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Exploring Benzimidazole Chemistry: Synthesis, Biological activity, and Molecular Docking Studies for Alzheimer's Treatment

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ABSRACT

Alzheimer's disease (AD) is a significant global health challenge, creating an urgent need for new therapeutic agents. This study explores benzimidazole derivatives as promising candidates for AD treatment. We conducted a comprehensive analysis of these compounds, focusing on their structure-activity relationship (SAR) in combating AD. The detailed SAR analysis identifies the structural features that enhance therapeutic effectiveness, guiding the design of a series of novel benzimidazole-based molecules. These compounds were thoroughly studied using computational methods, including molecular docking, to predict their binding affinities and interactions with AD-related targets. We also assessed the pharmacokinetic properties, including absorption, distribution, metabolism, and excretion (ADME), of the designed compounds to ensure they exhibit favorable drug-like properties and good bioavailability. The molecular docking studies provided valuable insights into how benzimidazole derivatives interact with key enzymes involved in AD, such as acetylcholinesterase and beta-secretase. Our findings highlight the potential of benzimidazole derivatives as potent anti-Alzheimer agents, offering a promising path for therapeutic development. By integrating SAR analysis, computational modeling, pharmacokinetic profiling, and molecular docking studies, we have established a solid framework for identifying effective compounds for AD treatment. This comprehensive approach not only enhances our understanding of benzimidazole derivatives but also sets the stage for future in vivo studies and clinical trials, ultimately aiming to reduce the global burden of Alzheimer's disease.

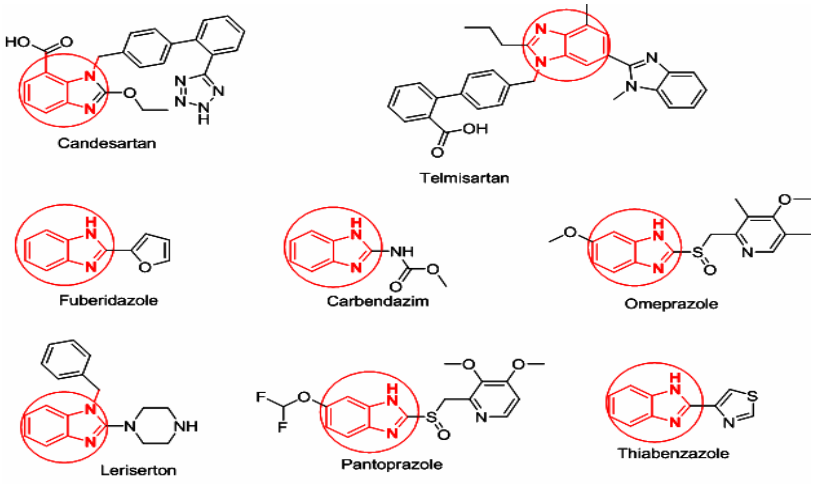
Keywords: Alzheimer's disease (AD), Benzimidazole derivatives, Structure-activity relationship (SAR), Molecular docking, Pharmacokinetic profiling (ADME).

INTRODUCTION

The heterocyclic ring benzoimidazole is created by combining imidazole with benzene containing the chemical formula $C_7H_6N_2$ and weighing 118.14 g/mol. 1H-benzimidazole is benzimidazole's IUPAC name. The presence of two nitrogen-containing, five-membered planar rings that

are amphoteric and have two equivalent tautomers makes up the imidazole ring, which is responsible for the tautomerization of benzimidazole. A lot of research is being done on nitrogen-containing heterocyclic in the hopes of finding new drugs to treat different diseases[1]. Vitamin B12 was initially shown to include 5,6-dimethyl-1-(α-D-ribofuranosyl) benzimidazole in the early 1950s. Due to its ability to selectively target a wide range of enzymes and protein receptors, its fundamental structure is essential to medicinal chemistry research. Furthermore, other fields, such as anti-hypertensive drugs, frequently employ benzimidazole derivatives (such as Telmisartan, Candesartan), as well as antifungal medications (such as Carbendazim, Fuberidazole), as anti-histamine drugs (e.g. Leriserton, Climizole), as proton-pump inhibitor agents (e.g. Omeprazole, Pantoprazole) and as anthelmintic agents (e.g. Thiabendazole, Albendazole)[1]

Globally, the prevalence of neurodegenerative illnesses is rising as the population ages. Alzheimer's disease (AD) is a kind of dementia that affects roughly 70% of people; by 2050, there will be 100 million individuals worldwide. Memory loss, language impairment, and a progressive loss of cognitive function are the hallmarks of this neurodegenerative disease. One of the primary causes of memory loss in Alzheimer's patients is thought to be a lack of cholinergic neurotransmission[2]. Acetylcholinesterase inhibitors (AChEI) are a useful tool for enhancing cholinergic transmission. When searching for novel, highly effective acetylcholinesterase inhibitors, it's critical to possess several heterocyclic rings with strong inhibitory activity, such as galantamine, donepezil, and tacrine, which are medications used to treat Alzheimer's disease. Certain compounds of imidazole's, including benzimidazole, play a role in discovery of new derivatives with AChEI activity[3].



Benzimidazole as core moiety in different categorical drug

Fig. 1. illustrated some Benzimidazole as a core moiety in different categorical drug

Overview of Alzheimer's Disease

Alo is Alzheimer first identified Alzheimer's disease (AD) in 1907; it is recognized as a degenerative disorder of the central nervous system (CNS) characterized by early-onset senile dementia[3]. This type of dementia is the most common form and represents a severely advanced brain neurodegenerative illness. Alzheimer's disease damages the area of the brain responsible for thought, language, and memory[4]. Several factors are thought to be important in the initiation and progression of AD, despite the fact that its etiology is unknown. Amyloid-β (A) deposits and associated extracellular plaques, oxidative stress, low acetylcholine (ACh) levels, and neuro fibrillary tangles resulting from tau-hyper phosphorylation are thought to be the typical clinical symptoms[5].

Alzheimer's Disease (AD) is characterized by reduced cortical cholinergic neurotransmission. Enhancing the activity of cholinergic neurons is considered a key strategy for developing effective drugs to manage AD. This approach involves modulating the levels of the enzyme acetylcholinesterase (AChE) in the central nervous system. Acetylcholinesterase plays a vital role by rapidly breaking down the neurotransmitter acetylcholine, thereby terminating cholinergic transmission at the postsynaptic

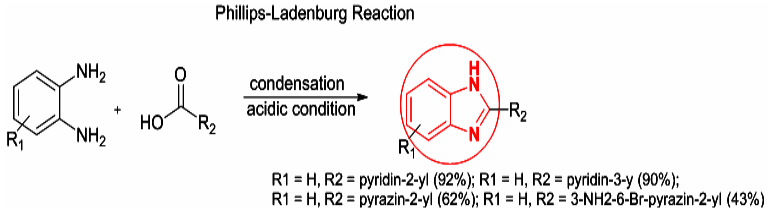
membrane[6]. Inhibiting AChE leads to the accumulation of acetylcholine in the synapses, which boosts acetylcholine effects, improves cholinergic nervous system functioning, and enhances cognitive abilities. Therefore, targeting AChE inhibition is crucial for controlling AD[7].

As researchers further investigate the extensive possibilities of benzimidazole derivatives, it's crucial to examine their structure-activity relationships, pharmacokinetics, and mechanisms of action in greater detail. This thorough knowledge will lay the foundation for a more strategic design and development of more potent and selective benzimidazole-based therapeutic agents, addressing a wide range of medical needs[8]. Further research and exploration of this fascinating class of compounds hold immense promise for the development of novel therapeutic agents, ultimately contributing to the advancement of human health and well-being.

Synthesis

Phillips-Ladenburg reaction

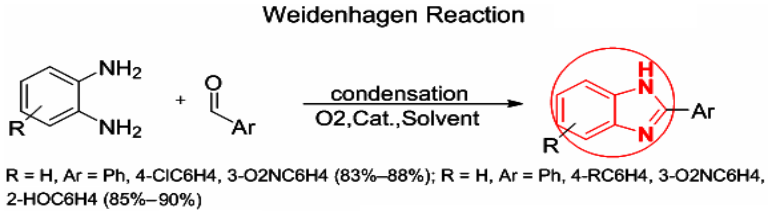
The Phillips-Ladenburg reaction involves the reaction of benzene-1,2-diamine with a carboxylic acid in the presence of a dilute acidic environment, Scheme 1 resulting in the formation of desired derivatives.[9]



Scheme 1. Philips-Ladenburg Reaction

The Weidenhagen Reaction

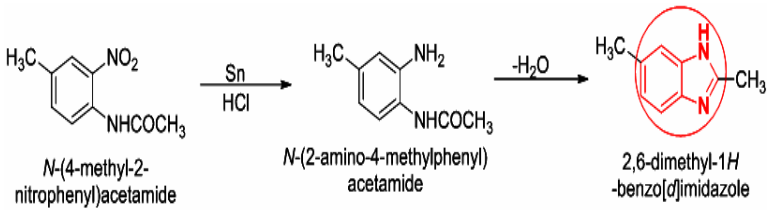
The Weidenhagen reaction produces compounds by reacting 1,2-diaminobenzene with aldehydes or ketones in water/alcohol, Scheme 2 using copper (II) salts as oxidizing agentsto facilitate cyclization and oxidation, from the carbonyl compound.[9]



Scheme 2. Weidenhagen Reaction

Hoebrecker Synthesis

Hoebrecker reduced 2-nitro-4-methylacetanilide to form benzimidazole.[10] Scheme 3.



Scheme 3. Hoebrecker Synthesis

Application of Benzimidazole derivatives

Benzimidazole as an Anti-Alzheimer agent:

Ozkay Y *et al.,* a study was carried out to evaluate the anticholinesterase characteristics of several benzimidazole derivatives due to their biological significance. The most potent derivatives were found to be compounds 4f and 4g, which displayed IC_{50} values of 0.091 mM and 0.134 mM, respectively, in comparison to the reference medication donepezil[11].

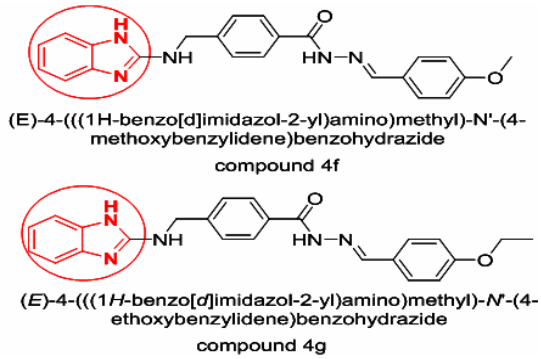


Fig. 2. Compound 4f and Compound 4g

Gurjar, A *et al.,* study aimed to combat Alzheimer's disease by investigating benzimidazole analogues targeting the key enzyme involved in Aβ peptide formation. They identified analogues 11 and 14 as the most promising candidates, exhibiting both BACE1 inhibition and neuroprotective effects, as well as aiding in memory retention compared to the standard drug donepezil[12].

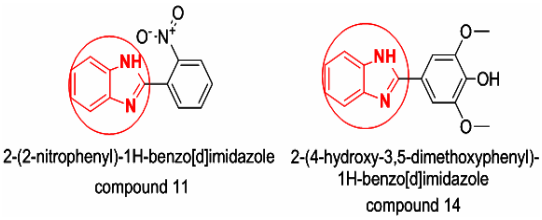


Fig. 3. Compound 11 and Compound 14

Alim, Z *et al.,* constructed ACH inhibitor as a target molecule in drug development studies for Alzheimer's disease. They synthesized 4 benzimidazole acetamide derivatives, which have the inhibition effect against human erythrocyte carbonic anhydrase 1 and 2, as well as ACHE. They found that compound 9a, 9b, 10a, and 10b has good inhibitor activity. The IC_{50} values for carbonic anhydrase 1 were 7.21 µm, 4.72 µm, 6.08 µm, and 8.23 µm. On the other hand, in comparison to the reference medication donepezil, the IC_{50} values for compounds 9a, 9b, 10a, and 10b for carbonic anhydrase 2 were 8.64 µm, 7.07 µm, 4.12 µm, and 5.93 µm[13].

Ozturk, O *et al.,* constructed 22 novel benzimidazole derivatives to evaluate the BCHE inhibition activity and they found that compound 2j and 3f exhibit potent and selective BCHE inhibition with IC_{50} value of 1.13 and 1.46 µm compared to the standard drug[14].

Yoon, Y *et al.,* created two novel classes of compounds with the fundamental structure of benzimidazole, intended to function as ACHE and BCHE inhibitors. Compound 5IIC was discovered to have the strongest inhibitory action; its IC_{50} values for ACHE and BUCHE are 5.12 µm and 8.63 µm, respectively[3].

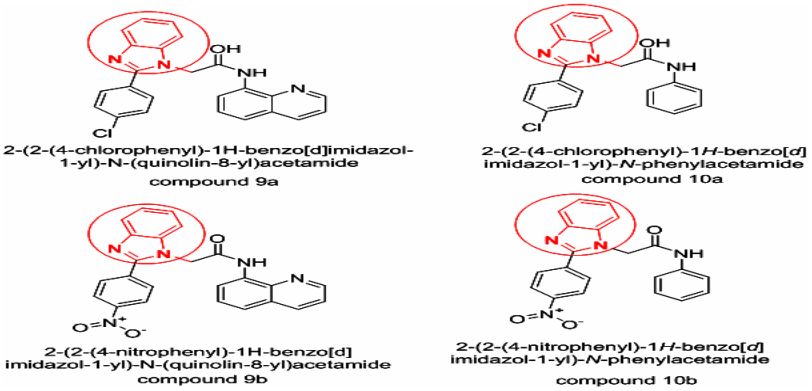


Fig. 4. Compound 9a, 9b, 10a and 10b

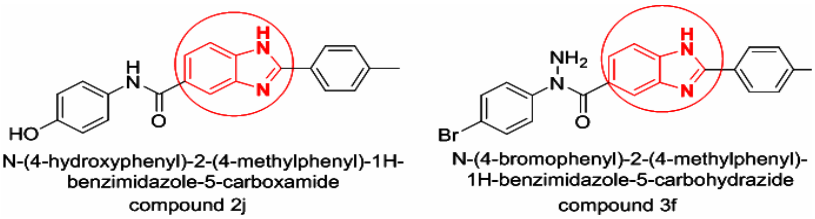


Fig. 5. Compound 2j and Compound 3f

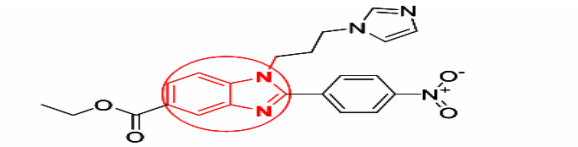


Fig. 6. Compound 5II-c

Adalat, B *et al.,* constructed 10 analogues of benzimidazole derivatives and they found that compound 1b, 1c, 1g, 2c, and 2e has the highest inhibitory activity against ACHE and BCHE with the IC_{50} value 1.30, 0.60, 2.40, 1.50, and 0.60 µm compared to the standard drug donepezil[15].

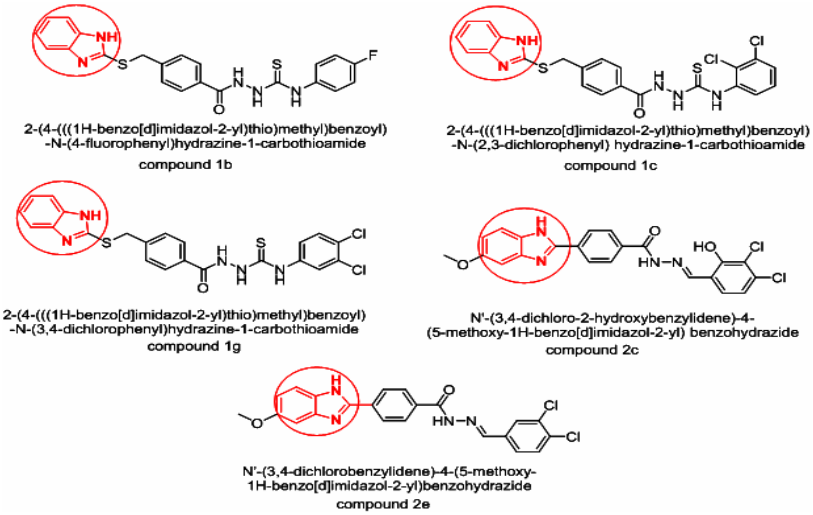
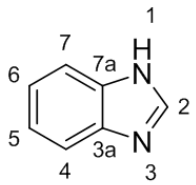


Fig. 7. Compound 1b, 1c, 1g, 2c and 2e

MATERIALS AND METHODS

SAR of benzimidazole as an anti-alzheimer agent



1*H*-benzo[*d*]imidazole

Through an extensive literature review, we carefully studied the chemical modifications to the benzimidazole ring system and their effects on the inhibition of acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE)., crucial for understanding potential therapeutic approaches for diseases like Alzheimer's. It highlights:

- The strategic placement of a phenyl group at the first position and a benzyl group at the second position, coupled with either hydroxyl (-OH) or chlorine (-Cl) substituents at the fourth position on both rings, significantly boosts the inhibitory efficacy against the target enzymes[3].
- It is demonstrated that this inhibitory activity can be further enhanced by adding a 4-nitrophenyl group at the second position of the benzimidazole ring system and offering the possibility of additional hydrophobic group replacements at the fourth position on the phenyl ring.
- This enhancement is attributed to the specific electronic and steric effects imparted by these substituents, which are meticulously optimized for maximum interaction with the enzyme's active site[16].
- Additionally, substituting a dichlorophenol group at the second position and a methoxy group at the fifth position has proven to be a highly effective modification strategy. This combination not only increases the molecule's affinity for the enzyme but also

suggests the potential for further activity improvement through additional hydrophobic substitutions[11].

These findings, deeply rooted in the principles of medicinal chemistry and enzyme inhibition kinetics, following these points offer valuable insights into the design of more effective inhibitors for AChE and BuChE.

Design of the molecules:-

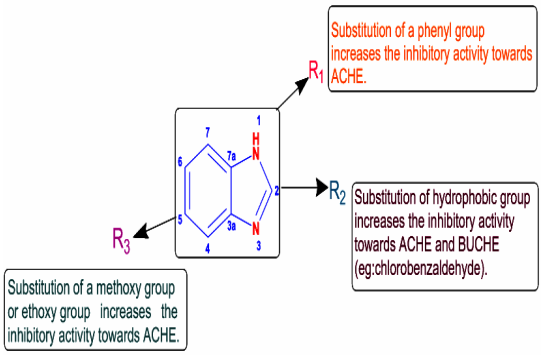


Fig. 8. SAR

- The substitution of a phenyl group at the 1st position of the benzimidazole ring has been observed to enhance the activity towards acetylcholinesterase (ACHE)[3].
- The substitution of hydrophobic groups at the 2nd position of the benzimidazole ring has been demonstrated to enhance inhibitory activity towards both acetylcholinesterase (ACHE) and butyrylcholinesterase (BUCHE).
- Notable examples include chlorobenzaldehyde, bromobenzaldehyde, N, N-dimethyl aniline, and (tert-butyl) benzaldehyde[16].
- The incorporation of either a methoxy group or an ethoxy group at the 5th position of the benzimidazole ring has been demonstrated to enhance inhibitory activity towards acetylcholinesterase (ACHE)[11].

Molecular Docking study:-

Molecular docking studies was carried out on the crystal structure of 4ey7 which was retrieved from PDB data bank.

Protein 4ey7:

- β Classification: OXIDOREDUCTASE
- Organism(s): Sinorhizobium meliloti 1021
- Expression System: Escherichia coli
- Mutation(s): No

Experimental Data:

- β Method: X-RAY DIFFRACTION
- Resolution: 1.80 Å
- R-Value Free: 0.197
- R-Value Work: 0.167
- R-Value Observed: 0.168

Software used and its version: -

1. BIOVIA Discovery Studio Visualizer version 24.1.0.23298
2. UCSF Chimera version 1.17.3

System parameters

Table 1:

PC	DELI
Operating System	Windows11 Pro
Processor	Intel-Core
RAM	32GB
Hard disc	1TB

Pharmaco kinetic study

A pharmacokinetic study is a scientific investigation that examines how a drug is absorbed, distributed, metabolized, and excreted in the body over time. It involves measuring drug concentrations in biological fluids like blood or urine and uses this data to understand the drug's behaviour in the body. The study helps determine the optimal dosage, frequency, and route of administration to ensure safety and efficacy.

Computational Pharmacokinetic Study was carried out by calculating ADME parameters using Swiss ADME[17] and Protox-II online tool[18]. The toxicity prediction study was conducted using the Protox-II online tool.

- β Toxic doses are often represented as LD50 values in mg/kg of body weight.
- β The median lethal dose (LD_{50}) is the amount at which 50% of test subjects die after exposure to a chemical.

Table 2:

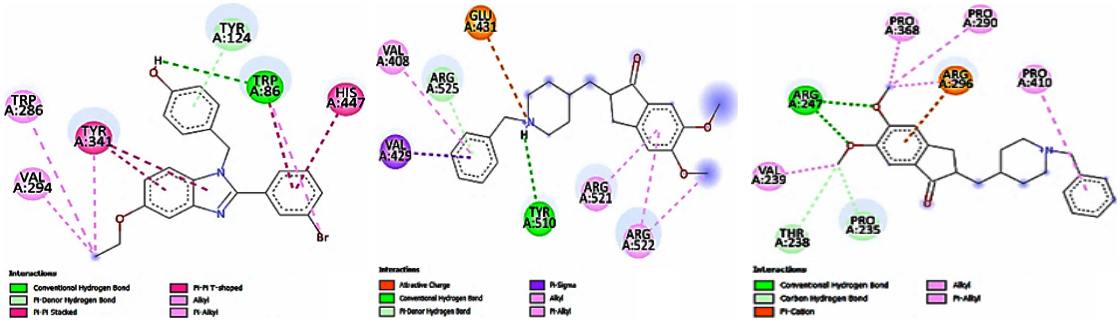
Sr. No	Formula	Molecular Weight (g/mol)	Log P	GI Absorption	Lipins Ki	Bioavailbili-ty Score	Synthei-ctic Asscess-ibility	LD_{50} Value	Predicted Toxicity Data
I-1	$C_{15}H_{11}BrN_2O_2$	331.16	2.39	High	0	0.55	2.16	800mg/kg	Class-IV
I-2	$C_{15}H_{11}BrN_2O_2$	331.16	2.14	High	0	0.55	2.23	800mg/kg	Class-IV
I-3	$C_{16}H_{13}BrN_2O_2$	345.19	2.65	High	0	0.55	2.26	800mg/kg	Class-IV
I-4	$C_{16}H_{13}BrN_2O_2$	345.19	2.33	High	0	0.55	2.33	4500mg/kg	Class-V
I-5	$C_{22}H_{19}BrN_2O_2$	423.3	3.69	High	0	0.55	2.66	400mg/kg	Class-IV
I-6	$C_{22}H_{19}BrN_2O_2$	423.3	3.57	High	0	0.55	2.76	400mg/kg	Class-IV
I-7	$C_{22}H_{19}BrN_2O_2$	423.3	3.57	High	0	0.55	2.76	400mg/kg	Class-IV
I-8	$C_{21}H_{17}BrN_2O_2$	409.28	3.28	High	0	0.55	2.54	400mg/kg	Class-IV
I-9	$C_{21}H_{17}BrN_2O_2$	409.28	3.28	High	0	0.55	2.54	400mg/kg	Class-IV
I-10	$C_{21}H_{17}BrN_2O_2$	409.28	3.17	High	0	0.55	2.64	400mg/kg	Class-IV
I-11	$C_{16}H_{13}ClN_2O_2$	300.74	2.58	High	0	0.55	2.19	800mg/kg	Class-IV
I-12	$C_{16}H_{13}ClN_2O_2$	300.74	2.58	High	0	0.55	2.14	800mg/kg	Class-IV
I-13	$C_{22}H_{19}ClN_2O_2$	378.85	3.4	High	0	0.55	2.54	400mg/kg	Class-IV
I-14	$C_{22}H_{19}ClN_2O_2$	378.85	3.48	High	0	0.55	2.61	400mg/kg	Class-IV
I-15	$C_{22}H_{19}ClN_2O_2$	378.85	3.48	High	0	0.55	2.61	400mg/kg	Class-IV
I-16	$C_{21}H_{17}ClN_2O_2$	364.83	3.23	High	0	0.55	2.48	400mg/kg	Class-IV
I-17	$C_{21}H_{17}ClN_2O_2$	364.83	3.07	High	0	0.55	2.49	400mg/kg	Class-IV
I-18	$C_{21}H_{17}ClN_2O_2$	364.83	3.07	High	0	0.55	2.49	400mg/kg	Class-IV
I-19	$C_{16}H_{13}N_3O_4$	311.29	1.8	High	0	0.55	2.48	800mg/kg	Class-IV
I-20	$C_{16}H_{13}N_3O_4$	311.29	1.74	High	0	0.55	2.54	800mg/kg	Class-IV
I-21	$C_{19}H_{20}N_2O_2$	308.37	2.79	High	0	0.55	2.41	800mg/kg	Class-IV
I-22	$C_{19}H_{20}N_2O_2$	308.37	2.86	High	0	0.55	2.41	800mg/kg	Class-IV
I-23	$C_{20}H_{22}N_2O_2$	322.4	2.99	High	0	0.55	2.52	800mg/kg	Class-IV
I-24	$C_{20}H_{22}N_2O_2$	322.4	2.85	High	0	0.55	2.52	800mg/kg	Class-IV
I-25	$C_{24}H_{25}N_3O_2$	387.47	3.4	High	0	0.55	2.86	837mg/kg	Class-IV
I-26	$C_{24}H_{25}N_3O_2$	387.47	3.47	High	0	0.55	2.92	837mg/kg	Class-IV
I-27	$C_{24}H_{25}N_3O_2$	387.47	3.47	High	0	0.55	2.92	837mg/kg	Class-IV
I-28	$C_{23}H_{23}N_3O_2$	373.45	3.24	High	0	0.55	2.74	400mg/kg	Class-IV
I-29	$C_{23}H_{23}N_3O_2$	373.45	2.94	High	0	0.55	2.8	837mg/kg	Class-IV
I-30	$C_{23}H_{23}N_3O_2$	373.45	2.94	High	0	0.55	2.8	837mg/kg	Class-IV

Table 3: Interaction table of the synthesized compounds

Sr. No	Name	H-bond interaction	Other interaction
1	Donepezil	ARG:247	VAL:239, THR:238, PRO:235, ARG:296, PRO:368, PRO:290, PRO:420
2	Co-crystal ligand	TYR:510	VAL:408, ARG:525, GLU:431, VAL:429, ARG:521, ARG:522
3	I-6	TRP:86	TRP:286, TYR:341, VAL:294, TYR:124, HIS:447
4	I-15	ASN:87	TYR:124, HIS:447, TRP:86, TYR:341, TRP:286
5	I-2	ARG:296	TRP:286, TYR:337, HIS:447, TYR:341, PHE:338, TYR:72
6	I-12	ARG:296PHE:295	HIS:447, TYR:337, TRP:86, PHE:338, TYR:341, TYR:72, TRP:286
7	I-8	GLY:121	HIS:447, PHE:297, TRP:236, PHE:295, ASP:74, TYR:341, TRP:286, PHE:338

Docking interaction of standard drug proposed derivatives:-
Donepezil, Donepezil with co-crystal ligand and

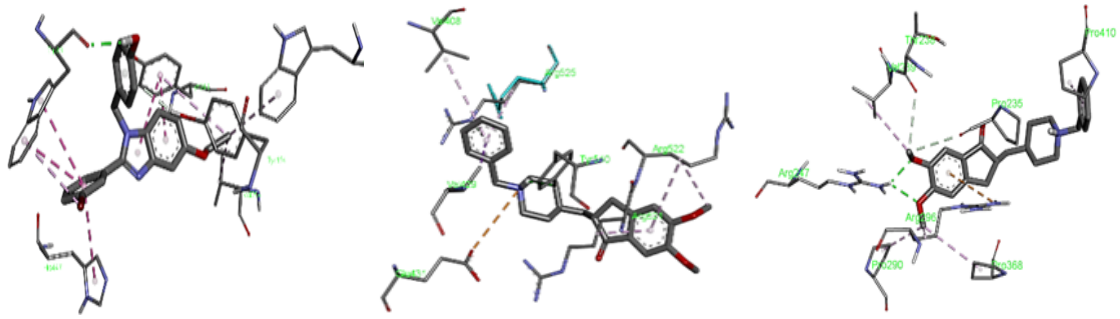
Compound I-6



COMPOUND I-6 (2-D)
DOCKING SCORE: -10.3

CO-CRYSTAL LIGAND (2-D)
DOCKING SCORE: -7.2

DONEPEZIL (2-D)
DOCKING SCORE:-8.1



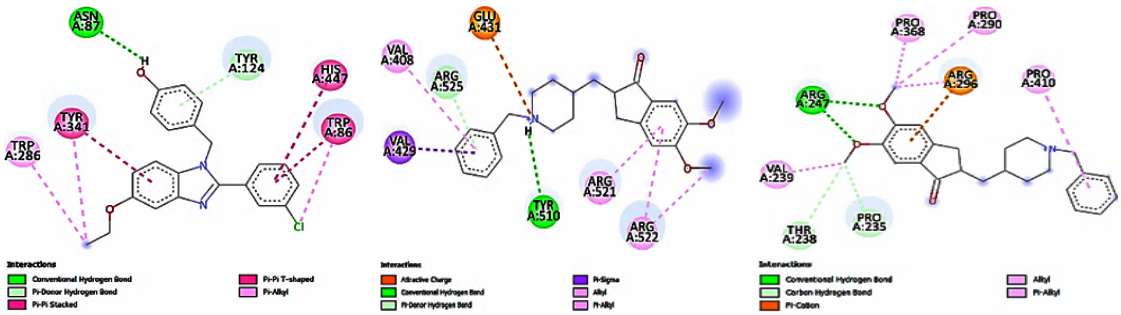
COMPOUND I-6 (3-D)

CO-CRYSTAL LIGAND (3-D)

DONEPEZIL (3-D)

Fig. 9.

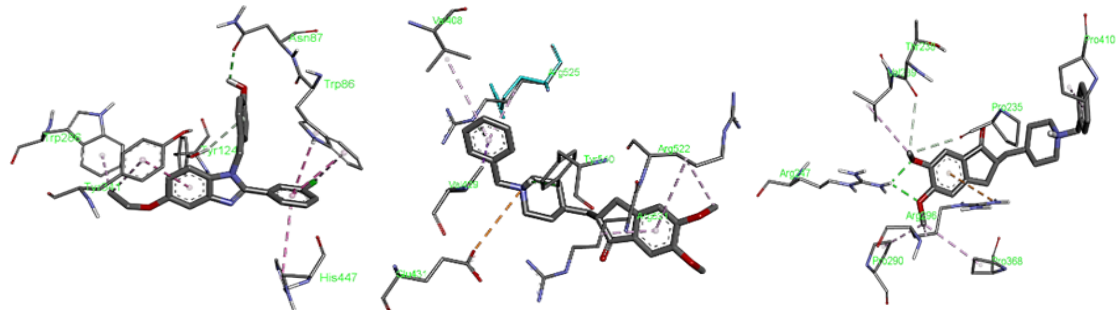
Compound I-15



COMPOUND I-15 (2-D)
DOCKING SCORE: -10.3

CO-CRYSTAL LIGAND (2-D)
DOCKING SCORE: -7.2

DONEPEZIL (2-D)
DOCKING SCORE: -8.1



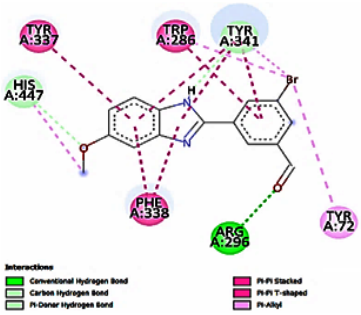
COMPOUND I-15 (3-D)

CO-CRYSTAL LIGAND (3-D)

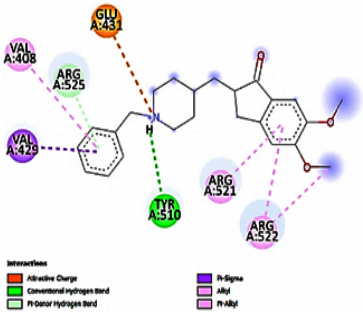
DONEPEZIL (3-D)

Fig. 10.

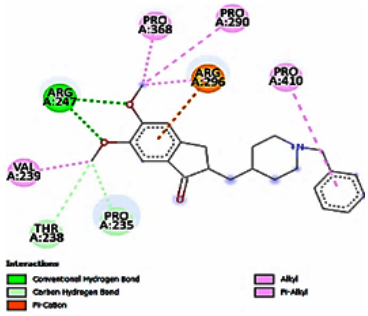
Compound I-2



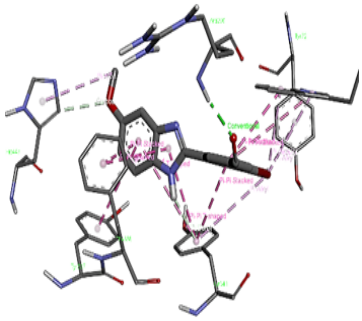
COMPOUND I-2 (2-D)
DOCKING SCORE: -10.0



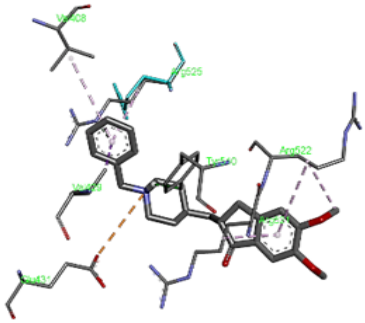
CO-CRYSTAL LIGAND (2-D)
DOCKING SCORE: -7.2



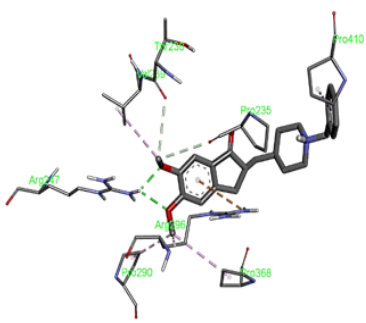
DONEPEZIL (2-D)
DOCKING SCORE: -8.1



COMPOUND I-2 (3-D)



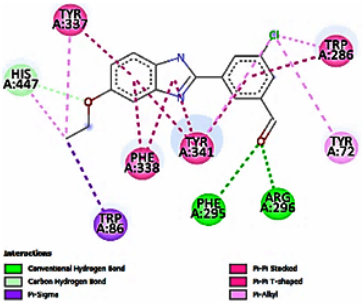
CO-CRYSTAL LIGAND (3-D)



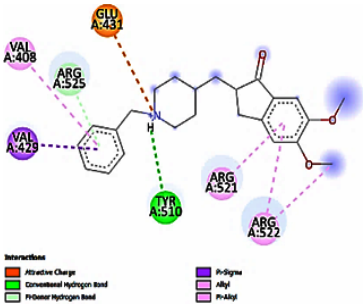
DONEPEZIL (3-D)

Fig. 11.

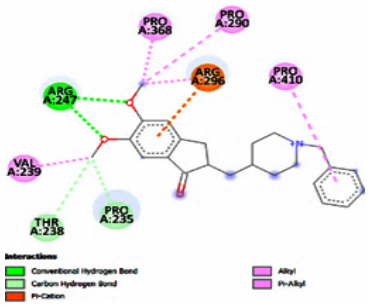
Compound I-12



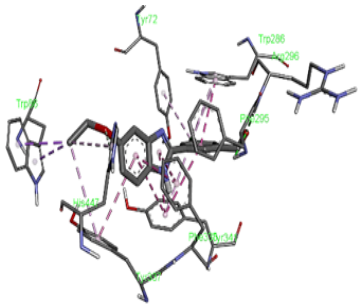
COMPOUND I-12 (2-D)
DOCKING SCORE: -10.0



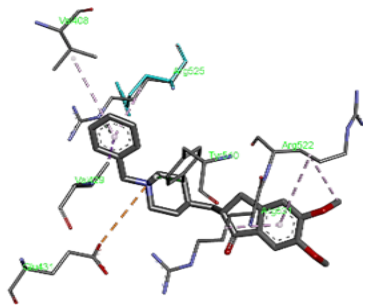
CO-CRYSTAL LIGAND (2-D)
DOCKING SCORE: -7.2



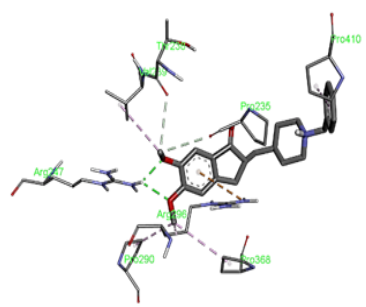
DONEPEZIL (2-D)
DOCKING SCORE: -8.1



COMPOUND I-12 (3-D)



CO-CRYSTAL LIGAND (3-D)



DONEPEZIL (3-D)

Fig. 12.

Compound I-8

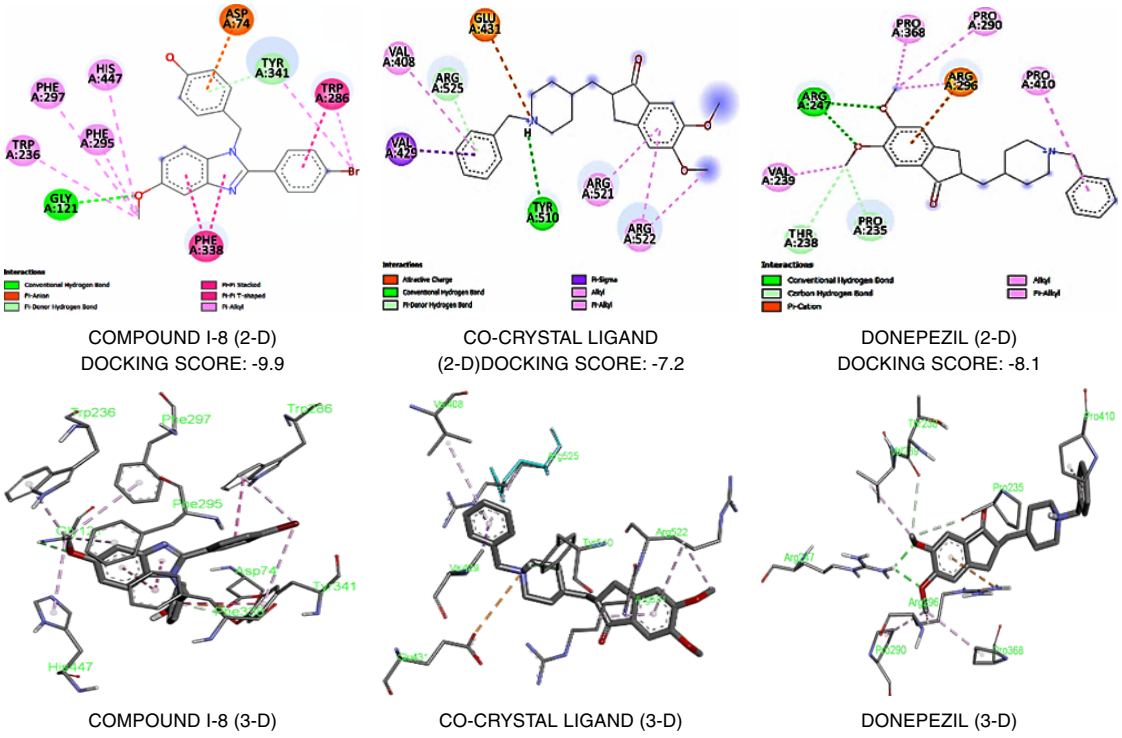


Fig. 13.

CONCLUSION

In conclusion, this research article presents an overview of benzimidazole derivatives with a particular focuson their anti-alzheimer potential. Benzimidazole and its derivatives exhibit a wide range of pharmacological activities, including anti-viral, anthelmintic and antifungal effects.However,their anti-alzheimeractivity is particularly noteworthy.The synthesis and reactions of benzimidazole provide a platform for the generation of diverse derivatives with tailored properties. Through structure-activity relationship (SAR) studies, it has been observed that specific modificationsat different positionson the benzimidazole ring can significantly enhance their anti-alzheimer activity.

Ache and Buche enzymes are crucial for memory and cognition,as they facilitate the breakdown of Ach, disrupting communication between nerve cells and contributing to Alzheimer's disease. Consequently, pharmaceutical efforts have concentrated on developing cholinesterase inhibitors to address cognitive disorders. Our research has centered on novel compounds synthesized from ring-fused benzimidazoles as key structures, aiming to target these enzymes for potential therapeutic interventions.In this study, we investigated the potential of ring-fused benzimidazoles as neuroprotective therapeutics targeting Ache and Buche enzymes implicated in Alzheimer's disease. Through the synthesis of 30 novel compounds and subsequent in-silico studies, we demonstrated that these compounds exhibit promising binding affinity against Ache and Buche. These findings suggest that benzimidazole derivatives hold potential as effective treatments for cognitive disorders, offering a promising avenue for future pharmaceutical research in the field of neuroprotection.

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Conflict of interest

We assert clearly that we have no conflicts of interest.

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