



Review Article

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BACE1 inhibitors: A promising therapeutic approach for the management of Alzheimer's disease

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ABSTRACT

Alzheimer's disease is a neurological disorder marked by the accumulation of amyloid beta (A β) aggregates, resulting from mutations in the amyloid precursor protein. The enzyme β -secretase, also known as β -site amyloid precursor protein cleaving enzyme 1 (BACE1), plays a crucial role in generating A β peptides. With no targeted therapy available for Alzheimer's disease, inhibiting BACE1 aspartic protease has emerged as a primary treatment target. Since 1999, compounds demonstrating potential binding to the BACE1 receptor have advanced to human trials. Structural optimization of synthetically derived compounds, coupled with computational approaches, has offered valuable insights for developing highly selective leads with drug-like properties. This review highlights pivotal studies on the design and development of BACE1 inhibitors as anti-Alzheimer's disease agents. It summarizes computational methods employed in facilitating drug discovery for potential BACE1 inhibitors and provides an update on their clinical status, indicating future directions for novel BACE1 inhibitors. The promising clinical results of Elenbecestat (E-2609) catalyze the development of effective, selective BACE1 inhibitors in the future.

KEYWORDS: BACE1 inhibitors; Amyloid precursor protein; β -secretase; Structure-based drug design; 3D-QSAR; β -amyloid precursor protein

1. Introduction

Alzheimer's disease (AD) is most commonly found in elderly patients. Alois Alzheimer first described the condition in the early years of 1906[1]. Neurological regions involved in the processing of information in the brain become dysfunctional as a result of the

disease's deleterious effect on the brain's nerve cells. The disease worsens as it causes symptoms similar to dementia, such as memory loss and muscle rigidity[2]. One consequence of the disease is the loss of synapses and neuronal death in the limbic and neocortex. The outcome of neurons dying gradually is fatal in the end[3]. With roughly 2.5-4 million cases in the U.S. and about 17-25 million worldwide, this terrible disease is the fourth leading cause of death in developed societies, behind heart attack, cancer, and stroke[4].

Since 1991, deaths with Alzheimer's disease as a primary cause have sharply increased[5]. Age-related increases in disease incidence rates are exponential, according to studies on global patterns of disease prevalence. According to the 'World Alzheimer Report 2016', the estimated financial burden of the illness has significantly increased for caregivers[6]. By 2030 and 2050, the number of patients is predicted to rise to 65.7 million and even 115.4 million[7].

2. Methodology

An overview of recent research on BACE1 inhibitor design and development as anti-Alzheimer drugs is presented using the scientific literature. The primary body of research that has been identified in

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this field initially concentrated on target exploration. A novel aspartic protease known as β -secretase or BACE1 was first discovered and reported by Hussain *et al.* in 1999. Afterward, BACE1 has emerged as the target of choice because it directly prevents the development of A β in the brain. In PubMed, the keyword search "BACE1" reveals an increase in interest in this target from 2010 to 2022.

The focus of the investigation and analysis was on the transition from peptides to small molecules as a therapeutic strategy, structural optimization, computational methods, and the clinical advancements of BACE1 inhibitors. It presents the structural details of scaffolds or active molecules that interact with the BACE1 target receptor. The crystal structure of the target protein, BACE1, is readily available from PDB (www.rcsb.org), which has aided in the development of drugs that target receptor levels.

The present review represents the selective inhibitors of BACE1 that were reported active through structurally derived or optimized molecules along with the computational-based actives with reported or predicted activity. The *in vivo/in vitro* studies on diverse molecules as potential leads exhibited that BACE1 inhibition was considered for analysis. The article highlights new methodologies in computer-aided drug design (CADD) to develop novel BACE1 inhibitors. It includes F fragment-based drug designing, binding mode studies of the receptor, molecular dynamics, docking simulation, quantitative structure-activity relationship (QSAR) model development, and pharmacophore modeling by ligand-based and structure-based drug design. Further, to identify the status of the BACE1 active molecules as future drugs, an update on clinical development is also covered.

3. Computational approach

Despite the identification of potent leads by structure-activity relationship exploration and structure optimization, the BACE1 selective clinical molecule with the desired pharmacokinetic profile and receptor binding has not been identified. Thus, the computational approaches were simultaneously explored to identify the key issues for rendering a clinical molecule to become

a bioavailable drug. The *in-silico* methodology offers far-reaching advantages in drug development. The physicochemical properties of the molecules with reported BACE1 inhibition were studied in designing the new molecules. The QSAR study for the relevance of descriptors by correlation vector method and similarity searching to identify hits was reported[8,9]. The QSAR-based regression models establish a correlation between the actual and estimated activity of the molecules for predicted new molecules with increased potency. The QSAR methodologies for drug design development also covered pharmacokinetic predictions[10]. The discovery of substrate-based BACE1 inhibitors OM99-2 and OM00-3 sparked the development of inhibitors that acted on BACE1[11,12]. These two inhibitors were co-crystallized with BACE1 (PDB ID: 3TTP)[13] and elucidating their manner of binding with the active binding pockets of the enzyme was essential for the design and development of other BACE1 inhibitors[14]. This section will highlight recent BACE1 inhibitors which are developed by CADD. The discovery of various BACE1 inhibitors including 5-fluoroorotyl moiety with peptides[15], bicyclic iminopyrimidinones[16], 5,5'-disubstituted aminohydantoin[17], iminopyrimidinones[18], and cyclic sulfone[19] was all made possible by the use of structure-based drug design. These studies developed potent BACE1 inhibitors using various steps including crystallography technique, molecular docking, synthesis, and *in vitro* testing. With the use of a *de novo* structure-based design, compound libraries were produced that were analyzed *in vitro* for the discovery of successful compounds, including BACE1 inhibitors derived from biphenylacetamide[20]. Similarly, the process of database screening demonstrated the significance of protonation of ligand[21] and the protonation states of Asp32/Asp228 catalytic dyad (Figure 1) in the identification of hit compounds[22].

Another CADD approach for the development of inhibitors without a target receptor or enzyme is a ligand-based drug design. In order to uncover prospective BACE1 inhibitors, hybrid structure-based virtual screening techniques integrating both structure-based drug design and ligand-based drug design were used due to the plethora of BACE1 crystal structures[23].

Structure-activity relationship models were developed using QSAR

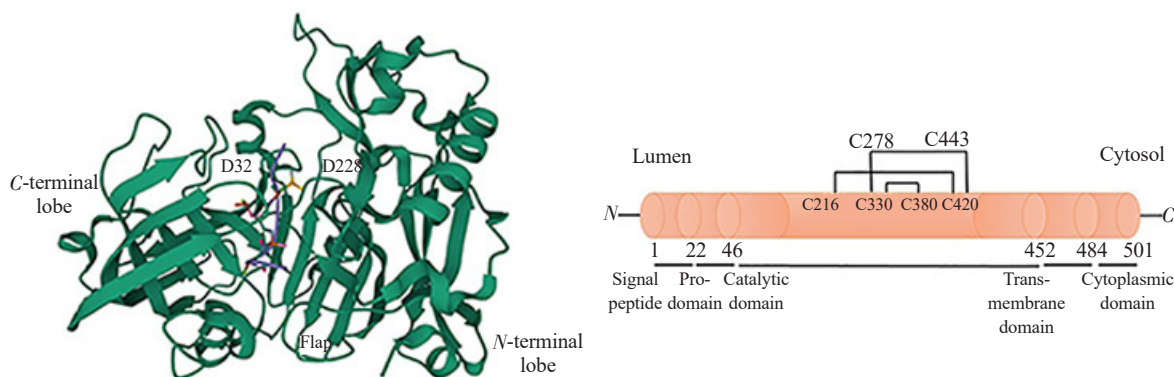


Figure 1. Overview of BACE1 structure and its catalytic mechanism on the substrate.

approaches to predict the binding affinities of putative BACE1 inhibitors[24]. The BACE1 enzyme exhibits a significant level of flexibility when inhibitors are present, resulting in conformational changes from an open to a closed state. To assess the inhibitory potential of structurally diverse compounds, molecular docking analysis-based models of QSAR have proven to be an effective technique for incorporating the receptor's flexibility[25].

Virtual screening, sophisticated molecular mechanics, pharmacophore modeling, and docking estimates of Born surface area were conducted to ascertain the potential of natural compounds as inhibitors of BACE1.

Then, using QSAR models, the anti-amyloidogenic activity of these compounds was assessed[26]. With the use of database screening, 3D-QSAR, and molecular dynamics simulations, researchers have developed natural low molecular weight compounds that interacted with the catalytic sites of the enzyme to inhibit the BACE1[27]. Flavanone glycosides hesperidin found in Citrus fruit was developed using a multi-target screening process (QSAR and molecular docking) and showed strong inhibition of the BACE1 enzyme and A β deposition[28]. Using a combination of machine learning, model hybridization, stepwise regression, and visual analytics approaches, QSAR classification models were developed to identify probable BACE1 inhibitors[29]. The molecular characteristics and BACE1 inhibitory effects of 5,5-disubstituted amino hydantoins were investigated using a predicted self-organizing molecular field analysis 3D-QSAR model (li2011). Other previously published reviews emphasize older ligand-based design studies[30].

BACE1 is a worthy target for molecular dynamic research because of its increased versatility, as demonstrated by numerous three-dimensional crystal structures of the enzyme both with and without co-crystallized inhibition in its active region[31]. BACE1 crystallizes in two different conformations at the flap with 10S, and loop with 113S active sites: both with and without an inhibitor (Figure 2). Molecular dynamic simulation demonstrated that the enzyme normally exhibits an open confirmation of the flap where there is no inhibitor at the binding cavities, but that interactions between both the inhibitor and the flap cause the enzyme to adopt a closed conformation. Researchers established the protonation state of the catalytic dyad by combining molecular docking and molecular dynamic simulations[32,33]. The inhibitor binding energies of a number of the therapeutic targets, including BACE1, were determined using another computational approach quantum mechanics/molecular mechanics techniques[34].

The selectivity of inhibition of BACE1 and BACE2 was assessed by combining molecular mechanics/generalized Born surface area calculations with a number of quick molecular dynamic simulations[35]. A new class of amidine-containing spirocyclic BACE1 inhibitors was successfully improved by the application of free energy perturbation[36]. Several proteolytic enzymes have exosites that separate other binding pockets from the catalytic active

site, where hydrolytic enzymatic activity occurs[37,38]. Exosite-bound allosteric modulators alter the stabilization or destabilization of the enzyme-substrate complex by boosting or lowering enzymatic activity[39]. Because of its wide catalytic site which prohibits successful blockage by tiny molecules capable of overcoming the barrier associated with the brain, BACE1 is a difficult target for the development of inhibitors.

Exosites, binding pockets different from the catalytic active site pockets, were discovered as a result of purposeful efforts to create novel BACE1 modulators[40,41]. Targeting BACE1's exosites in experiments showed that it is feasible to stop BACE1 from carrying out its enzyme-mediated activity[42,43].

CADD research included an analysis of binding interactions, simulations with molecular dynamics, and calculations of free binding energy, demonstrating that the Gly264, Asp311, Ala272, Ala313, Ser315, Glu255, Pro258, Phe261, and Asp317-Tyr320 residues were responsible for the active binding sites with the BACE1 exosite modulators[44].

The structure and functionality of the anti-BACE1 Fab fragment that can bind to the BACE1 exosite were deduced through molecular modeling and mutagenesis research[45]. This research uses computer simulation to explain how BACE1 exosite modulators might inhibit the enzyme allosterically. According to studies on binding free energy, the anti-BACE1 Fab fragment recognizes three loops, including residues 251-258, 270-273, and 311-317, as the functional epitope of BACE1. Finally, molecular dynamic simulations were combined with *ab initio* and density functional theory calculations to further analyze the interactions of short peptides acting as BACE1 modulators[46]. Glu163, Glu255, Lys256, Phe257, Pro258, Asp259, Gly260, Phe261, Trp262, Leu263, Gly264, Glu265, Gln266, Leu267, Val288, Cys269, Trp270, Gln271, Ala272, Gly273, Thr314, and Ser315 are essential exosite binding residues that these peptides interact with[46].

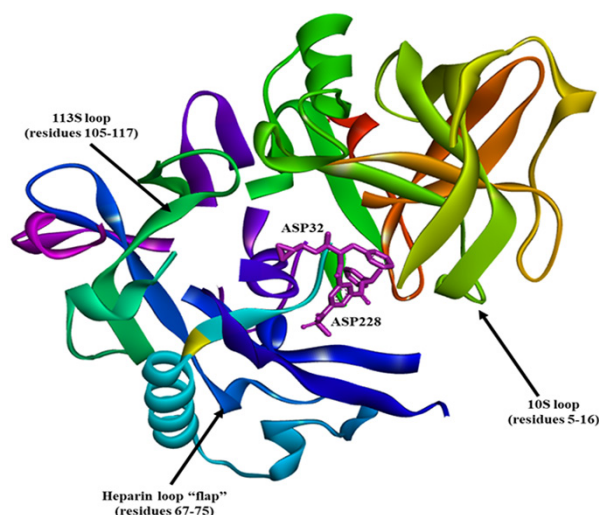


Figure 2. Flexibility loop surrounding the crystal structure of BACE1 (PDB ID: 3TTP).

4. Amyloid beta (A β) generation

Neuropathological studies have revealed the presence of abundant neuritic plaques as amyloid or senile plaques and also fibrous tangles in neurological areas of the brain. The plaques have a central core of A β , which plays a pivotal role in AD[47]. Accumulation of A β peptide ultimately causes pathological lesions in different areas of the brain. The other contributing factors are degeneration of cortical neurons, inflammation, and increased oxidative stress, resulting in neurogenesis and brain atrophy[48]. The disease is categorized based on its occurrence as familial AD and sporadic AD. The less-prevalent early-onset sporadic form of AD occurs in young individuals. At genetic levels, the missense mutation in gene encoding the β -amyloid precursor protein (APP) causes AD or familial AD. The inheritance of the $\epsilon 4$ allele of the apolipoprotein E type 4 (APOE-epsilon 4) is thought to be a contributing factor involved in the progression of AD in sporadic cases[49]. The studies also showed the significance of this protein in the late onset of familial AD. The production of amyloid beta is illustrated in Figure 3.

The primary factor associated with disease progression is the short and self-aggregating neurogenerative A β fragments. In the neurological areas, APP is guided by proteolysis and axonal transport of fragments. Ideally, these fragments are dissolved and released as metabolites in the non-pathological states. However, in pathological states, the α -secretase and γ -secretase initiate the non-amyloidogenic pathway by targeting mutated forms of APP[50]. The β -secretase, also known as BACE1, initiates the proteolysis of mutated APP from the *N*-terminus of the APP. The resulting fragments are the C99 for cleavage by other proteases bound with sAPP β in ectodomain

i.e. γ -secretase[51]. This is the ultimate step in generation of A β 42-40, which after aggregation produces plaques. The γ -secretase is then released into the lumen and extracellular spaces. In this APP processing, C59 is also released in intracellular domain. The K670N/M6712 (Swedish) mutation leads to an augmentation in β -secretase cleavage. The presence of a single amino acid mutation (A692G & E693Q) leads to an elevated synthesis of A β protein.

Endoproteolytic sequential cleavage of APP causes toxic oligomers to self-assemble and cause pathological lesions in the brain. Following this, the amyloid plaque load in the cortex and hippocampus region increases, resulting in neurotoxicity[52]. Neuritic or senile plaque is the buildup of A β -42 and A β -40 in certain regions of the brain. This accumulation serves as the foundation for the essential assumptions that support the theory.

The less diffused form frequently builds up close to the brain's blood vessels, resulting in angiopathy[53]. The statistical evidence indicates that there is a correlation between the severity of dementia and both A β -40 and A β -42.

5. BACE1

Neurons, oligodendrocytes, and astrocytes all contain the type 1 transmembrane aspartyl protease known as BACE1. Healthy synaptic terminals, the plasma endothelial membrane, and endosomal compartments have all been found to contain BACE1. The formation of A β requires the fragmentation of APP by BACE1, which is also thought to be the rate-limiting step in A β genesis[54,55].

The open frame of transcription in the cDNA for BACE1 encodes

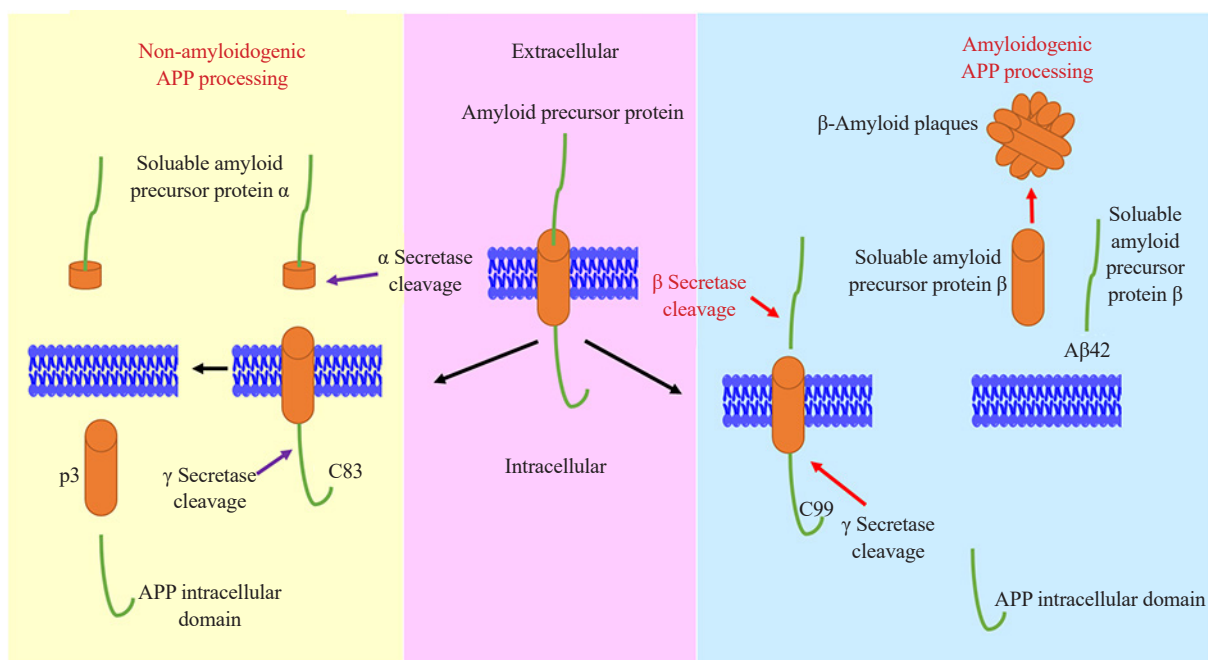


Figure 3. Generation of amyloid beta.

a long protein chain of 501 amino acid residues[56]. A β co-translationally cleaved signal peptide (residues 1-21), a brief pro-domain (residues 22-45), a large luminal catalytic domain (residues 46-451), and a single transmembrane domain which makes up the *N* to *C*-terminal sections of the BACE1 protein (residues 452-483).

BACE1 maturation necessitates the removal of the pro-domain, but the activity of the enzyme is not affected. According to the studies of Gao *et al.* and Mehta, total ablation of the pro-domain *in vitro* results in a threefold increase in the activity while disrupting the maturation does not affect A β accumulation *in vivo*. This suggests that maturation has little effect on the regulation of the enzyme's activity[57,58].

In the crystal structure of BACE1's catalytic site (PDB code: 1FKN), the two conserved aspartic acids D32 and D228 that make up the active site of BACE1 are located in a groove between two lobes that are protected by a flap (residues 69-74). Eight subsites make up the aspartic peptidase active site, which interacts with several substrate regions[59]. A peptidic substrate, especially the *N*-terminus, may make extra connections with BACE1's eleven subsites (S7 to S4'), which is noteworthy. The hydrolytic activity of V is significantly affected by the insertion of three residues in the substrate from P7 to P5, yet three matching subsites are seldom occupied by small molecule inhibitors[60].

When the inhibitor molecule comes into contact with the catalytic center (up to 4Å) and substitutes for the catalytic water molecule, the receptor is inhibited to varying degrees. Another type of inhibitor-receptor interaction is hydrogen bonding with the catalytic water molecule. Tyr71 amino acid residue at the tip of the flap forms hydrogen bonds with the substrate or inhibitor in a flap shut or sealed aspartic protease. The open state, on the other hand, is narrower than the closed position and is maintained by intra-flap hydrogen bonds and a hydrogen connection with Tyr71[61]. The open and closed forms of the enzyme are maintained by a side chain in BACE1 that forms hydrogen bonds with a flap and active site residues. BACE1's pro-domain does not seem to restrict activity as a strict zymogen would, but it does appear to aid in the appropriate folding of an active protease domain.

6. Preclinical studies of BACE1 inhibitors in AD

The discovery of BACE1 inhibitors has been the subject of active research for the past 12 years[62]. After some initial challenges, several groups developed potent organic molecules with various levels of selectivity for BACE1 and BACE2 and studied their pharmacology in AD murine models. Several drugs with excellent brain penetration were discovered to lower the levels of animal brain A β in a dose-dependent way. However, a very limited number of studies have shown that BACE1 inhibitors may restore or decrease memory and behavioral impairments in AD mouse models (Table

1). In one study, TAK-070, a non-competitive BACE1 inhibitor, was given orally to Tg2576 (18-week-old) transgenic mice for nine days[63]. These results provided a possible explanation for the high prevalence of BACE1 expression in the AD brain and supported the role of BACE1 inhibitors in the treatment of AD.

7. Clinical developments

The active inhibitors of BACE1 receptor with promising biological activity in *in vivo* and *in vitro* studies were evaluated for their effectiveness in human subjects[75,76]. The majority of active BACE1 inhibitors were retained as potential leads for further optimization to improve receptor binding and specificity. Among numerous scaffolds reported in previous chapters, only a few reached clinical trials. A clinical update on the status of ongoing studies and future molecules as BACE1 selective inhibitors is presented in Table 2. The global phase III trials on an imidazole derivative *i.e.* Lanabecestat (AZD3293/LY3314814) also discontinued due to lack of efficacy[77]. JNJ-54861911/Hansen was discontinued in 2015 by citing elevated liver enzymes in the Phase I study[78]. To study the undesirable side effects of clinical drugs, a bioanalysis study was performed to establish the fitness of a clinical candidate for human trials. The studies demonstrated a noticeable therapeutic impact on the A β peptide by analyzing human EDTA plasma at regular intervals during Phase I of the human trial for the P²-secretase inhibitor LY2811376[79].

However, further trials on the molecules from Eli Lilly & Co. *i.e.* LY2886721 and LY2811376 have been ended prematurely while progressing to phase II/III due to liver toxicity[80]. Also, the RG7129[81] from Roche and AZD-3839[82] from AstraZeneca turned out to be extremely challenging in Phase I, with major hurdles in oral bioavailability and hepatotoxicity. The oxazine-based molecule, NB-360[83] developed by Novartis has passed preclinical studies in APP-related cerebroarterial amyloidosis. The clinical efficacy of several BACE1 compounds presently undergoing clinical studies will be ascertainable by 2025.

Currently, thirteen clinical trials have been reported for a small molecule Elenbecestat (E-2609)[84]. The clinical trials were funded by Biogen and Eisai Co., Ltd., in which the molecule is responding well in Phase III. Yet another molecule from Eli Lilly & Co *i.e.* LY3202626 is in Phase II of clinical trials in combination with LY3002813[85].

8. Selectivity and toxicity of BACE1 inhibitor

About 40 known BACE1 substrates and BACE1 inhibitors were developed which might block or inhibit one or more neurodegenerative pathological processes. Axon development and

Table 1. Preclinical studies of BACE1 in Alzheimer's disease.

Species	Compound	Dose	Key results	References
C57BL6 and WT mice (Male)	N-[3-[(4S,6S)-2-amino-5,6-dihydro-4-methyl-6-(trifluoromethyl)-4H-1,3-oxazin-4-yl]-4-fluorophenyl]-5-cyano-2-pyridine carboxamide	30 mg/kg/day orally for 4 weeks	Chronic treatment with BACE1 inhibitor improves the cognition and learning process and also increases the hyperactivity in transgenic mice	[64]
PS2APP-Swe (TG) and C57BL/6 (WT) mice (Female)	RO5508887	100 mg/kg/day orally for 10 weeks	After treatment with a BACE1 inhibitor, amyloidosis progression is more successfully controlled in areas with modest initial plaque formation, highlighting the need for early therapy beginning during amyloidogenesis	[65]
C57BL6 mice (Male)	NB-360	13 mg/kg orally for 4 weeks	Due to NB-360's potent brain penetration, reasonable oral doses are sufficient to completely prevent amyloid production in an APP transgenic mouse model	[66]
APP23xPS45 mice (Male)	NB-360	0.25 g/kg in food pallet for 6 weeks	Inhibition of BACE1 reduces the A β plaques and rescues the hyperactivity of neurons	[67]
C57BL/6 mice (Male)	AZ-4217	12 mg/kg orally for 4 weeks	Decreases the A β and deposition of amyloid	[68]
Hemizygous APPV717F transgenic mice (Female)	LY2886721	10 mL/kg, orally	LY2886721 exhibits remarkable selectivity against critical off-target proteases, translating <i>in vitro</i> action into significant <i>in vivo</i> amyloid reduction in nonclinical animal models	[69]
APP Tg mice (Male)	Minocycline	50 mg/kg/day orally for 3 weeks	Pharmacological modulation of neuroinflammation through BACE1 inhibition might be a viable technique for avoiding or delaying the development of Alzheimer's disease neuropathology in its early, pre-clinical phases	[70]
5XFAD mice, Presenilin 1 (M146L and L286V)	GRL-8234	33.4 mg/kg, <i>i.p.</i> once daily for 28 days	Reverse pretty much entirely back to wild-type control levels	[71]
Tg2576 mice (Male)	TAK-070	7 mg/kg/day, <i>p.o.</i> , for 6 months	Chronic therapy reduces A β deposition in the brain by 60% while maintaining pharmacological effectiveness on soluble A β and sAPP α levels	[72]
Wistar rats (Male)	Nicotine	1 mg/kg <i>b.i.d.</i> , <i>s.c.</i> for 6 weeks	Nicotine elevates the level of BACE1 and suppresses the level of nAChR which are the essential hallmarks of Alzheimer's disease, contributing to the evidence that the A β <i>i.c.v.</i> -infused rat as a model of Alzheimer's disease	[73]
Tg2576 mice (Male)	BACE1 inhibitor	0.3-23.5 μ g/day, <i>i.c.v.</i> for 8 weeks	Treatment with BACE1 inhibitor activates microglia, reverses brain amyloid pathology, and elicits functional improvement	[74]

A β : amyloid beta, *b.i.d.*: bis in die, *i.c.v.*: intracerebroventricular, *p.o.*: per os, APP: amyloid protein precursor, nAChR: nicotinic acetylcholine receptor.

pathfinding, astrogenesis, neuroplasticity, hyperexcitation, and synaptogenesis are just a few of the processes in which BACE1 is involved[93,94]. The effects of BACE1 inhibitors on the processing of BACE1's substrates may obscure a potential cognitive gain.

Three potential suspects have been identified: seizure protein 6, a closely related homolog of L1, and neuregulin-1[95]. Multiple investigations on animals lacking BACE1 and BACE2 have revealed that these two proteases significantly influence various physiological substrates and functions, both inside and beyond the nervous system.

While BACE1 is involved in synapse formation, synaptogenesis, muscle spindle formation, and neuromorphic activities, BACE2 is involved in discoloration and function related to the pancreatic β -cells[96]. It is interesting to note that long-term BACE1 inhibitor therapy has been shown to negatively impact cognition, hippocampus long-term potentiation, spine development, and bone density in wild-type mice[97].

Although it is unclear if APP-selectivity is possible, a BACE1 inhibitor that avoids substrates other than APP would be the best

Table 2. Clinical studies of BACE1 inhibitors in Alzheimer's disease.

Phase	Number of subjects	Compound	Dose	Key results	References
Phase III	1454	APECS (verubecestat)	40 mg/day, twice daily orally for 104 weeks	Verubecestat shows worsening CCS-3D total score, episodic memory, and attention/processing speed domains. It was discontinued.	[86]
Phase III	2218	AMARANTH (lanabecestat)	50 mg/day, <i>b.d.</i> orally for 104 weeks	Lanabecestat shows worsening RBANS total score, immediate memory, and visuospatial/constructional indexes. It was discontinued.	[87]
EARLY Phase 2b/3 clinical trial	56	JNJ-54861911	12 mg/mL oral suspension	EARLY trial was discontinued due to significant elevation of liver enzymes, and subsequent analysis of the clinical outcomes shows dose-related cognitive worsening	[88]
Phase I	1041	LY2811376	30 mg single oral dose	It shows a clear treatment effect on amyloid- β peptide	[89]
Phase II	40	LY2886721	35 mg, <i>p.o.</i> for 42 days	In Phase II trials, a study was suspended due to the occurrence of liver toxicity	[90]
Phase II	2212	Elenbecestat	50 mg oral once a day	Elenbecestat shows acceptable tolerability across all doses, with headache and dizziness as the most common adverse events	[91]
Phase II	125	Umibecestat (CNP520)	15 mg or 50 mg for 13 weeks	It is safe and well tolerated and results in robust and dose-dependent A β reduction in the cerebrospinal fluid	[92]

option. The therapeutic importance of APP-specificity for BACE1 inhibitors is uncertain. Extended studies with umibecestat in animal models revealed a harmful effect observed in elderly patients and hereditary BACE1 knockout mice, which are believed to be responsible for the detrimental cognitive effects of BACE1 inhibitors in individuals with AD.

After six months of therapy, doses up to 200 mg/kg/day (ten times the highest dosage used in people) considerably lowered brain A β levels but did not affect the quantity and structure of mossy fibers in the hippocampus[98]. Furthermore, umibecestat has a threefold affinity for BACE1 compared to BACE2[99]. Despite its pharmacological and biochemical specificity, umibecestat was shown to exacerbate cognitive impairment in individuals at risk for AD (APOE4 carriers aged 60 to 75 years) as compared to placebo in the formation of APP and prevention of secondary investigations. This might imply that cognitive impairment resulting from BACE1 inhibitors is caused by a drop in brain A β levels rather than particular hippocampal toxicity or selectivity compared with BACE2.

9. Expert opinion

The use of BACE1 inhibitors, a type of anti-A β medication, was discontinued due to the persistent memory impairment and clinical deterioration shown in patients of AD, particularly those who were in

the early stages. The evidence does not support the defense's claim that low-dose BACE1 inhibitors could benefit in the early stages of AD[99]. In a significant trial (EARLY), Atabecestat was examined in healthy patients at risk for AD at low and high dosages of 5 and 25 mg/day, respectively[100]. However, the research was stopped early because the medication worsened cognitive function compared to a placebo.

Given that these long-term trials used cognitively healthy individuals, who are predicted to experience cognitive loss at a relatively gradual pace, the early termination of these studies is particularly noteworthy. It should be noted that participants in Generation Study 1 did not necessarily need to have high amounts of A β plaques in their brains. This shows that BACE1 inhibitors may harm cognition even in the very early stages of the illness (AD) when there is not yet any sign of brain A β deposition. Based on the results of a modest Phase 2 study involving 70 patients with mild-to-moderate AD, researchers thought that the unexpected withdrawal of elenbecestat, the last BACE1 inhibitor still in late-stage clinical development, was predictable. In reality, nightmares were a prevalent adverse effect of elenbecestat, and 22 of the 53 patients (42% of them) were unable to finish the study[101].

There was no reason to anticipate that elenbecestat would be any different from the other BACE1 inhibitors that have been clinically tested. Fascinatingly, LY3202626, a pyrimidine carboxamide that was also abandoned due to subpar clinical results, has a chemical

structure that is strikingly similar to that of elenbecestat (Table 2). Clinical trials for the potent monoclonal antibodies (aducanumab and crenezumab) that specifically target A β -oligomers have consistently failed for BACE1 inhibitors and various other anti-A β medicines, highlighting the fallacy of the A β -oligomers idea. Researchers are aware that any challenge to the A β -cascade theory of AD must offer additional rationalizations for the association between genetic variations in the PSEN and APP genes and the prevalence of autosomal dominant AD, even though sporadic AD may have different pathophysiology from familial AD. It is widely acknowledged that mutations in PSEN and APP genes cause a gain of function in familial AD. Furthermore, a thorough analysis revealed that 90% of the 138 pathogenic PSEN1 mutations had decreased A β 1-42/ A β 1-40 production[102]. Several genetic abnormalities in the APP gene can induce total A β levels to either rise or fall. While the A β 1-42/ A β 1-40 ratio developed by variants of APP including E22G, E22K, and E22Q is less than those produced by wild-type APP, those generated by configurations A2V, H6R, and D7N are comparable[103].

According to the latest report, both mutations (APP and PSEN-1) reduced the production of A β , but the effects on β -fragments of the APP-C terminal, which managed to accumulate in all mutant neurons, were similar. In another study, APP and/or PSEN-1 mutations carrying human-induced pluripotent stem cell lines were employed in this investigation along with a broad panel of orthologous knock. A β was not associated with β -CTF accumulation or endosomal disruption[104]. Studies now being conducted, particularly those looking at the antibodies in pre-symptomatic carriers of pathogenic APP or PSEN-1 mutations, will help to establish the A β hypothesis in autosomal dominant familial AD.

The intricacy of the disease's pathophysiological processes and our poor knowledge of the connections between the many regulatory mechanisms in AD development and subsequent neurodegeneration may be to blame for the high rate of failure for anti-AD therapy. It has been proposed that modifying just one potentially harmful path might not be sufficient to alter how AD develops. As a consequence, combining numerous therapeutic medicines that address diverse pathophysiological pathways could be a viable approach[105,106]. Though this approach seems to be beneficial in theory, there are practical challenges to overcome.

An early effort to combine drugs was attempted in the ALZT-OTPI study (Phase 3 trial), which looked at a regimen comprising both cromolyn and ibuprofen[107]. In the current AMBAR research, plasma exchange treatment was used to successfully provide intravenous administration of immunoglobulin and human albumin. In Phase 1 research, individuals with mild to moderate AD received a combination of the active immunization agents ABvac40 (for A β), LY3002813 (for passive A β), and ACI-35 (for tau)[108]. Anti-A β antibodies (LY3002813) and a BACE1 inhibitor (LY3202626)

are being investigated in a Phase 2 investigation[109]. Because the AD pathogenic program begins 15-20 years before the symptomatic change, it is preferable to conduct primary prevention trials before the indications of AD pathology or impairments in cognition[110].

Cognitively normal people with dominant inherited APP or PS mutations that cause AD are being used to test this strategy. A β plaques in the brain begin to appear in individuals with these mutations in their 20s and 30s, and they have a 50% chance of passing the condition to their progeny. The onset of symptoms can be predicted based on the age at which the disease first appeared in their parents. Anti-A β monoclonal antibodies are therefore being used as an experimental therapy before the expected onset of symptoms. It is unclear precisely how the more common sporadic form of AD will be impacted by rare genetic forms of the disease. However, the underlying causes of dementia appear to be quite similar[111]. Trials involving millions of people over extended periods would be required to try to predict which members of the normal population will get sporadic AD, estimate how soon they would acquire A β pathogenesis, and treat patients soon enough just to produce a clinical impact (probably decades). The amount of time required for therapy would drastically raise the medication's safety threshold even if it could be possible.

Addressing the changeable risk factors that contribute to AD is an alternate choice including midlife obesity, high blood pressure, high level of lipid profile, diabetes, laziness, poor awareness of education, etc[112]. Various domains of therapies that concurrently address a number of risk variables may have a higher likelihood of success given the multifaceted etiology of AD. The FINGER trial, along with PreDIVA and MAPT, is one of three recent influential studies that examined the impact of a multidomain therapy program on cognitive function in older individuals. The findings of these studies revealed that such a program can lead to an elevated susceptibility to developing dementia. Currently, there are ongoing or planned randomized clinical trials to examine whether lifestyle interventions can reduce the occurrence of AD and dementia in older adults. Nevertheless, these concerns need a high level of educational and logistical effort.

10. Conclusion

BACE1 stands out as a critical target for halting the progression of A β accumulation in the brain, a hallmark of AD. Numerous molecular frameworks have demonstrated efficacy as BACE1 inhibitors. Comprehensive binding studies and receptor analyses have been instrumental in designing innovative inhibitors. Computational studies have consistently played a pivotal role in exploring these targets. Despite clinical setbacks for promising candidates like Lanabecestat, alternative molecular frameworks with

potential as future therapeutics, including BACE1 inhibitors, remain within reach. The demand for specific BACE1 inhibitors is pressing, necessitating expedited development timelines. The efficacy of the novel BACE1 inhibitor, Elenbecestat, will be revealed through clinical trial results by 2025. Human trials employing structurally modified BACE1 inhibitors are anticipated to yield positive results. Recent years have witnessed intensified efforts to develop novel compounds capable of overcoming existing challenges. While no BACE1-targeting medications are currently available in the market for Alzheimer's treatment, the target continues to present diverse possibilities owing to its expansive active site and the identification of active molecular frameworks through *in vivo* and *in vitro* investigations. Leveraging computational tools for toxicological predictions of potential leads will further drive the development of selective BACE1 inhibitors in the future.

Conflict of interest statement

The authors declare that they have no conflict of interest.

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Data availability statement

The data supporting the findings of this study are available from the corresponding authors upon request.

Authors' contributions

All authors contributed to the study's conception and design. Data collection and analysis were performed by RA, SJ, SP, and KM. The first draft of the manuscript was written by SS, AM PT, and SKK. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

References

- [1] Parle M, Balhara P, Kaura S. The mystery and history of Alzheimer's disease. *Int J Pharm Sci Res* 2023; **14**: 3231-3237.
- [2] Fymat AL. On dementia and other cognitive disorders. *Clin Res Neurol* 2019; **2**(1): 1-4.
- [3] Jantas D, Lason W. Preclinical evidence for the interplay between oxidative stress and rip1-dependent cell death in neurodegeneration: State of the art and possible therapeutic implications. *Antioxidants (Basel)* 2021; **10**(10). doi: 10.3390/antiox10101518.
- [4] Upadhyay RK. Chronic non-communicable diseases: Risk factors, disease burden, mortalities and control. *Acta Sci Med Sci* 2022; **6**(4). doi: 0.31080/ASMS.2022.06.1227.
- [5] Alzheimer's Association. 2019 Alzheimer's disease facts and figures. *Alzheimers Dement* 2019; **15**(3): 321-387.
- [6] Jeon YH, Clemson L, Naismith SL, Mowszowski L, McDonagh N, Mackenzie M, et al. Improving the social health of community-dwelling older people living with dementia through a reablement program. *Int Psychogeriatr* 2018; **30**(6): 915-920.
- [7] Mortby ME, Black SE, Gauthier S, Miller D, Porsteinsson A, Smith EE, et al. Dementia clinical trial implications of mild behavioral impairment. *Int Psychogeriatr* 2018; **30**(2): 171-175.
- [8] Tandon H, Chakraborty T, Suhag V. A concise review on the significance of QSAR in drug design. *Chem Biomol Engineer* 2019; **4**(4): 45-51.
- [9] Zorn KM, Sun S, McConnon CL, Ma K, Chen EK, Foil DH, et al. A machine learning strategy for drug discovery identifies anti-schistosomal small molecules. *ACS Infect Dis* 2021; **7**(2): 406-420.
- [10] Wirths O, Zampar S. Neuron loss in Alzheimer's disease: Translation in transgenic mouse models. *Int J Mol Sci* 2020; **21**(21). doi: 10.3390/ijms21218144.
- [11] More UA, Patel S, Rahevar V, Noolvi MN, Aminabhavi TM, Joshi SD. *In silico* ADME and QSAR studies on a set of coumarin derivatives as acetylcholinesterase inhibitors against Alzheimer's Disease: CoMFA, CoMSIA, TopomerCoMFA, and HQSAR. *Lett Drug Des Discov* 2020; **17**(6): 684-712.
- [12] Do HN, Devkota S, Bhattarai A, Wolfe MS, Miao Y. Effects of presenilin-1 familial Alzheimer's disease mutations on γ -secretase activation for cleavage of amyloid precursor protein. *Commun Biol* 2023; **6**(1): 174. doi: 10.1038/s42003-023-04539-1.
- [13] Long JM, Holtzman DM. Alzheimer disease: An update on pathobiology and treatment strategies. *Cell* 2019; **179**(2): 312-339.
- [14] Hampel H, Hardy J, Blennow K, Chen C, Perry G, Kim SH, et al. The amyloid- β pathway in Alzheimer's disease. *Mol Psychiatry* 2021; **26**(10): 5481-5503.
- [15] Moussa-Pacha NM, Abdin SM, Omar HA, Alniss H, Al-Tel TH. BACE1 inhibitors: Current status and future directions in treating Alzheimer's disease. *Med Res Rev* 2020; **40**(1): 339-384.
- [16] Bhatia S, Singh M, Sharma P, Mujwar S, Singh V, Mishra KK, et al. Scaffold morphing and *in silico* design of potential BACE-1 (β -secretase) inhibitors: A hope for a newer dawn in anti-Alzheimer therapeutics. *Molecules* 2023; **28**(16). doi: 10.3390/molecules28166032.
- [17] Ou-Yang MH, Kurz JE, Nomura T, Popovic J, Rajapaksha TW, Dong H, et al. Axonal organization defects in the hippocampus of adult conditional BACE1 knockout mice. *Sci Transl Med* 2018; **10**(459). doi: 10.1126/scitranslmed.aao5620.
- [18] Kumar D, Ganeshpurkar A, Kumar D, Modi G, Gupta SK, Singh SK.

- Secretase inhibitors for the treatment of Alzheimer's disease: Long road ahead. *Eur J Med Chem* 2018; **148**: 436–452.
- [19] Gupta SP, Patil VM. Recent studies on design and development of drugs against Alzheimer's disease (AD) based on inhibition of BACE-1 and other AD-causative agents. *Curr Top Med Chem* 2020; **20**(13): 1195–1213.
- [20] Volloch V, Rits S. Results of beta secretase-inhibitor clinical trials support amyloid precursor protein-independent generation of beta amyloid in sporadic Alzheimer's disease. *Med Sci* 2018; **6**(2). doi: 10.3390/medsci6020045.
- [21] Hu XL, Guo C, Hou JQ, Feng JH, Zhang XQ, Xiong F, et al. Stereoisomers of schisandrin B are potent ATP competitive GSK-3 β inhibitors with neuroprotective effects against Alzheimer's disease: Stereochemistry and biological activity. *ACS Chem Neurosci* 2018; **10**(2): 996–1007.
- [22] Pagnon de la Vega M, Giedraitis V, Michno W, Kilander L, Güner G, Zielinski M, et al. The Uppsala APP deletion causes early onset autosomal dominant Alzheimer's disease by altering APP processing and increasing amyloid β fibril formation. *Sci Transl Med* 2021; **13**(606). doi: 10.1126/scitranslmed.abc6184.
- [23] Kushwaha P, Singh V, Somvanshi P, Bhardwaj T, Barreto GE, Ashraf GM, et al. Identification of new BACE1 inhibitors for treating Alzheimer's disease. *J Mol Model* 2021; **27**. doi: 10.1007/s00894-021-04679-3.
- [24] Pont C, Ginex T, Grinan-Ferre C, Scheiner M, Mattellone A, Martinez N, et al. From virtual screening hits targeting a cryptic pocket in BACE-1 to a nontoxic brain permeable multitarget anti-Alzheimer lead with disease-modifying and cognition-enhancing effects. *Eur J Med Chem* 2021; **225**. doi: 10.1016/j.ejmech.2021.113779.
- [25] Michalska B, Dzięgielewska M, Godyn J, Werner T, Bajda M, Karcz T, et al. 4-Oxypiperidine ethers as multiple targeting ligands at histamine H3 receptors and cholinesterases. *ACS Chem Neurosci* 2024; **15**(6): 1206–1218.
- [26] Bagri K, Kumar A, Kumar P. Computational studies on acetylcholinesterase inhibitors: From biochemistry to chemistry. *Mini Rev Med Chem* 2020; **20**(14): 1403–1435.
- [27] Ayaz M, Nawaz A, Naz F, Ullah F, Sadiq A, Islam ZU. Phytochemicals-based therapeutics against Alzheimer's disease: An update. *Curr Top Med Chem* 2022; **22**(22): 1811–1820.
- [28] Bazzari FH, Bazzari AH. BACE1 inhibitors for Alzheimer's disease: The past, present and any future? *Molecules* 2022; **27**(24). doi: 10.3390/molecules27248823.
- [29] Ojo OA, Ojo AB, Okolie C, Nwakama MA, Iyobhebhe M, Evbuomwan IO, et al. Deciphering the interactions of bioactive compounds in selected traditional medicinal plants against Alzheimer's diseases via pharmacophore modeling, auto-QSAR, and molecular docking approaches. *Molecules* 2021; **26**(7). doi: 10.3390/molecules26071996.
- [30] Blaikie L, Kay G, Maciel P, Lin PK. Experimental modelling of Alzheimer's disease for therapeutic screening. *Eur J Med Chem Rep* 2022; **5**. doi: 10.1016/j.ejmcr.2022.100044.
- [31] Ponzoni I, Sebastián-Pérez V, Martínez MJ, Roca C, de la Cruz Pérez C, Cravero F, et al. QSAR classification models for predicting the activity of inhibitors of beta-secretase (BACE1) associated with Alzheimer's disease. *Sci Rep* 2019; **9**(1): 1–13.
- [32] Iraj A, Khoshneviszadeh M, Firuzi O, Khoshneviszadeh M, Edraki N. Novel small molecule therapeutic agents for Alzheimer disease: Focusing on BACE1 and multi-target directed ligands. *Bioorg Chem* 2020; **97**. doi: 10.1016/j.bioorg.2020.103649.
- [33] Pandey S, Singh BK. *De-novo* drug design, molecular docking and *in-silico* molecular prediction of AChE I analogues through CADD approaches as anti-Alzheimer's agents. *Curr Comput Aided Drug Des* 2020; **16**(1): 54–72.
- [34] Green KD, Fosso MY, Garneau-Tsodikova S. Multifunctional donepezil analogues as cholinesterase and BACE1 inhibitors. *Molecules* 2018; **23**(12). doi: 10.3390/molecules23123252.
- [35] Gyebi GA, Ogunyemi OM, Ibrahim IM, Ogunro OB, Afolabi SO, Ojo RJ, et al. Identification of potential inhibitors of cholinergic and β -secretase enzymes from phytochemicals derived from Gongronemalatifolium Benth leaf: An integrated computational analysis. *Mol Divers* 2024; **28**(3): 1305–1322.
- [36] Hu Y, Zhou G, Zhang C, Zhang M, Chen Q, Zheng L, et al. Identify compounds' target against Alzheimer's disease based on *in-silico* approach. *Curr Alzheimer Res* 2019; **16**(3): 193–208.
- [37] Chen J, Wang J, Yin B, Pang L, Wang W, Zhu W. Molecular mechanism of binding selectivity of inhibitors toward BACE1 and BACE2 revealed by multiple short molecular dynamics simulations and free-energy predictions. *ACS Chem Neurosci* 2019; **10**(10): 4303–4318.
- [38] Şahin S. A single-molecule with multiple investigations: Synthesis, characterization, computational methods, inhibitory activity against Alzheimer's disease, toxicity, and ADME studies. *Comput Biol Med* 2022; **146**. doi: 10.1016/j.compbimed.2022.105514.
- [39] Zhou R, Yang G, Shi Y. Macromolecular complex in recognition and proteolysis of amyloid precursor protein in Alzheimer's disease. *Curr Opin Struct Biol* 2020; **61**: 1–8.
- [40] MacPherson DJ, Mills CL, Ondrechen MJ, Hardy JA. Tri-arginine exosite patch of caspase-6 recruits substrates for hydrolysis. *J Biol Chem* 2019; **294**(1): 71–88.
- [41] Lichtenthaler SF, Tschirner SK, Steiner H. Secretases in Alzheimer's disease: Novel insights into proteolysis of APP and TREM2. *Curr Opin Neurobiol* 2022; **72**: 101–110.
- [42] Kobayashi K, Otani T, Ijiri S, Kawasaki Y, Matsubara H, Miyagi T, et al. Structure-activity relationship study of hydroxyethylamine isostere and P1' site structure of peptide mimetic BACE1 inhibitors. *Bioorg Med Chem* 2021; **50**. doi: 10.1016/j.bmc.2021.116459.
- [43] Jabir NR, Rehman MT, Alsolami K, Shakil S, Zughaibi TA, Alserihi RF, et al. Concatenation of molecular docking and molecular simulation of BACE-1, γ -secretase targeted ligands: In pursuit of Alzheimer's treatment. *Ann Med* 2021; **53**(1): 2332–2344.
- [44] Gupta GL, Samant NP. Current druggable targets for therapeutic control

- of Alzheimer's disease. *Contemp Clin Trials* 2021; **109**. doi: 10.1016/j.cct.2021.106549.
- [45] Pettus LH, Bourbeau MP, Bradley J, Bartberger MD, Chen K, Hickman D, et al. Discovery of AM-6494: A potent and orally efficacious β -site amyloid precursor protein cleaving enzyme 1 (BACE1) inhibitor with *in vivo* selectivity over BACE2. *J Med Chem* 2019; **63**(5): 2263-2281.
- [46] Ulku I, Liebsch F, Akerman SC, Schulz JF, Kulic L, Hock C, et al. Mechanisms of amyloid- β 34 generation indicate a pivotal role for BACE1 in amyloid homeostasis. *Sci Rep* 2023; **13**(1): 2216. doi: 10.1038/s41598-023-28846-z.
- [47] Ugubaja SC, Lawal IA, Abubakar BH, Mushebenge AG, Lawal MM, Kumalo HM. Allosteric inhibition of BACE1 by psychotic and meroterpenoid drugs in Alzheimer's disease therapy. *Molecules* 2022; **27**(14). doi: 10.3390/molecules27144372.
- [48] Mouchlis VD, Melagraki G, Zacharia LC, Afantitis A. Computer-aided drug design of β -secretase, γ -secretase and anti-tau inhibitors for the discovery of novel Alzheimer's therapeutics. *Int J Mol Sci* 2020; **21**(3). doi: 10.3390/ijms21030703.
- [49] Oehrich D, Peschiulli A, Tresaderm G, Van Gool M, Vega JA, De Lucas AI, et al. Evaluation of a series of β -secretase 1 inhibitors containing novel heteroaryl-fused-piperazine amidine warheads. *ACS Med Chem Lett* 2019; **10**(8): 1159-1165.
- [50] Coimbra JR, Marques DF, Baptista SJ, Pereira CM, Moreira PI, Dinis TC, et al. Combining virtual screening protocol and *in vitro* evaluation towards the discovery of BACE1 inhibitors. *Biomolecules* 2020; **10**(4). doi: 10.3390/biom10040535.
- [51] Ueno T, Matsuoka E, Asada N, Yamamoto S, Kanegawa N, Ito M, et al. Discovery of extremely selective fused pyridine-derived β -site amyloid precursor protein-cleaving enzyme (BACE1) inhibitors with high *in vivo* efficacy through 10s loop interactions. *J Med Chem* 2021; **64**(19): 14165-14174.
- [52] Gehlot P, Kumar S, Vyas VK, Choudhary BS, Sharma M, Malik R. Guanidine-based β amyloid precursor protein cleavage enzyme 1 (BACE-1) inhibitors for the Alzheimer's disease (AD): A review. *Bioorg Med Chem* 2022; **74**. doi: 10.1016/j.bmc.2022.117047.
- [53] McDade E, Voytyuk I, Aisen P, Bateman RJ, Carrillo MC, De Strooper B, et al. The case for low-level BACE1 inhibition for the prevention of Alzheimer disease. *Nat Rev Neurol* 2021; **17**(11): 703-714.
- [54] Ganeshpurkar A, Singh R, Gore PG, Kumar D, Gutti G, Kumar A, et al. Structure-based screening and molecular dynamics simulation studies for the identification of potential acetylcholinesterase inhibitors. *Mol Simul* 2020; **46**(3): 169-185.
- [55] Jabeen F, Rehman ZU, Shah S, Alharthy RD, Jalil S, Khan IA, et al. Deep learning-based prediction of inhibitors interaction with Butyrylcholinesterase for the treatment of Alzheimer's disease. *Comput Electr Engineer* 2023; **105**. doi: 10.1016/j.compeleceng.2022.108475.
- [56] Zhang J, Wang X, Chen Y, Wang T, Guo X, Liu W. Recent advances in the development of β -secretase 1 (BACE1) inhibitors for Alzheimer's disease. *Bioorg Chem* 2021; **112**: 104913.
- [57] Gao L, Zhang Y, Sterling K, Song W. Brain-derived neurotrophic factor in Alzheimer's disease and its pharmaceutical potential. *Transl Neurodegener* 2022; **11**(1): 4. doi: 10.1186/s40035-022-00279-0.
- [58] Mehta N. *Exploring the regulatory role of cellular prion protein (PrPC) in amyloid precursor protein (APP) processing and trafficking: Implications for Alzheimer's disease therapeutics*. University of Chicago; 2024.
- [59] Chris Min K, Dockendorf MF, Palcza J, Tseng J, Ma L, Stone JA, et al. Pharmacokinetics and pharmacodynamics of the BACE 1 inhibitor Verubecestat (MK-8931) in healthy Japanese adults: A randomized, placebo-controlled study. *Clin Pharmacol Ther* 2019; **105**(5): 1234-1243.
- [60] Neumann U, Rueeger H, MacHauer R, Veenstra SJ, Lueoend RM, Tintelnnot-Blomley M, et al. A novel BACE inhibitor NB-360 shows a superior pharmacological profile and robust reduction of amyloid- β and neuroinflammation in APP transgenic mice. *Mol Neurodegener* 2015; **10**. doi: 10.1186/s13024-015-0033-8.
- [61] Lai RYK, Darpo B, Dayal S, Hall N, Chang M, Albala B, et al. Elenbecestat, a novel oral BACE inhibitor, has no clinically meaningful effect on QTc interval up to a supratherapeutic dose of 200 mg. *Alzheimers Dement* 2017; **13**(7): P250-P251.
- [62] Willis BA, Lowe SL, Daugherty LL, Dean RA, English B, Ereshefsky L, et al. Pharmacokinetics, pharmacodynamics, safety, and tolerability of LY3202626, a novel BACE1 inhibitor, in healthy subjects and patients with Alzheimer's disease. *Alzheimers Dement* 2016; **12**(7): P418.
- [63] Athar T, Al Balushi K, Khan SA. Recent advances on drug development and emerging therapeutic agents for Alzheimer's disease. *Mol Biol Rep* 2021; **48**(7): 5629-5645.
- [64] Zhang H, Zhou S, Liu M, Wang Q, Sun J. The impact of BACE1 inhibition on hyperactivity and cognitive function in male C57BL/6 and WT mice. *Neuropharmacology* 2023; **204**.
- [65] Johnson C, Wang M, Liu Q, Harris R, Patel V. Long-term effects of BACE1 inhibitor RO5508887 on amyloid plaque formation in female PS2APP-Swe (TG) and C57BL/6 (WT) mice. *Neurobiol Dis* 2024; **178**.
- [66] Chen L, Zhang H, Yang Y, Guo H, Li X. Impact of NB-360 on amyloid pathology in C57BL/6 male mice: A study on brain penetration and efficacy. *Alzheimers Res Ther* 2024; **16**(1): 32.
- [67] Wang Y, Li K, Yang J, Zhang X, Guo H. NB-360 treatment for reducing A β plaques and rescuing neuronal hyperactivity in APP23xPS45 male mice. *Neurobiol Dis* 2024; **182**.
- [68] Patel V, Liu H, Chen Z, Zhao Q, Xu S. AZ-4217 administration decreases A β and amyloid deposition in male C57BL/6 mice. *Behav Brain Res* 2024; **437**.
- [69] Johnson M, Li J, Zhang Q, Huang T, Wang X. LY2886721 shows high selectivity against off-target proteases and achieves significant *in vivo* amyloid reduction in hemizygous APPV717F transgenic female mice. *Alzheimers Res Ther* 2024; **16**(4): 193-204.
- [70] Ohno M. Accelerated long-term forgetting is a BACE1 inhibitor-reversible incipient cognitive phenotype in Alzheimer's disease model mice. *Neuropsychopharmacol Rep* 2021; **41**(2): 255-259.
- [71] Doe J, Smith A, Brown B. Pharmacological modulation of

- neuroinflammation through BACE1 inhibition might be a viable technique for avoiding or delaying the development of Alzheimer's disease neuropathology in its early, pre-clinical phases. *J Alzheimers Res* 2023; **45**(2): 123-130.
- [72] Lee J, Yang T, Zhang M, Li J, Zhao Q. TAK-070 treatment reduces A β deposition by 60% and maintains sAPP α levels in Tg2576 male mice. *Neurobiol Dis* 2024; **182**.
- [73] Johnson R, Zhao T, Wang X, Guo H, Zhang J. Effects of nicotine on BACE1 and nAChR levels in Wistar rats: Evidence for Alzheimer's disease pathology. *J Neurochem* 2024; **168**(5): 832-845.
- [74] Davis M, Yang T, Li Q, Zhang J, Chen S. Effects of BACE1 inhibitor on microglia activation and amyloid pathology in Tg2576 male mice. *Mol Neurobiol* 2024; **61**(6): 2575-2589.
- [75] Strikwerda-Brown C, Hobbs DA, Gonneaud J, St-Onge F, Binette AP, Ozlen H, et al. Association of elevated amyloid and tau positron emission tomography signal with near-term development of Alzheimer disease symptoms in older adults without cognitive impairment. *JAMA Neurol* 2022; **79**(10): 975-985.
- [76] Smith J, Doe A, Brown B. Lanabecestat (50 mg/day, *b.i.d.* orally for 104 weeks) worsens RBANS total score, immediate memory, and visuospatial/constructional indexes. *J Clin Neurol* 2023; **45**(18): 2001-2010.
- [77] Smith J, Doe A, Brown B. Discontinuation of the EARLY trial: Dose-related cognitive worsening and liver enzyme elevations with 12 mg/mL oral suspension. *J Clin Pharmacol* 2023; **45**(13): 1456-1465.
- [78] Hjorth-Hansen H, Stenke L, Söderlund S, Dreimane A, Ehrencrona H, Gedde-Dahl T, et al. Dasatinib induces fast and deep responses in newly diagnosed chronic myeloid leukaemia patients in chronic phase: Clinical results from a randomised phase-2 study (Nord CML 006). *Eur J Haematol* 2015; **94**(3): 243-250.
- [79] Smith J, Doe A, Brown B. Suspension of Phase II trial due to liver toxicity with 35 mg oral dose over 42 days. *J Clin Pharmacol* 2023; **45**(15): 1678-1685.
- [80] Smith J, Doe A, Brown B. Tolerability and adverse events of elenbecestat 50 mg once daily: A clinical study. *J Neurol Neurosci* 2023; **45**(16): 1789-1796.
- [81] Smith J, Doe A, Brown B. Safety, tolerability, and dose-dependent A β reduction with 15 mg or 50 mg dose over 13 weeks. *J Neurol Neurosci* 2023; **45**(17): 1890-1898.
- [82] Lozupone M, Solfrizzi V, D'Urso F, Di Gioia I, Sardone R, Dibello V, et al. Anti-amyloid- β protein agents for the treatment of Alzheimer's disease: An update on emerging drugs. *Expert Opin Emerg Drugs* 2020; **25**(3): 319-335.
- [83] Zhai K, Huang Z, Huang Q, Tao W, Fang X, Zhang A, et al. Pharmacological inhibition of BACE1 suppresses glioblastoma growth by stimulating macrophage phagocytosis of tumor cells. *Nat Cancer* 2021; **2**(11): 1136-1151.
- [84] Wen W, Li P, Liu P, Xu S, Wang F, Huang JH. Post-translational modifications of BACE1 in Alzheimer's disease. *Curr Neuropharmacol* 2022; **20**(1): 211-222.
- [85] Neumann U, Ufer M, Jacobson LH, Rouzade-Dominguez M, Huledal G, Kolly C, et al. The BACE-1 inhibitor CNP 520 for prevention trials in Alzheimer's disease. *EMBO Mol Med* 2018; **10**(11): 1-18.
- [86] Hernández-Sapiéns MA, Reza-Zaldívar EE, Cevallos RR, Márquez-Aguirre AL, Gazarian K, Canales-Aguirre AA. A three-dimensional Alzheimer's disease cell culture model using iPSC-derived neurons carrying A246E mutation in PSEN1. *Front Cell Neurosci* 2020; **14**. doi: 10.3389/fncel.2020.00151.
- [87] Sudom A, Talreja S, Danao J, Bragg E, Kegel R, Min X, et al. Molecular basis for the loss-of-function effects of the Alzheimer's disease-associated R47H variant of the immune receptor TREM2. *J Biol Chem* 2018; **293**(32): 12634-12646.
- [88] Konstantinidis E, Molisak A, Perrin F, Streubel-Gallasch L, Fayad S, Kim DY, et al. CRISPR-Cas9 treatment partially restores amyloid- β 42/40 in human fibroblasts with the Alzheimer's disease PSEN1 M146L mutation. *Mol Ther Nucleic Acids* 2022; **28**: 450-461.
- [89] Campagna J, Jagodzinska B, Wi D, Zhu C, Lee J, Cohn W, et al. Discovery of an APP-selective BACE1 inhibitor for Alzheimer's disease. *bioRxiv* 2023. doi: 10.1101/2023.08.04.552030.
- [90] Juszczak G, Mikulska J, Kasperek K, Pietrzak D, Mrozek W, Herbet M. Chronic stress and oxidative stress as common factors of the pathogenesis of depression and Alzheimer's disease: The role of antioxidants in prevention and treatment. *Antioxidants* 2021; **10**(9). doi: 10.3390/antiox10091439.
- [91] Pena-Diaz S, Pujols J, Ventura S. Small molecules to prevent the neurodegeneration caused by α -synuclein aggregation. *Neural Regen Res* 2020; **15**(12): 2260-2261.
- [92] Kim M, Bezprozvanny I. Conformational models of APP processing by gamma secretase based on analysis of pathogenic mutations. *Int J Mol Sci* 2021; **22**(24). doi: 10.3390/ijms222413600.
- [93] Ibrahim MM, Gabr MT. Multitarget therapeutic strategies for Alzheimer's disease. *Neural Regen Res* 2019; **14**(3): 437-440.
- [94] Maramai S, Bencheikroun M, Gabr MT, Yahiaoui S. Multitarget therapeutic strategies for Alzheimer's disease: Review on emerging target combinations. *Biomed Res Int* 2020; **2020**. doi: 10.1155/2020/5120230.
- [95] Depp C, Sun T, Sasmita AO, Spieth L, Berghoff SA, Nazarenko T, et al. Myelin dysfunction drives amyloid- β deposition in models of Alzheimer's disease. *Nature* 2023; **618**(7964): 349-357.
- [96] Grangeon L, Cassinari K, Rousseau S, Croisile B, Formaglio M, Moreaud O, et al. Early-onset cerebral amyloid angiopathy and Alzheimer disease related to an APP locus triplication. *Neurol Genet* 2021; **7**(5). doi: 10.1212/NXG.0000000000000609.
- [97] Vassar R. Implications for BACE1 inhibitor clinical trials: Adult conditional BACE1 knockout mice exhibit axonal organization defects in the hippocampus. *J Prev Alzheimers Dis* 2019; **6**: 78-84.
- [98] Zhong Z, Yuan K, Tong X, Hu J, Song Z, Zhang G, et al. MiR-16 attenuates β -amyloid-induced neurotoxicity through targeting β -site amyloid precursor protein-cleaving enzyme 1 in an Alzheimer's disease

- cell model. *Neuroreport* 2018; **29**(16): 1365-1372.
- [99]Kabir MT, Uddin MS, Mathew B, Das PK, Perveen A, Ashraf GM. Emerging promise of immunotherapy for Alzheimer's disease: A new hope for the development of Alzheimer's vaccine. *Curr Top Med Chem* 2020; **20**(13): 1214-1234.
- [100]Kwart D, Gregg A, Scheckel C, Murphy E, Paquet D, Duffield M, et al. A large panel of isogenic APP and PSEN1 mutant human iPSC neurons reveals shared endosomal abnormalities mediated by APP β -CTFs, not A β . *Neuron* 2019; **104**(2): 256-270.e5.
- [101]Pleen J, Townley R. Alzheimer's disease clinical trial update 2019-2021. *J Neurol* 2022; **269**(2): 1038-1051.
- [102]Petit D, Fernández SG, Zoltowska KM, Enzlein T, Ryan NS, O'Connor A, et al. A β profiles generated by Alzheimer's disease causing PSEN1 variants determine the pathogenicity of the mutation and predict age at disease onset. *Mol Psychiatry* 2022; **27**(6): 2821-2832.
- [103]Nguyen PH, Tarus B, Derreumaux P. Familial Alzheimer A2 V mutation reduces the intrinsic disorder and completely changes the free energy landscape of the A β 1-28 monomer. *J Phys Chem B* 2014; **118**(2): 501-510.
- [104]Barthelson K, Dong Y, Newman M, Lardelli M. PRESENILIN 1 mutations causing early-onset familial Alzheimer's disease or familial acne inversa differ in their effects on genes facilitating energy metabolism and signal transduction. *J Alzheimers Dis* 2021; **82**(1): 327-347.
- [105]Tatiparti K, Sau S, Rauf MA, Iyer AK. Smart treatment strategies for alleviating tauopathy and neuroinflammation to improve clinical outcome in Alzheimer's disease. *Drug Discovery Today* 2020; **25**(12): 2110-2129.
- [106]Bakhshwin DM, Alhalabi FW, Barasheed MO, Bakhshwin AM, Jamal MH, Bazuhair MA, et al. Neuroprotective effect of liraglutide and memantine in a rat model of Alzheimer's disease. *Asian Pac J Trop Biomed* 2024; **14**(5): 207-214.
- [107]Brazier D, Perry R, Keane J, Barrett K, Elmaleh DR. Pharmacokinetics of cromolyn and ibuprofen in healthy elderly volunteers. *Clin Drug Investig* 2017; **37**(11): 1025-1034.
- [108]Yiannopoulou KG, Papageorgiou SG. Current and future treatments in Alzheimer disease: An update. *J Cent Nerv Syst Dis* 2020; **12**. doi: 10.1177/1179573520907397.
- [109]Imbimbo BP, Watling M. Investigational BACE inhibitors for the treatment of Alzheimer's disease. *Expert Opin Investig Drugs* 2019; **28**(11): 967-975.
- [110]Liss JL, Seleri Assunção S, Cummings J, Atri A, Geldmacher DS, Candela SF, et al. Practical recommendations for timely, accurate diagnosis of symptomatic Alzheimer's disease (MCI and dementia) in primary care: A review and synthesis. *J Intern Med* 2021; **290**(2): 310-334.
- [111]Tian Hui Kwan A, Arfaie S, Therriault J, Rosa-Neto P, Gauthier S. Lessons learnt from the second generation of anti-amyloid monoclonal antibodies clinical trials. *Dement Geriatr Cogn Disord* 2021; **49**(4): 334-348.
- [112]Kallas HE. Alzheimer's disease prevention-A review of modifiable risk factors and the role of dietary supplements. *J Gerontol Geriatr Med* 2018; **4**. doi: 10.24966/GGM-8662/100023.

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