chemistry proceedings

MDPI

*Proceeding Paper*

# Design, Synthesis and Characterization of Novel Benzimidazole Derivatives as Multi-Targeted Anti-Alzheimer's Agents Integrated with Computational Screening †

**Avantika Agrawal, Umesh Verma and Achal Mishra ***

Department of Pharmacy, Guru Ghasidas Vishwavidyalaya, Bilaspur 495009, Chhattisgarh, India; agrawalavantika1@gmail.com (A.A.); u12161325@gmail.com (U.V.)
* Correspondence: achal.mishra@ggu.ac.in; Tel.: +91-96910-54057
† Presented at the 30th International Electronic Conference on Synthetic Organic Chemistry, 5–19 November 2026; Available online: https://sciforum.net/event/ecsoc-30/home.

**Abstract**

Alzheimer's disease (AD) has a complex manifestation mechanism. To address this, multi-target-ligand designing has been done over the available single-target therapies. Benzimidazole derivatives, known for their biological diversity, were strategically designed and screened based on their ADMET profile and binding affinity. The highest scoring derivatives were synthesized using a highly sustainable synthetic protocol and characterized by IR and 1H-NMR spectral studies. This study resulted in potential analogs against Alzheimer's disease, warranting further experimental validation through in vitro and in vivo studies. Overall, this study provides a pre-validated computational blueprint and a ready-to-use synthetic protocol for the development of novel therapeutics for AD.

**Keywords:** N-1 substituted benzimidazole derivatives; cholinesterase inhibitors; multi-target-directed ligands (MTDLs)

## 1. Introduction

Alzheimer's disease is a complicated, heterogeneous neurodegenerative disorder that features the interaction between cholinergic dysfunction, the accumulation of amyloid-beta peptide, hyperphosphorylation of tau protein, and neuroinflammation [1]. Abnormalities in the cholinergic system are among the leading pathological features of the disease, along with senile plaques, neurofibrillary tangles, and massive loss of neurons. Taking into account the complex nature of the pathology of the disease that is associated with the progression of cholinergic dysfunction and neurofibrillary tangles, existing single-target therapies are inefficient in modifying Alzheimer's disease [2]. Therefore, there is a necessity for multi-target molecules to tackle different pathological stages of the disease to stop its progression. MTDLs, acting on acetylcholinesterase, butyrylcholinesterase, and β-secretase as well as amyloid receptors simultaneously, have become promising agents since they are able to not only affect the cholinergic system but also prevent the amyloidogenic pathway from progressing [3].

Benzimidazole derivatives are promising because of an easy, versatile manner of modifications, which these compounds allow, to make their derivatives more active against neurodegenerative diseases [1,4]. With that in mind, the new benzimidazole analogs with substituted aryl/alkyl amide and benzylic substituents at N-1 were strategically designed according to the literature to explore the multi-target aspect of these compounds [4,5].

Check for updates

Academic Editor: Julio A. Seijas

Published: 13 November 2026

**Copyright:** © 2026 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license.

Combining the screening of the designed library of benzimidazole derivatives using computational methods, like drug likeness profiling along with molecular docking, facilitates the refinement and validation of these compounds by determining their binding affinities for various targets, such as acetylcholinesterase (AChE) and butyrylcholinesterase (BChE), allowing rational structure–activity optimization. The use of benzimidazole derivatives with N-benzyl-type substituents and amide/carbamate functionalities has been reported in the literature for the development of anti-Alzheimer drugs and demonstrated activity against cholinesterases and β-secretase [5–7]. Thus, in the present study, a library comprising 51 derivatives of benzimidazole was created and screened based on their ADMET data and predicted binding affinities for AChE, BChE, BACE1, and amyloid β-proteins. Subsequently, the most promising analogs were synthesized via a sustainable synthetic procedure, with completion of the reaction confirmed by TLC and identification of the structures verified by physicochemical (melting point, solubility) and spectral (IR, $^1$H-NMR) analytical methods. Together, this integrated computational and experimental workflow will provide a vigorous, pre-validated blueprint and a ready-to-use synthetic route aimed at accelerating the development of novel therapeutics for Alzheimer's disease.

## 2. Materials and Methods

### *2.1. Computational Screening*

ADMET screening was performed using the SWISS ADME web server (https://www.swissadme.ch/index.php; accessed on 14 August 2025) for the rationally designed 51 analogs of N-1 substituted benzimidazole derivatives. All 17 screened drug-like compounds were docked into the selected targets using Glide's extra precision (XP) method in the Schrödinger suite (release 2025-2). For docking studies, the target proteins were downloaded from RCSB PDB. The PDB IDs for the target proteins were as follows: AChE-4EY7; BChE-6QAA; BACE1-2OHT; and Aβ-2BEG. The target proteins were prepared with the help of the protein preparation tool in the Schrödinger suite. The qualifying ligands were prepared using the LigPrep module (within Schrödinger release 2025-2) and saved in 'sdf' format for future use.

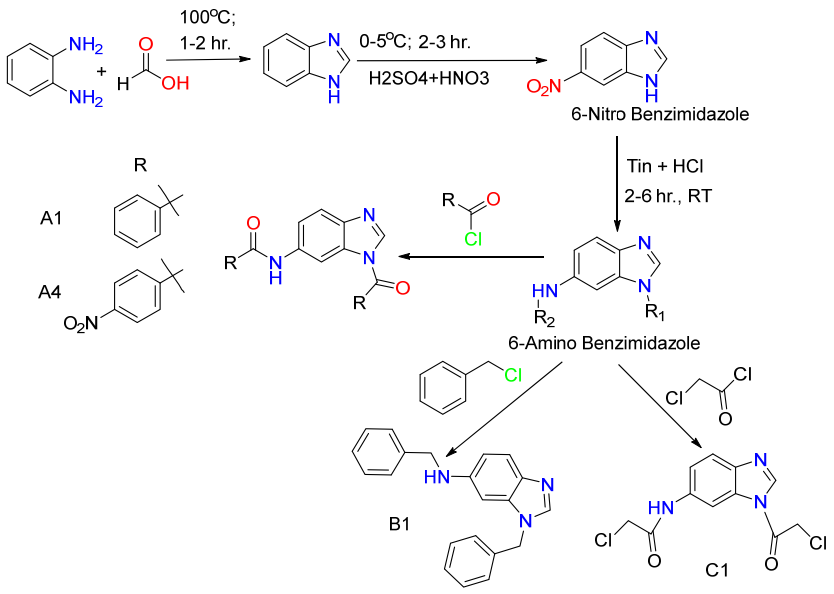
### *2.2. Chemistry*

#### 2.2.1. General Information, Instrumentation and Chemicals

All reactants and solvents used in the present study for synthesis and characterization were purchased from an authorized dealer, Shreya chemicals, Bilaspur, India. The commercial producers included various chemical units namely Sigma-Aldrich (Bengaluru, India), Fischer Scientific (Mumbai, India), and Loba Chemie (Mumbai, India) The chemicals procured were of analytical grade and used directly without any further purification. The progress of the reactions and the nature of the product mixtures were monitored by the thin-layer chromatography (TLC) method, where the TLC plates (silica G 60-120 mesh from Loba Chemie) were visualized under UV light at 254 nm. The solvent mixture used was methanol and chloroform in a ratio (1:4). The melting points of intermediates and final compounds were determined using the capillary melting point apparatus with an open-end capillary. The proton NMR spectra of the final compounds were recorded on a Bruker Avance (400 MHz) instrument (Bruker, Ettlingen, Germany) using TMS as an internal reference on the 'δ' scale. The solvents used are deuterated DMSO, methanol, and chloroform. Infrared spectra were also recorded using Perkin-Elmer Spectrum IR Version 10.6.2 FT-IR (PerkinElmer, Shelton, CT, USA) that covered spectral range from 4000 to 450 $cm^{-1}$, and elemental analysis was performed using a Thermo Scientific Flash 2000 analyzer(Thermo Fisher Scientific S.p.A., Milan, Italy).

2.2.2. General Procedure for Synthesis

The main scaffold of the suggested series of compounds, i.e., benzimidazole, was first synthesized by mixing ortho-phenylenediamine (0.03 M) with formic acid and refluxing at 100 °C for two hours with continuous stirring (Scheme 1). The resulting mixture was then neutralized with 10% NaOH solution, and the precipitate was filtered using Whatman filter paper, washed with cold water, dried, and recrystallized using alcohol. Further, nitration was carried out using concentrated nitric acid in the presence of conc. H2SO4 at temperature 0–5 °C with continuous stirring for 2–3 h. The resulting 6-nitrobenzimidazole (in ethanol solution) was reduced to 6-aminobenzimidazole in the presence of tin powder (1.424 g) by reacting with conc. HCl, maintaining the temperature between 0 and 5 °C. The reaction mixture was kept for 2–6 h at room temperature with continuous stirring. The residual tin and $Sn(OH)_2$ were filtered away, and the mixture was neutralized using 10% NaOH solution. The resulting precipitate was then filtered, washed with cold water, dried, and recrystallized using ethanol. This was used as the base for preparing other derivatives. Reaction with 2.32 mL (0.02 M) of benzoyl chloride solution gave compound **A1**, 1.32 g (0.006 M) of 4-nitrobenzoyl chloride solution gave compound **A4**, 1 mL (0.006 M) of benzyl chloride solution gave compound **B1**, and 1.32 g (0.006 M) of chloro-acetyl chloride solution resulted in synthesis of compound **C1** (Scheme 1).




**Scheme 1.** Synthesis of **A1**, **A4**, **B1**, and **C1** compounds.

## 3. Results and Discussion

Based on our computational outcomes, we synthesized four prioritized compounds that exhibited drug likeness along with significant binding affinity towards the four sets of selected anti-Alzheimer's targets.

### *3.1. ADMET Study Evaluation*

The 51 benzimidazole-based compound library, after in silico pharmacokinetic and drug-likeness property evaluation through SwissADME, resulted in 17 hits. The ADMET information from this study indicates that most of these filtered compounds meet the classical pharmacokinetic and drug-likeness standards (Supplementary Tables S1 and S2). All of the 17 substances passed the Lipinski's Rule of Five (MW < 500, HBD ≤ 5, HBA ≤ 10, cLogP ≤ 5), showing that they do not possess any significant large or polar groups. Veber's rule (TPSA ≤ 140 $Å^2$, rotors ≤ 10) was also satisfied, indicating a balanced polarity

among the filtered compounds. Some candidates, like **A8**, **A9**, and **A10**, seem to violate some rules because of their higher PSA or LogP values; these values could potentially hinder their absorption when consumed orally. The filters defined by Ghose, Egan, and Muegge that set additional cutoffs (e.g., Muegge: MW 200–600, logP −2 to 5, TPSA ≤ 150) were also evaluated. For the compounds analyzed, most satisfied these parameters also, proving their potential for drug-likeness. Each of the analyzed substances also received a bioavailability score of 0.55 units, which indicates more than 10% oral bioavailability in rats. Further, the synthetic accessibility (SA) score for these 17 compounds was between 1.96 and 2.57, well below the threshold value (i.e., 4), reflecting their easy two-to-three step synthetic feasibility.

For a compound to be able to cross the blood–brain barrier (BBB) for CNS penetration, it has been reported that TPSA less than approximately 90 Å$^2$ is favourable with the ideal range being 60 to 85 Å$^2$ [8]. In the data set, as revealed from the SwissADME's BOILEDEgg model (Figure 1), all the filtered 17 compounds showed BBB permeability along with good intestinal absorption (HIA predicted high for all). In addition, the presence of P-glycoprotein (P-gp) efflux capacity also matters because P-gp substrates would be expected to have limited CNS penetration, while the presence of P-gp inhibitors would also pose the possibility of toxic drug interactions. Based on our analysis, except for **A8** and **A10** (which were predicted as P-gp substrates), all other compounds met our criteria for CNS penetration and did not show any features of P-gp efflux (i.e., these compounds were neither substrates nor inhibitors). Further, though not revealed here, the compounds were predicted as substrates for the CYP enzyme system, indicating their effective metabolism and absence of potential drug–drug interactions.

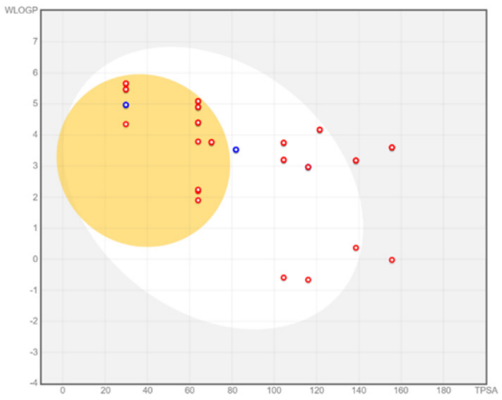



**Figure 1.** BOILED-Egg showing the BBB permeability and intestinal absorption of the designed compounds. Blue dot-compound predicted as P-gp substrates; Red dot-compound predicted as P-gp non-substrates; Yellow egg yolk-high BBB permeation; Egg white-High GI absorption; Grey region-low GI or BBB permeability.

### *3.2. Docking Study Evaluation*

Outcomes of the docking study are provided in the Supplementary Table S3 and Figures S1–S4. In the case of acetylcholinesterase (AChE), the results indicate that donepezil (−9.106 kcal/mol) made hydrogen bonds with Phe295/Tyr72/Tyr341 along with some hydrophobic interactions with Trp86, Trp286, Tyr337, and Phe338, which are all active site residues forming the PAS and CAS gorge of the enzyme. The benzimidazole derivative **A1** (−10.652 kcal/mol) also exhibited hydrogen bonds with the oxyanion hole (Gly121) and the acyl pocket (Phe295), along with strong interactions within the PAS site (Trp86, Tyr337, Phe338, Tyr341), while compound **A4** mostly formed H-bonds with the peripheral residues (Asn87, Ser125). Compound **B1** (−12.758 kcal/mol) forms direct bonds with His447 and Tyr124 along with other interactions covering the gorge area from the entrance

to the bottom simultaneously, confirming its binding capacity. This mechanism of binding through two binding sites at once, PAS + CAS, is regarded as very valuable as blockade of PAS can inhibit AChE-mediated Aβ aggregation. The compound **C1** (−8.973 kcal/mol) also overall exhibited moderate binding to the AChE target, making bonds with His447 and the acyl pocket residues, i.e., Phe295, Val294, and Phe338.

BChE is reported to have a similar active site architecture to AChE but has a wider and less aromatic acyl pocket. In the case of BChE, relative to its co-crystal ligand with binding affinity −9.81 kcal/mol, compounds **B1** (−9.453 kcal/mol) and **C1** (−9.188 kcal/mol) formed H-bonds with His438, which is part of the catalytic triad of BChE, with **B1** creating additional hydrophobic interactions with Trp231, Ala328, Phe329, and His438. **A1** and **A4**, on the other hand, exhibited comparatively lower affinity, with binding energy being −8.431 kcal/mol and −6.186 kcal/mol. Still, as these ligands showed considerable binding interactions towards BChE, they can be regarded as a balanced type of dual-inhibitor (AChE and BChE), a finding that is consistent with previously published results featuring the benzamide derivatives [9].

As for BACE1, the co-crystal ligand with binding affinity −8.411 kcal/mol has outperformed all four of the designed compounds, forming H-bonds with Gln73 (flap) and Phe108 (in the S1/S3 pocket), with Asp32 and Asp228 being part of its contact shell. **A1**, **A4**, **B1**, and **C1** exhibited relatively weaker binding affinities: −5.281 kcal/mol, −3.492 kcal/mol, −4.51 kcal/mol, and −5.133 kcal/mol. Neverthless, they were able to form sufficient H-bonds and hydrophobic interactions as listed in Supplementary Table S3 and the 2D and 3D interactions shown in the supplementary information. Benzamide derivatives have been previously reported to be effective in inhibiting the BACE1 enzyme [5]. Considering this, the present set of prioritized compounds can be considered as moderate inhibitors.

Aβ fibril model is a pentamer target. Compound **A1**, with binding energy −8.267 kcal/mol, forms bonds across four different chains (A, B, C, D), where it simultaneously binds Leu17 (KLVFF core) in A, B, and C strands together with hydrophobic interactions with Val40/Ala42. Interaction with the C-oligomer Val40/Ala42 terminal residues reflects its ability to interfere in interchain packing responsible for fibril formation, making it a superior aggregation/beta-sheet inhibitor. **A4**, with binding energy of −5.742 kcal/mol, seems to bind only one chain (E) and interacts with KLVFF (Leu17/Val18/Phe19) and terminal (Val39/40) residues. In comparison with **A1**, this compound definitely does not establish cross-chain connections. On the contrary, **B1** (−5.453 kcal/mol) touches three chains (C, D, and E) at KLVFF/C terminal but makes no hydrogen bonds, which can be likely due to the absence of -OH or carbonyl group in this compound, which is required for forming a competitive H-bond with the Aβ backbone [10]. Finally, **C1** (−5.095 kcal/mol), like **A1**, bonds with A, B, C, and D chains with H-bond with C-chain Leu17, acting as a moderate Aβ aggregation inhibitor. The overview based on the interaction pattern of the prioritized compounds with the selected anti-Alzheimer's targets has been summarized in Table 1 below.

Regarding multi-target-directed ligand (MTDL) design, **A1**, **B1**, and **C1** are the most defensible leads among the present set of compounds. **B1**, due to its binding to the catalytic triad residues along the dual-site (PAS + CAS) of AChE plus sufficient BChE affinity, can be considered as a dual cholinesterase inhibitor with moderate affinity for BACE1 target. On the other hand, **A1** has shown strong affinity for AChE and Aβ anti-aggregation. Conversely, **C1** has exhibited a balanced activity profile across the selected four targets. In addition to our present finding, this benzimidazole scaffold's plausibility across the selected targets is also supported by a broader review of benzazole pharmacophores, where a similar set of residues have been reported for ligand interaction [11].

**Table 1.** Summary of the interaction pattern.

| Ligand | AChE | BChE | BACE1 | Aβ | Overall Pattern |
|---|---|---|---|---|---|
| **A1** | Very strong (exceeds co-crystal) | Moderate | Moderate | Very strong | Potential for AChE + Aβ dual inhibition along with moderate activity against BChE and BACE1 |
| **A4** | Moderate | Comparatively weak, still active | Weak | Weak | Least competitive |
| **B1** | Very strong (best His447/PAS coverage) | Strong (near to co-crystal) | Moderate | Weak | Potential for AChE + BChE dual cholinesterase activity |
| **C1** | Strong | Moderate | Moderate | Moderate | Balanced activity pattern relative to all targets |

### *3.3. Compound Characterization*

**A1:** N-(1-benzoyl-1H-benzimidazol-6-yl) benzamide, light yellow, Yield: 92%, M.P.: 125–135 °C, Rf value: 0.7, $^1$H NMR (400 MHz, Chloroform-*d*) δ 9.94 (s, 1H), 8.56 (s, 1H), 7.98–7.94 (m, 4H), 7.75–7.71 (m, 2H), 7.58 (dd,1H), 7.52–7.49 (m, 4H), 7.46–7.42 (m, 2H).

**A4:** 4-nitro-N-(1-(4-nitrobenzyl)-1H-benzimidazol-6yl) benzamide, Pink color, Yield: 92.3%, M.P.: 105–115 °C, Rf value: 0.66, $^1$H NMR (400 MHz, DMSO) δ 8.57 (s, 1H), 8.38–8.36 (m, 2H), 8.32–8.30 (m, 2H), 8.24–8.22 (m, 2H), 8.02–8.00 (m, 2H), 7.75–7.72 (m, 2H), 7.59 (dd, 1H).

**B1:** N,1-dibenzyl-1H-Benzimidazol-6 amine, Brown color, Yield: 70%, M.P.: 145–155 °C, Rf value: 0.6, $^1$H NMR (400 MHz, DMSO) δ 8.17 (s,1H), 7.49 (d, 1H), 7.37–7.26 (m, 8H), 7.13 (dd,2H), 6.99 (dd,1H), 6.89 (d, 1H), 5.48 (d,2H), 5.35 (d,1H), 4.37 (s,2H).

**C1:** 2-chloro-N-(1-(2-chloroacetyl)-1H-benzo[d]imidazol-6-yl) acetamide, Light Brown color, Yield: 57.6%, M.P.: 135–145 °C, Rf value: 0.54, $^1$H NMR (400 MHz, Chloroform-d) δ 9.51 (s, 1H), 8.56 (s, 1H), 7.71 (d,1H), 7.66 (d,1H), 7.50–7.48 (dd,1H), 4.75 (s, 2H), 4.21 (s, 2H).

The FT-IR and proton NMR spectral data for all the studied compounds are available in the Supplementary Information Figures S5–S12 and Tables S4–S7.

## 4. Conclusions

In this study, we fruitfully implemented an integrated in silico-to-synthesis workflow for finding new candidates based on the benzimidazole structure for multi-target activity against Alzheimer's disease. Using this approach, we initially designed 51 N-1 substituted benzimidazole derivatives, from which 17 candidates displaying drug-like properties were selected based on their ADMET property predictions. These selected compounds were then screened by molecular docking against four biological targets: AChE, BChE, BACE1, and Aβ. The results demonstrated distinct features of interaction of the selected compounds with the designated biological targets. Among prioritized derivatives, compound **B1** demonstrated the best dual cholinesterase affinity (AChE + BChE); compound **A1** exhibited strong binding to AChE along with Aβ target; while **C1** revealed the most balanced interaction profile with all the investigated biological targets. Based on their predicted activity performance, these compounds were successfully synthesized and characterized spectroscopically. This further validated the synthetic feasibility of the proposed scaffold design. In conclusion, compounds **A1**, **B1**, and **C1** can be considered to be the most promising ones for the further development of multi-targeted drugs for Alzheimer's disease. Nevertheless, even though the biological activities of the studied compounds were predicted computationally, confirmation of their biochemical and anti-aggregation activity is essential using in vitro and in vivo methods to confirm their efficacy, selectivity, and safety. This study therefore

provides a rationally prioritized and experimentally accessible approach for further SAR optimization of benzimidazole-based MTDLs for AD.

**Supplementary Materials:** The following supporting information can be downloaded at https://www.mdpi.com/article/10.3390/chemproc2026022171/s1, Table S1. Physicochemical properties of the screened set of molecules; Table S2. Different toxicity properties of the screened set of molecules. Table S3. Binding affinity and different interactions of the prioritized compounds against the selected Alzheimer's disease targets; Figure S1. (a) 4EY7 Co-crystalized Donepezil; (b) **A1** docked in 4EY7 AChE; (c) **A4** docked in 4EY7 AChE; (d) **B1** docked in 4EY7 AChE; (e) **C1** docked in 4EY7 AChE; Figure S2. (a) 6QAA Co-crystalized Ligand; (b) **A1** docked in 6QAA BChE; (c) **A4** docked in 6QAA BChE; (d) **B1** docked in 6QAA BChE; (e) **C1** docked in 6QAA BChE; Figure S3. (a) 4IVT Co-crystalized Ligand; (b) **A1** docked in 4IVT BACE1; (c) **A4** docked in 4IVT BACE1; (d) **B1** docked in 4IVT BACE1; (e) **C1** docked in 4IVT BACE1; Figure S4. (a) **A1** docked in 2BEG Aβ; (b) **A4** docked in 2BEG Aβ; (c) **B1** docked in 2BEG Aβ;(d) **C1** docked in 2BEG Aβ; Figure S5. FT-IR spectra for compound **A1**; Table S4. Different FT-IR peaks of compound **A1**; Figure S6. FT-IR spectra of compound **A4**; Table S5. Different FT-IR peaks of compound **A4**; Figure S7. FT-IR spectra of compound **B1**; Table S6. Different FT-IR peaks of compound **B1**; Figure S8. FT-IR spectra of compound **C1**; Table S7. Different FT-IR peaks of compound **C1**; Figure S9. $^{1}$H NMR spectra of compound **A1**; Figure S10. Different $^{1}$H NMR peaks of compound **A4**; Figure S11. $^{1}$H NMR spectra of compound **B1**; Figure S12. $^{1}$H NMR spectra of compound **C1**.

**Author Contributions:** Conceptualization, A.A., A.M. and U.V.; methodology, A.A. and U.V.; software, A.A.; validation, A.A., A.M. and U.V.; formal analysis, A.M.; resources, A.M.; data curation, A.A. and U.V.; writing—original draft preparation, A.A.; writing—review and editing, A.A. and A.M.; supervision, A.M. All authors have read and agreed to the published version of the manuscript.

**Funding:** This research received no external funding.

**Institutional Review Board Statement:** Not applicable.

**Informed Consent Statement:** Not applicable.

**Data Availability Statement:** The original contributions presented in this study are included in the article. Further inquiries can be directed to the corresponding author.

**Acknowledgments:** Authors greatly acknowledge the Department of Pharmacy, Guru Ghasidas Vishwavidyalaya, for extending their support in providing the lab facility to conduct this research work.

**Conflicts of Interest:** The authors declare no conflict of interest.

## Abbreviations

The following abbreviations are used in this manuscript:

| | |
|---|---|
| AD | Alzheimer's Disease |
| MTDLs | Multi-Target-Directed Ligands |
| AChE | Acetylcholinesterase |
| BChE | Butyrylcholinesterase |
| BACE1 | Beta Secretase 1 |
| Aβ | Amyloid β-Proteins |
| TLC | Thin-Layer Chromatography |
| FT-IR | Fourier-Transform Infrared Spectroscopy |
| 1H NMR | Proton Nuclear Magnetic Resonance |
| MW | Molecular Weight |
| HBD | Hydrogen Bond Donor |
| HBA | Hydrogen Bond Acceptor |
| TPSA | Total Polar Surface Area |
| BBB | Blood–Brain Barrier Permeability |
| HIA | Human Intestinal Absorption |
| PAS | Peripheral Anionic Site |

| | |
|---|---|
| CAS | Catalytic Active Site |
| CNS | Central Nervous System |
| P-gp | P-glycoprotein |
| SA | Synthetic Accessibility |

## References


1. Gavade, S.; Dubey, S.; Tiwari, P. Benzimidazole derivatives in Alzheimer's therapy: Exploring multi-target pathways. *Curr. Protein Pept. Sci.* **2026**, *27*, 546–563. [CrossRef] [PubMed]
2. Hossain, M.S.; Hussain, M.H. Multi-target drug design in Alzheimer's disease treatment: Emerging technologies, advantages, challenges, and limitations. *Pharmacol. Res. Perspect.* **2025**, *13*, e70131. [CrossRef] [PubMed]
3. Almaghrabi, M. Multitarget-directed ligands for Alzheimer's disease: Recent novel MTDLs and mechanistic insights. *Pharmaceuticals* **2025**, *18*, 1685. [CrossRef] [PubMed]
4. Tahlan, S.; Kumar, S.; Narasimhan, B. Pharmacological significance of heterocyclic 1H-benzimidazole scaffolds: A review. *BMC Chem.* **2019**, *13*, 101. [CrossRef] [PubMed]
5. Drozdowska, D.; Maliszewski, D.; Wróbel, A.; Ratkiewicz, A.; Sienkiewicz, M. New benzamides as multi-targeted compounds: A study on synthesis, AChE and BACE1 inhibitory activity and molecular docking. *Int. J. Mol. Sci.* **2023**, *24*, 14901. [CrossRef] [PubMed]
6. Chaves, S.; Resta, S.; Rinaldo, F.; Costa, M.; Josselin, R.; Gwizdala, K.; Piemontese, L.; Capriati, V.; Pereira-Santos, A.R.; Cardoso, S.M.; et al. Design, synthesis, and in vitro evaluation of hydroxybenzimidazole-donepezil analogues as multitarget-directed ligands for the treatment of Alzheimer's disease. *Molecules* **2020**, *25*, 985. [CrossRef] [PubMed]
7. Spatz, P.; Zimmermann, T.; Steinmüller, S.; Hofmann, J.; Maurice, T.; Decker, M. Novel benzimidazole-based pseudo-irreversible butyrylcholinesterase inhibitors with neuroprotective activity in an Alzheimer's disease mouse model. *RSC Med. Chem.* **2022**, *13*, 944–954. [CrossRef] [PubMed]
8. Pajouhesh, H.; Lenz, G.R. Medicinal chemical properties of successful central nervous system drugs. *NeuroRx* **2005**, *2*, 541–553. [CrossRef] [PubMed]
9. Du, C.; Wang, L.; Guan, Q.; Yang, H.; Chen, T.; Liu, Y.; Li, Q.; Lyu, W.; Lu, X.; Chen, Y.; et al. N-benzyl benzamide derivatives as selective sub-nanomolar butyrylcholinesterase inhibitors for possible treatment in advanced Alzheimer's disease. *J. Med. Chem.* **2022**, *65*, 11365–11387. [CrossRef] [PubMed]
10. Itoh, S.G.; Okumura, H. Promotion and inhibition of amyloid-β peptide aggregation: Molecular dynamics studies. *Int. J. Mol. Sci.* **2021**, *22*, 1859. [CrossRef] [PubMed]
11. Rosales Hernández, M.C.; Olvera-Valdez, M.; Velazquez Toledano, J.; Mendieta Wejebe, J.E.; Fragoso Morales, L.G.; Cruz, A. Exploring the benzazoles derivatives as pharmacophores for AChE, BACE1, and as anti-Aβ aggregation to find multitarget compounds against Alzheimer's disease. *Molecules* **2024**, *29*, 4780. [CrossRef] [PubMed]


**Disclaimer/Publisher's Note:** The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.