Full Length Research Article
Advancements in Life Sciences – International Quarterly Journal of Biological Sciences

ARTICLE INFO

Date Received: 24/08/2023;
Date Revised: 30/07/2024;
Available Online: 31/08/2025;

Author's Affiliation:
1. Department of Pathology and Laboratory Medicine, Security Forces Hospital Program, Riyadh - Saudi Arabia
2. College of Medicine, Alfaisal University, Riyadh - Saudi Arabia
3. Department of Family and Community Medicine, College of Medicine, King Saud University (KSU), Riyadh - Saudi Arabia
4. University Family Medicine Center, King Saud University Medical City, King Saud University, Riyadh - Saudi Arabia
5. Department of Clinical Laboratory Sciences, College of Applied Medical Sciences, Taif University – Saudi Arabia
6. Department of Life Sciences, School of Natural Sciences, Shiv Nadar Institution of Eminence Deemed to be University, NH91, Tehsil Dadri, Gautam Buddha Nagar, Uttar Pradesh - India

***Corresponding Author:**
Farah Anjum
Email: f2023anjum@gmail.com

How to Cite:
Hazazi A, Alshehri NA, Bakhuraysah M, Alsaeedi FA, Alharthi A, Ahamed A, Abu Dahsh SA, Albayadh M, Anjum F (2025). Identification of Novel Natural BACE1 Inhibitors for Alzheimer's Disease via *In Silico* Approach Adv. Life Sci. 12(2): 384-388.

Keywords:
Alzheimer's Disease; Amyloid Beta; Beta-Secretase 1; Natural Compounds

Open Access

Identification of Novel Natural BACE1 Inhibitors for Alzheimer's Disease via *In Silico* Approach

Ali Hazazi[1,2], Norah Ali Alshehri[3,4], Maha Bakhuraysah[5], Fouzeyyah Ali Alsaeedi[5], Afaf Alharthi[5], Aaliya Ahamed[6], Sarh Ali Abu Dahsh[1], Mohammed Albayadh[1], Farah Anjum[5*]

Abstract

Background: Alzheimer's disease (AD) is a neurological ailment that causes progressive memory loss as neurons die. Beta-secretase 1 (BACE1) is a key enzyme in the production of amyloid beta, which is a characteristic of Alzheimer's disease. Developing new BACE1 inhibitors with no cytotoxicity is a promising method to treat AD.

Methods: The goal of this study was to find new BACE1 inhibitors by screening natural compounds in the ZINC database against the BACE1 active site. The compounds were screened against BACE1 using the PyRx 0.8 program. The SwissADME web server was used to determine the ADMET properties of hit compounds.

Results: The hit compounds ZINC3875408, ZINC4098603, ZINC95561079, ZINC299817515, and ZINC67903362 exhibited higher binding affinities to BACE1 than the control compound AZD3293. The Asp32, Lys224, Tyr198, Thr329, Ile226, Val332, Arg128, Tyr71, Phe108, Lys107, Gly74, Gly13, Gly11, Gln12, Ile110, Trp115, Leu30, and Gly230 were the important binding residues of BACE1 protein with these compounds as well as the control compound. These compounds also have good drug-like qualities.

Conclusion: The compounds ZINC3875408, ZINC4098603, ZINC95561079, ZINC299817515, and ZINC67903362 can be used as BACE1 inhibitors to manage AD. However, experimental validation is needed to optimize these compounds as BACE1 inhibitors.

Introduction

Alzheimer's disease (AD) is a neurological ailment that causes gradual memory loss due to substantial neuron cell death [1]. This situation is irreversible because injured neurons cannot regrow [2]. The chance of getting AD grows with age. AD affects around 50 million individuals worldwide and it is expected that this figure will double every five years [3].

Although the cause of AD is uncertain, several hypotheses have been proposed [4]. These include loss of cholinergic neurotransmission, Aβ plaque deposition, hyperphosphorylated tau protein buildup, and increased oxidative stress [5]. In AD, neurons responsible for acetylcholine synthesis are damaged and lost [6], resulting in diminished production of this neurotransmitter and impaired communication between neuronal cells [7]. Two important hypotheses have been offered to explain these pathophysiological effects: the Cholinergic theory and the Amyloid hypothesis [8]. The Amyloid hypothesis suggests that extracellular clumps of Aβ peptides trigger the pathogenic cascade that leads to neuronal cell death in AD. BACE-1, an enzyme in the amyloidogenic signaling pathway, is crucial for the brain's production of neurotoxic Aβ peptides. Targeting BACE-1 can lower Aβ synthesis and β-secretase activity [9].

The discovery and development of new medications is a time-cosuming and costly process. Computer-aided drug discovery (CADD) enhances this workflow, particularly through virtual screening (VS) approaches, by expanding the pool of possible medications [10]. CADD, which combines computational and theoretical techniques, discovers potential agents that target certain proteins or receptors. Several authorized drugs were developed utilizing CADD [11]. CADD also predicts pharmacokinetics, drug-like characteristics, and toxicity of substances [12].

Methods

Protein preparation

The Protein Data Bank was used to obtain crystal structure of BACE1 (PDB ID: 2ZHV). The protein was prepared using Discovery studio (DS) visualizer 2021 and saved in .pdb form.

Ligand preparation

Natural compounds (N=300) were retrieved from the ZINC database, which was downloaded in .sdf format. Furthermore, these compounds were minimized and prepared for screening utilizing DS 2021's 'ligand preparation' tool.

Virtual screening

The PyRx 0.8 program [13] was used to screen the prepared compounds and determine the binding mechanism between the compounds and the BACE1 protein. PyRx is an open-source virtual screening program that is used to screen libraries of compounds against the target protein in CADD techniques. The compound-BACE1 complex with the highest negative binding affinity values was chosen for further study, and the binding interactions were then examined.

Physiochemical properties

The SwissADME web server was used to determine the physicochemical properties of the hit compounds [14]. The parameters evaluated included physicochemical properties, water solubility, pharmacokinetics, and Lipinski's rule of five.

Results

In this study, natural compounds from ZINC database have been screened against the catalytic site of BACE1 protein. Among them, 18 compounds or hits were found to exhibit stronger interaction with BACE1 protein than the control compound AZD3293 (Table 1). The top 5 hits (ZINC3875408, ZINC4098603, ZINC95561079, ZINC299817515, and ZINC67903362) were selected for in-depth analysis based on their binding affinity values as well as interaction with key residues of BACE1 protein.

S. No.	Compounds	Binding affinity (kcal/mol)
1.	ZINC3875408	-9.9
2.	ZINC4098603	-9.9
3.	ZINC95561079	-9.8
4.	ZINC299817515	-9.5
5.	ZINC67903362	-9.4
6.	ZINC256374349	-9.1
7.	ZINC257402882	-9.0
8.	ZINC256374343	-8.8
9.	ZINC257402881	-8.7
10.	ZINC43552595	-8.6
11.	ZINC97971596	-8.6
12.	ZINC139712128	-8.5
13.	ZINC238774737	-8.4
14.	ZINC253527818	-8.3
15.	ZINC253527821	-8.2
16.	ZINC253527823	-8.1
17.	ZINC253527824	-8.1
18.	ZINC584908972	-8.0
19.	AZD3293 (Control compound)	-7.9

Table 1: Binding affinity of top hit compounds having higher affinity than the control compound.

The top five compounds (ZINC3875408, ZINC4098603, ZINC95561079, ZINC299817515, and ZINC67903362) were superimposed to show that they share the same binding pocket on the BACE1 protein as the control compound, AZD3293 (Figure 1).

ZINC3875408 interacted with Gly11, Gln12, Gly13, Leu30, Asp32, Gly34, Ser35, Tyr71, Thr72, Gln73, Gly74, Lys107, Phe108, Ile110, Trp115, Ile118, Tyr198, Ile226, Asp228, Thr231, Thr232, Arg235, and Val332 residues of BACE1 (Figure 2A); while Gln12, Leu30, Asp32, Gly34, Ser35, Tyr71, Ile110, Phe108, Lys107, Trp115, Ile118, Ile226, Asp228, Gly230, Thr231, Thr232, Arg235, Lys224, Tyr198, Thr329, and Val332

residues were found to bind with ZINC4098603 (Figure 2B).

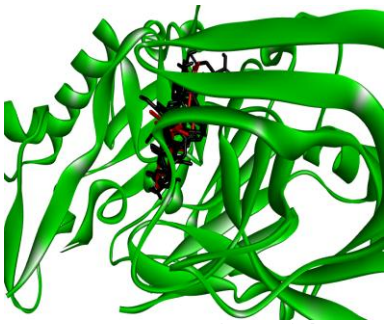

Figure 1: Superimpose view of top 5 hits ZINC3875408, ZINC4098603, ZINC95561079, ZINC299817515, and ZINC67903362 along with control AZD3293 (red) in the BACE1 active site. The 5 hits are shown in black color.

ZINC95561079 was observed to interact with Gly11, Gly13, Gln12, Leu30, Asp32, Gly34, Ser35, Tyr71, Ile110, Lys107, Phe108, Trp115, Ile118, Arg128, Tyr198, Gly230, Thr231, Thr232, Arg235, and Thr329 residues of BACE1 (Figure 2C). ZINC299817515 interacted with Asp32, Tyr71, Thr72, Gln73, Gly74, Lys75, Asp106, Lys107, Phe108, Ile110, Trp115, Ile118, Asp228, Gly230, Thr231, andArg235 residues of BACE1 (Figure 2D). In addition, ZINC67903362 binds with Gly11, Gly13, Gln12, Leu30, Asp32, Gly34, Ser35, Tyr71, Phe108, Ile110, Trp115, Ile118, Tyr198, Lys224, Ile226, Asp228, Gly230, Thr231, Thr232, Arg235, Thr329, and Val332 residues of BACE1 (Figure 2E). Furthermore, the control AZD3293 binds with Gly11, Gly13, Gln12, Leu30, Asp32, Tyr71, Gly74, Trp76, Lys107, Phe108, Ile110, Trp115, Arg128, Tyr198, Lys224, Ile226, Gly230, Thr329, and Val332 residues of BACE1 (Figure 2F).

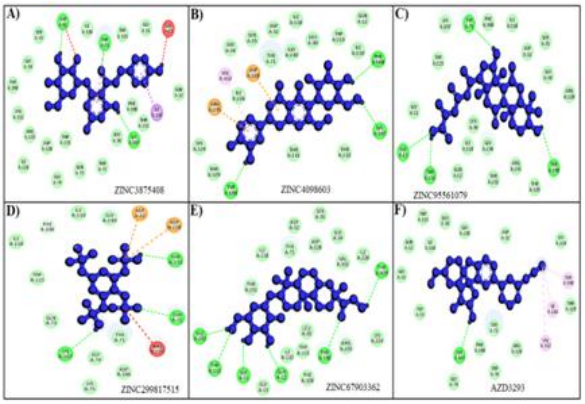

Figure 2: Interacting residues of BACE1 with ZINC3875408 (A), ZINC4098603 (B), ZINC95561079 (C), ZINC299817515 (D), ZINC67903362 (E), and AZD3293 (F).

A thorough examination of the physicochemical properties and adherence to drug-like criteria of the hits (ZINC3875408, ZINC4098603, ZINC95561079, ZINC299817515, and ZINC67903362) showed that they possess nearly essential characteristics required for their potential as future drug candidates (Tables 2).

Property	Model Name		Predicted Value				
			ZINC3875408	ZINC4098603	ZINC95561079	ZINC299817515	ZINC67903362
Physico-chemical Properties	MW (g/mol)		436.41	462.40	518.68	468.08	484.62
	HBA		10	11	7	18	8
	HBD		7	7	4	8	6
	TPSA (Å²)		177.14	190.28	132.13	306.28	139.84
Estimated Solubility	Log S		-2.71	-2.92	-4.23	-1.65	-3.53
	Solubility (mol/l)		1.95e-03	1.22e-03	5.82e-05	4.51e+01	2.96e-04
	Class		Soluble	Soluble	Moderately soluble	Soluble	Soluble
Pharmaco-kinetics	GI absorption		Low	Low	Low	Low	High
	BBB permeant		No	No	No	No	No
	log Kp (cm/s)		-8.58	-8.99	-7.69	-13.51	-8.11
Drug likeness	Number of violations	Lipinski	1	2	1	2	1
		Ghose	0	0	3	1	2
		Veber	1	1	0	1	0
		Egan	1	1	1	1	1
		Muegge	2	3	0	4	1

Table 2: Drug-like properties of top 5 hit compounds ZINC3875408, ZINC4098603, ZINC95561079, ZINC299817515, and ZINC67903362.

Discussion

The BACE1 is a crucial target for developing AD therapeutics [15]. AD-related Aβ accumulation and oxidative stress cause lipid bilayer weakening. Thin bilayers may enhance Aβ aggregation, while lipid oxidation can contribute to Aβ misfolding [16]. Aβ peptide aggregation causes cellular toxicity through the development of polymorphic oligomers, protofibrils, and fibrils [17,18]. Developing novel BACE1 inhibitors with low cytotoxicity is a promising approach to treating AD. This study screened natural compounds against BACE1 to find safe, non-toxic inhibitors. The top five compounds, ZINC3875408, ZINC4098603, ZINC95561079, ZINC299817515, and ZINC67903362 bind strongly to BACE1 protein and have favorable drug-like properties.

The H-bond is important for the stability of the ligand's binding to the target protein. Interestingly, the top five compounds (ZINC3875408, ZINC4098603, ZINC95561079, ZINC299817515, and ZINC67903362) form multiple H-bonds with the amino acid residues of BACE1. The Lys107 residue was the most frequently interacting H-bond with ZINC3875408, ZINC4098603, ZINC299817515, and the control AZD3293. ZINC95561079 formed H bonds with the Tyr71, Tyr198, Thr232, and Gly13 residues of the BACE1 protein. Furthermore, ZINC67903362 formed H bonds with the Thr329, Tyr198, Gln12, Gly11, Thr232, and Gly230 residues of the BACE1 protein.

AZD3293 is an oral inhibitor for AD that blocks Aβ deposition, potentially reducing or eliminating symptoms [19]. Phase I and II clinical investigations show that it has great therapeutic potential. Unlike first-generation BACE1 inhibitors, which had difficulty penetrating the blood-brain barrier (BBB) [20,21], AZD3293 penetrates the BBB effectively in humans [19]. In this study, BACE1 residues Asp32, Lys224, Tyr198, Thr329, Ile226, Val332, Arg128, Tyr71, Phe108, Lys107, Gly74, Gly13, Gly11, Gln12, Ile110, Trp115,

Leu30, and Gly230 interacted with AZD3293. Interestingly, the identified hits (ZINC3875408, ZINC4098603, ZINC95561079, ZINC299817515, and ZINC67903362) were also found to bind with these BACE1 residues, implying that these compounds bind to the same pocket as AZD3293.

The intensity of a ligand's binding to its target protein is measured in terms of binding affinity values, with a high (negative) value indicating efficient binding [22,23]. Notably, the identified hits (ZINC3875408, ZINC4098603, ZINC95561079, ZINC299817515, and ZINC67903362) had higher binding affinity values than the control (AZD3293), indicating that these compounds bind strongly and tightly to the BACE1 protein, and can be used as BACE1 inhibitors to manage the AD.

BACE1 is a key enzyme in the production of Aβ, which is a hallmark of AD. This study screened the natural compounds from the ZINC database to the BACE1 active site. The hit compounds ZINC3875408, ZINC4098603, ZINC95561079, ZINC299817515, and ZINC67903362 had high binding affinities for the BACE1 protein. BACE1 protein's key binding residues with these hit compounds and the control compound were Asp32, Lys224, Tyr198, Thr329, Ile226, Val332, Arg128, Tyr71, Trp76, Phe108, Lys107, Gly74, Gly13, Gly11, Gln12, Ile110, Trp115, Leu30, and Gly230. These compounds may be used as BACE1 inhibitors to treat AD.

Author Contributions

Conceptualization, Ali Hazazi, Farah Anjum, Norah Ali Alshehri and Mohammed Albayadh; Formal Analysis, Ali Hazazi, Farah Anjum, Fouzeyyah Ali Alsaeedi and Sarh Ali Abu Dahsh; Methodology, Maha Bakhuraysah, Afaf Alharthi and Norah Ali Alshehri; Original Draft Preparation, Afaf Alharthi, Mohammed Albayadh, Sarh Ali Abu Dahsh and Farah Anjum; Review & Editing, Ali Hazazi, Maha Bakhuraysah, Fouzeyyah Ali Alsaeedi, Farah Anjum and Aaliya Ahamed. All authors read and approved the final manuscript.

Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

References

1. Peeri Alloul K, Sauriol L, Kennedy W, Laurier C, Tessier G, *et al.* Alzheimer's disease: a review of the disease, its epidemiology and economic impact. Archives of Gerontology and Geriatrics, (1998); 27(3): 189-221.
2. Crous-Bou M, Minguillón C, Gramunt N, Molinuevo JL. Alzheimer's disease prevention: from risk factors to early intervention. Alzheimer's Research & Therapy, (2017); 9(1): 71.
3. Breijyeh Z, Karaman R. Comprehensive review on Alzheimer's disease: causes and treatment. Molecules, (2020); 25(24): 5789.
4. Madnani RS. Alzheimer's disease: A mini-review for the clinician. Frontiers in Neurology, (2023); 14: 1178588.
5. Buccellato FR, D'Anca M, Fenoglio C, Scarpini E, Galimberti D. Role of oxidative damage in alzheimer's disease and neurodegeneration: From pathogenic mechanisms to biomarker discovery. Antioxidants, (2021); 10(9): 1353.
6. Pepeu G, Giovannini MG. The fate of the brain cholinergic neurons in neurodegenerative diseases. Brain Research, (2017); 1670: 173-184.
7. Vecchio I, Sorrentino L, Paoletti A, Marra R, Arbitrio M. The state of the art on acetylcholinesterase inhibitors in the treatment of Alzheimer's disease. Journal of Central Nervous System Disease, (2021); 13: 11795735211029113.
8. Ju Y, Tam KY. Pathological mechanisms and therapeutic strategies for Alzheimer's disease. Neural Regeneration Research, (2022); 17(3): 543-549.
9. Taylor HA, Przemylska L, Clavane EM, Meakin PJ. BACE1: More than just a beta-secretase. Obesity Reviews, (2022); 23(7): e13430.
10. Sabe VT, Ntombela T, Jhamba LA, Maguire GE, Govender T, *et al.* Current trends in computer aided drug design and a highlight of drugs discovered via computational techniques: A review. European Journal of Medicinal Chemistry, (2021); 224: 113705.
11. Yu W, MacKerell AD, Jr. Computer-Aided Drug Design Methods. Methods in Molecular Biology, (2017); 1520: 85-106.
12. Kalyaanamoorthy S, Chen YP. Structure-based drug design to augment hit discovery. Drug Discovery Today, (2011); 16(17-18): 831-839.
13. Dallakyan S, Olson AJ. Small-molecule library screening by docking with PyRx. Methods in Molecular Biology, (2014): 243-250.
14. Daina A, Michielin O, Zoete V. SwissADME: a free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. Scientific Reports, (2017); 7: 42717.
15. Huang HJ, Lee CC, Chen CY. In silico design of BACE1 inhibitor for Alzheimer's disease by traditional Chinese medicine. BioMed Research International, (2014); 2014: 741703.
16. Korshavn KJ, Satriano C, Lin Y, Zhang R, Dulchavsky M, *et al.* Reduced lipid bilayer thickness regulates the aggregation and cytotoxicity of amyloid-beta. Journal of Biological Chemistry, (2017); 292(11): 4638-4650.
17. Kotler SA, Walsh P, Brender JR, Ramamoorthy A. Differences between amyloid-beta aggregation in solution and on the membrane: insights into elucidation of the mechanistic details of Alzheimer's disease. Chemical Society Reviews Journal, (2014); 43(19): 6692-6700.
18. Rajasekhar K, Narayanaswamy N, Murugan NA, Kuang G, Agren H, Govindaraju T. A high affinity red fluorescence and colorimetric probe for amyloid beta aggregates. Scientific Reports, (2016); 6: 23668.
19. Cebers G, Alexander RC, Haeberlein SB, Han D, Goldwater R, *et al.* AZD3293: Pharmacokinetic and pharmacodynamic effects in healthy subjects and patients with Alzheimer's disease. Journal of Alzheimer's Disease, (2017); 55(3): 1039-1053.
20. Butini S, Brogi S, Novellino E, Campiani G, Ghosh AK, *et al.* The structural evolution of beta-secretase inhibitors: a focus on the development of small-molecule inhibitors. Current Topics in Medicinal Chemistry, (2013); 13(15): 1787-1807.
21. Oehlrich D, Prokopcova H, Gijsen HJ. The evolution of amidine-based brain penetrant BACE1 inhibitors. Bioorganic & Medicinal Chemistry Letters, (2014); 24(9): 2033-2045.

22. Meng XY, Zhang HX, Mezei M, Cui M. Molecular docking: a powerful approach for structure-based drug discovery. Current Computer-Aided Drug Design, (2011); 7(2): 146-157.
23. Shaikh S, Aaqil H, Rizvi SM, Shakil S, Abuzenadah AM, *et al*. Comparative inhibition study of compounds identified in the methanolic extract of Apamarga kshara against trichomonas vaginalis carbamate kinase (TVCK): an enzoinformatics approach. Interdisciplinary Sciences: Computational Life, (2016); 8(4): 357-365.