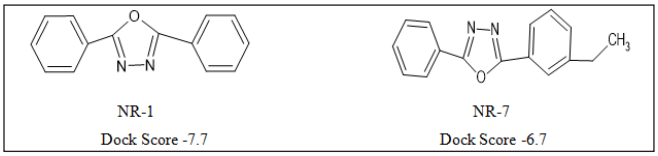

Figure 7.Structure and Dock Scores of NR-1 and NR-7

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Conflict of Interest: None

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