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Recent advancements in the therapeutic approaches for Alzheimer's disease treatment: current and future perspective†

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Alzheimer's disease (AD) is a complex, incurable neurological condition characterized by cognitive decline, cholinergic neuron reduction, and neuronal loss. Its exact pathology remains uncertain, but multiple treatment hypotheses have emerged. The current treatments, single or combined, alleviate only symptoms and struggle to manage AD due to its multifaceted pathology. The developmental drugs target pivotal disease factors involved in the envisaged hypotheses and include targets such as amyloid aggregation, hyperphosphorylated tau proteins, and receptors like cholinergic, adrenergic, *etc.* Present-day research focuses on multi-target directed ligands (MTDLs), which inhibit multiple factors simultaneously, helping slow the disease's progression. This review attempts to collate the recent information related to proposed hypotheses for AD etiology. It systematically organizes the advances in various therapeutic options for AD, with a particular emphasis on clinical candidates. Also, it is expected to help medicinal chemists design novel AD treatments based on available information, which could be helpful to AD patients.

1. Introduction

AD is a progressive neurodegenerative condition, particularly in those 65 years or older, and is a leading cause of dementia.[1] It gradually erodes cognitive abilities and interpersonal engagement due to brain cell degeneration. As of 2023, about 55 million people worldwide have dementia, with AD accounting for 60–70% of these cases. By 2050, this number is expected to reach 139 million due to the aging global population. Females are at a higher risk of AD. In India, over 4 million individuals have various forms of dementia, with Alzheimer's as the most widespread type.[2]

A century since AD's discovery, the disease's precise pathogenesis remains elusive and not fully comprehended. A combination of factors, encompassing the abnormal folding and aggregation of proteins, frequently associated with oxidative stress and the generation of free radicals, result in AD.[3] Further, bioenergetics, irregularities in mitochondrial function, and neuroinflammation processes are involved in its complications. Understanding these factors, aided by the latest research on AD pathogenesis, has laid the foundation for research into potential treatments. However, the absence of animal models accurately mirroring the human AD pathogenesis remains a significant hurdle.[4] Given the multifaceted nature of the disease, concentrating solely on one causative factor has proven ineffective or comparatively less impactful. Also, designing selective drugs that target causative factors is a significant challenge. Developing multi-target directed ligands (MTDLs) is another challenge, as it can lead to various side effects.[5] Biologicals have also been explored, such as aducanumab, lecanemab and donanemab, which are the sole approved disease-modifying drugs for Alzheimer's. These human monoclonal antibodies are specifically designed to target aggregated beta-amyloid proteins found in the brain lesions associated with AD. Other available treatments, mainly cholinergic drugs such as galantamine, rivastigmine, and donepezil, primarily focus on managing symptoms, as the degeneration of brain cells in Alzheimer's is irreversible. The inability to reverse brain cell damage remains a significant task in Alzheimer's therapy.[6]

The present review concisely discusses the latest findings and hypotheses concerning the underlying causes of AD to offer valuable insights and information to medicinal chemists. It discusses advancements in a broad spectrum of

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therapeutic strategies for AD, emphasizing promising candidates that have progressed to clinical trials, shedding light on their potential to offer effective treatment options.

2. Pathogenesis of AD

The precise mechanisms underlying the development of Alzheimer's disease (AD) are still not entirely elucidated. However, this complex condition has been linked to various symptoms and pathological features. These include the formation of neurofibrillary tangles (NFTs) within brain cells, the accumulation of amyloid-β (Aβ) in the form of senile plaques, increased oxidative stress, inflammation within neurons, and a decline in the functioning of cholinergic pathways, *etc.* While these factors are recognized in AD, the interplay and precise sequence of events leading to the disease are still under active investigation. A comprehensive understanding of AD's pathogenesis is crucial for the development of effective treatments and interventions for this devastating condition.[7] The following are proposed hypotheses with the current understanding of AD and the present understanding of the interactions (Fig. 1).

A. The amyloid hypothesis

The widely accepted hypothesis for AD is the amyloid-cascade pathway, centered around the amyloid precursor protein (APP). Under normal conditions, amyloid precursor protein (APP) is cleaved by α-secretase, followed by γ-secretase, yielding harmless fragments.[8] In AD, cleavage by β-secretase (BACE 1) followed by γ-secretase leads to the formation of amyloid β (Aβ) peptides, which aggregate and accumulate as extracellular plaques. Aβ is a hallmark of AD and comprises 37 to 43 amino acids, with the isoform Aβ42 being the most problematic. β-Amyloid peptides aggregate into plaques, triggering inflammation, brain damage, synaptic dysfunction, and tau protein hyperphosphorylation, leading to neurofibrillary tangle formation (Fig. 1).[9] BACE 1 is a key target for therapies aiming to reduce amyloid plaque production to slow AD progression.[10] The important milestones in the development of the amyloid cascade hypothesis and its practical utilization are presented in Table 1.

B. The tau (τ) protein hypothesis

The τ-protein is essential for microtubule stabilization, provides structural support, aids axonal transport, and promotes neuronal growth. Senile plaques trigger τ-protein hyperphosphorylation, leading to its aggregation with cytoskeletal proteins and reduced microtubule interaction. It elevates free τ-protein levels, promoting self-aggregation and fibril formation. Consequently, axonal transport is impaired, resulting in axonal degeneration due to disruption of nutrient transport. The compromised neurons eventually

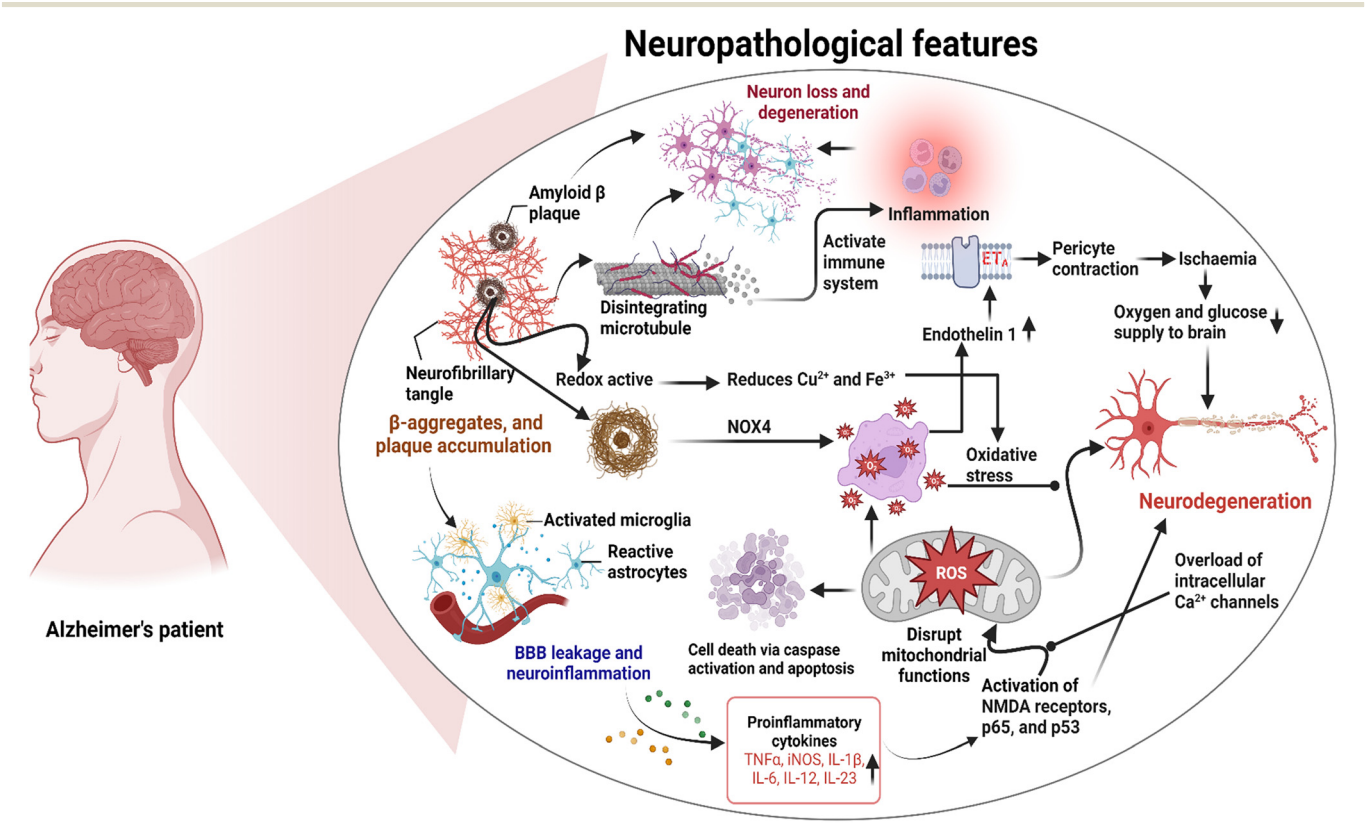


Fig. 1 Pathogenesis of AD summarizing the central role of amyloid beta plaques.

Table 1 Important events in developing the amyloid cascade hypothesis and practical implementations[11]

Year	Key research findings
1906	Senile plaques were first established
1984	Amyloid β protein (Aβ) was isolated as the principal constituent found within the plaques in the brains of individuals with AD
1987	The observation that the formation of Aβ resulted from the processing of amyloid precursor proteins
1990	Evidence of the neurotoxic properties of Aβ aggregates was presented
1992	The hypothesis of the amyloid cascade was put forward
1995	AD patients exhibit a significant decrease in CSF Aβ42 levels, revealing an established connection between Aβ and inflammation
1997	The discovery of the ability of Aβ42 to inhibit long-term potentiation
1998	The primary instigator of neuronal damage was identified as Aβ oligomers
2001	Evidence was provided to establish a connection between Aβ and the formation of neurofibrillary tangles
2004	The inaugural amyloid PET tracer, Pittsburgh compound-B (PIB), was formulated
2016	Light therapy led to a reduction in Aβ accumulation in both animal models of AD and patients
2017	The transfer of Aβ from the periphery through the blood–brain barrier into the brain is reported
2018	The ultrasensitive technology, Simoa, was devised for quantifying Aβ at sub-femtomolar concentrations
2021	Aducanumab became the inaugural FDA-approved medication for diminishing Aβ plaques
2023	FDA approval has been granted to lecanemab for the treatment of AD

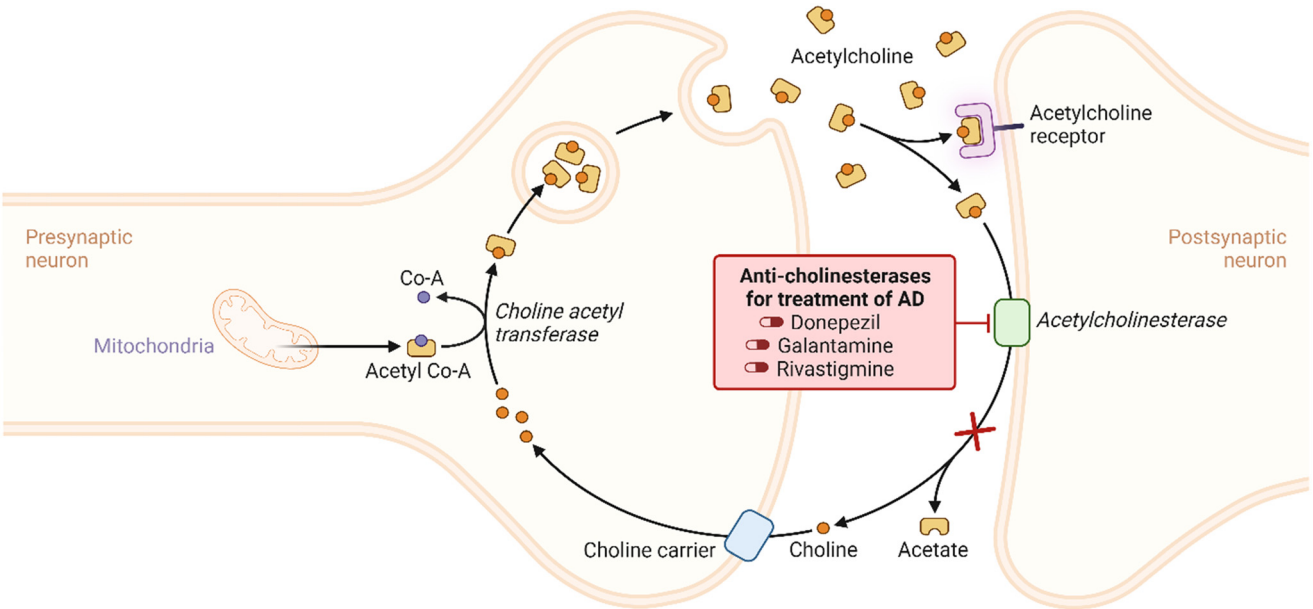


Fig. 2 The cholinergic hypothesis of AD with their reported inhibitors.

form neurofibrillary tangles (NTs), contributing to neurodegeneration (Fig. 1).[12]

C. The cholinergic deficit hypothesis

The cholinergic hypothesis posits that AD progression is primarily linked to the loss of cholinergic neurons and reduced acetyltransferase activity, resulting in decreased acetylcholine (ACh) (Fig. 2). As per the hypothesis, loss of limbic and neocortical cholinergic innervations due to neurofibrillary degeneration in the basal forebrain and associated loss of cholinergic neurotransmission results in decreased cognitive function. This degeneration primarily affects memory and cognition-related regions, like the hippocampus and frontal cortex, leading to compromised choline uptake, impaired ACh release, receptor imbalances, and disrupted neurotrophin support.[13]

D. Adrenergic hypothesis

In advanced AD, significant degeneration of noradrenergic neurons occurs in the locus coeruleus (LC), with a 30% loss during the transition to amnestic mild cognitive impairment (MIC) and an additional 25% reduction in AD progression. AD patients display variable adrenergic receptor expression, including decreased α1 adrenergic receptors (α1ARs) in the prefrontal cortex, hippocampus, and cerebellar hemisphere. Also, increased α1AR binding sites in specific layers, decreased α2 adrenergic receptors (α2ARs) in the nucleus basalis of Meynert, reduced β1 adrenergic receptors (β1ARs) in the cortex, and increased β2 adrenergic receptors (β2ARs) in the cortex and hippocampus. The role of beta-adrenergic receptor alterations in AD is still controversial. However, clinical investigations indicate that Amyloid beta peptide (Aβ) initiates subtle modifications in synaptic function during AD.

Specifically, Aβ interacts with β2 adrenergic receptors within the central noradrenergic system, influencing synaptic functions in prefrontal cortical neurons. This interaction leads to the internalization and degradation of β2-adrenergic receptors, subsequently impairing adrenergic and glutamatergic activities and impacting cognitive function in AD.[14]

E. Glutamatergic hypothesis

Glutamatergic networks in the hippocampal regions are essential for cognitive function, with *N*-methyl D-aspartate receptors (NMDARs) playing a pivotal role in synaptic strength and long-term potentiation (LTP) crucial for memory. AD patients exhibit lower levels of vesicular glutamate transporters (VGLUT-1 and VGLUT-2) in the prefrontal cortex, indicating disrupted glutamatergic synapses. Soluble Aβ oligomers further disrupt glutamatergic networks, inhibiting LTP and inducing NMDAR hyperactivation. It also causes activation of ligand-gated or ionotropic glutamate receptors (iGluRs), predominantly the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor subtype. The excess NMDAR activity raises intracellular Ca^{++} levels, triggering nitric oxide synthesis, free radical generation, oxidative stress (OS), apoptosis, and excitotoxic neuronal death. These changes further the AD pathogenesis caused by Aβ plaques by disrupting synaptic plasticity and neuronal function.[15] Fig. 3 illustrates the effect of normal synaptic transmission and long-term potentiation of the glutamatergic network in the brain.

F. Calcium homeostasis hypothesis

Calcium serves as a crucial intracellular messenger and is important in vital physiological processes. Its precise control relies on complex mechanisms, with mitochondria and the endoplasmic reticulum (ER) playing central roles. ATPase Ca^{2+} pumps and the Na^{+}–Ca^{2+} exchanger aid calcium efflux, while the ER membrane facilitates calcium exchange. Disruptions in these processes can lead to harmful intracellular calcium buildup, triggering protein cleavage, oxidative stress, energy disruption, and activation of proteins like β-amyloid and τ-protein. Aβ exacerbates calcium overload in AD by inducing oxidative stress and membrane pore formation, linking calcium dysregulation to AD pathology (Fig. 1).[16]

G. Oxidative stress hypothesis

Neurodegenerative disorders often involve an imbalance between reactive oxygen species (ROS) generation and antioxidant availability, resulting in cellular damage. AD exhibits disturbances in antioxidant enzyme activity, driven by Aβ's activation of NMDA receptors, which fosters ROS production. OS also contributes, in turn, to increased Aβ production and aggregation, as well as τ-protein hyperphosphorylation and polymerization (Fig. 1).[17]

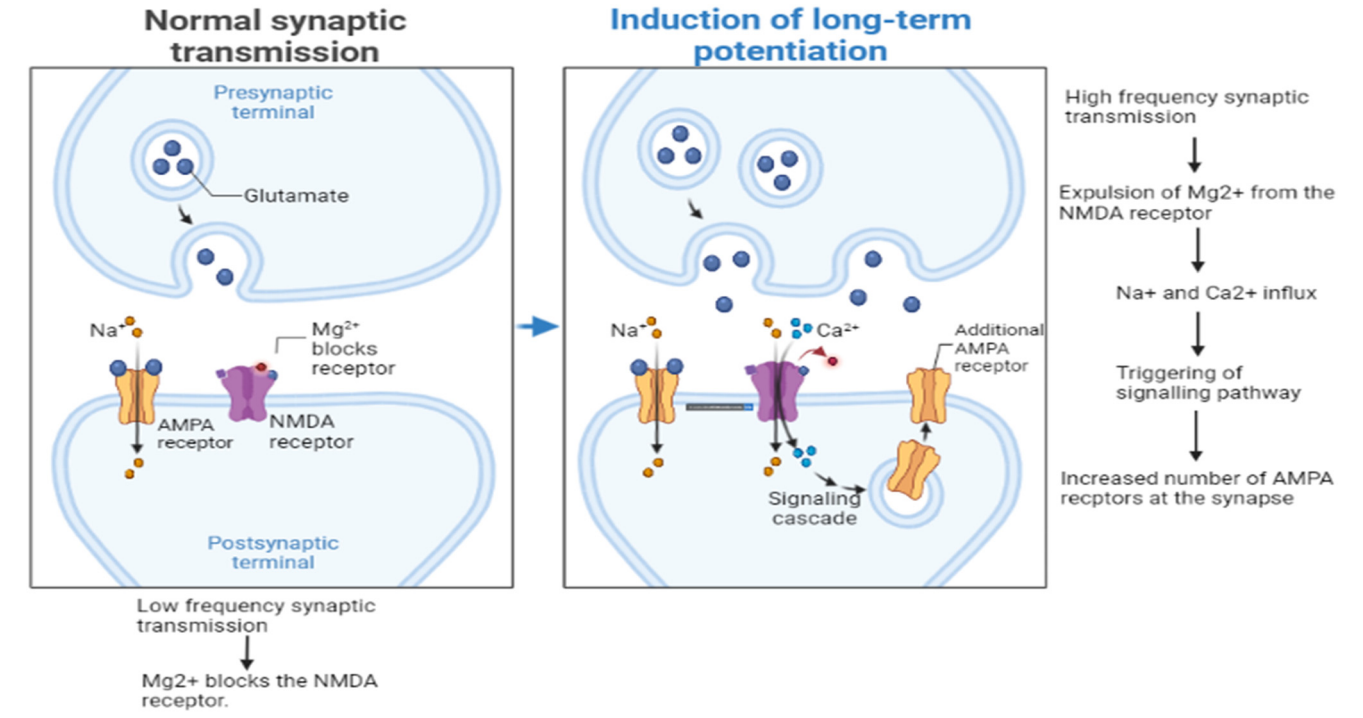


Fig. 3 Effect of normal synaptic transmission and long-term potentiation of the glutamatergic network in the brain.

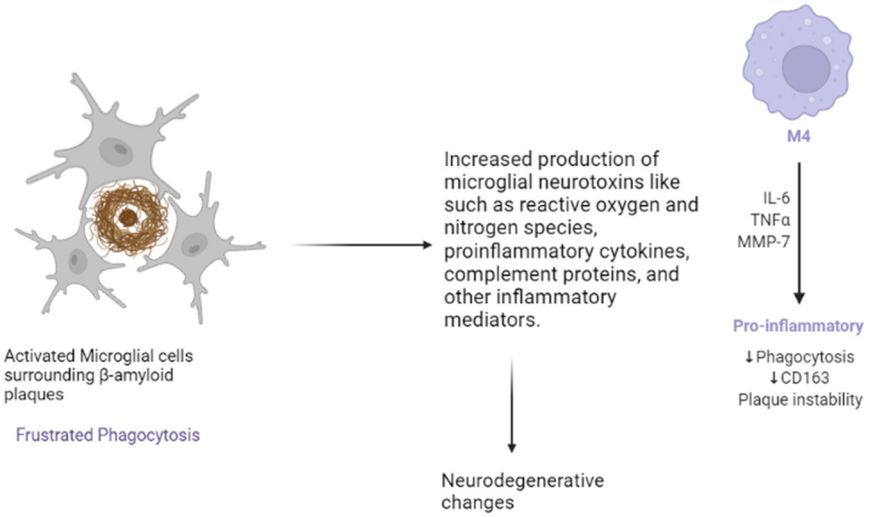


Fig. 4 Effects of activation of microglia.

H. Microgliosis

Microglia are the immune cells residing within the brain and are activated by β-amyloid plaques (Fig. 4). Upon activation, microglial cells release pro-inflammatory mediators, ROS, proteases, and complements, and secondly, as a defense mechanism, break down amyloid plaques. Though clusters of microglial cells gather around β-amyloid plaques, these are unable to break down the plaques effectively. This phenomenon, referred to as "frustrated phagocytosis," contributes to neurodegenerative alterations.[18]

I. Metal chelation hypothesis

β-Amyloid precipitates at low Zn^{2+} concentrations, Cu^{2+} and Fe^{3+} enhance aggregation, especially at slightly acidic pH (6.8). Elevated Cu^{2+} and Zn^{2+} levels in Alzheimer's patients are linked to apoE4 allele induction. β-Amyloid also possesses redox activity, reducing Cu^{2+} and Fe^{3+}, generating H_2O_2, leading to ROS formation, exacerbating the pathology (Fig. 1).[19]

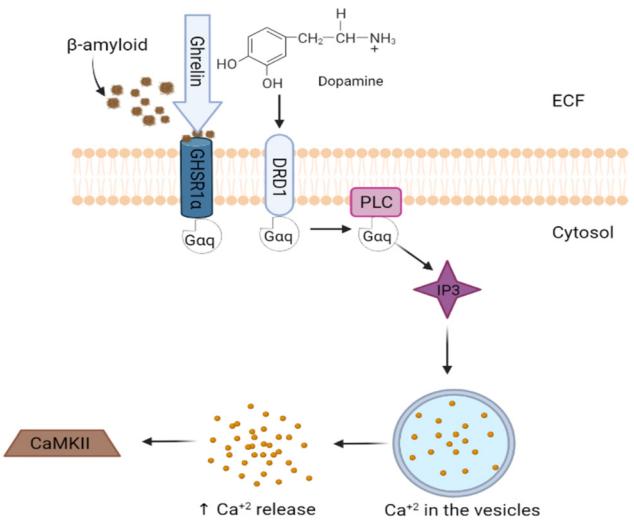


Fig. 5 Amyloid plaques interacting with ghrelin receptors.

J. Prion-like behaviour of plaques

Prions are self-propagating proteins linked to neurodegenerative disorders like Creutzfeldt–Jakob disease (CJD), Gerstmann–Sträussler–Scheinker syndrome (GSS), and fatal familial insomnia (FFI).[20] Aβ takes on a pathogenic conformation akin to prions, spreading in a cross-synaptic manner from specific brain regions. Tau protein also follows the same pattern with initially formed neurofibrillary tangles (NFTs), which are linked to cognitive decline.[21]

K. Ghrelin/GHSR1α signaling

GHSR1α, the ghrelin receptor in the hippocampus, regulates learning and memory through unique signaling involving Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) and dopamine receptor D1 (DRD1). AD involves early hippocampal damage, possibly related to GHSR1α loss, leading to synaptic stress and memory problems. AD patients have been reported to have increased hippocampal GHSR1α, possibly as an Aβ defense mechanism (Fig. 5).[22]

L. Cerebral capillaries constriction

Cerebrovascular disorders can lead to brain function alterations, and early signs of AD include angiogenesis damage and reduced cerebral blood flow. AD patients exhibit abnormal capillary contraction. Animal studies showed that introducing exogenous Aβ can lower cerebral blood flow in rats, triggering Aβ production. Aβ presence generates ROS *via* NOX, releasing endothelin (ET), which contracts pericytes *via* ETA receptors. This contraction causes pericyte necrosis, sustaining capillary constriction and resulting in ischemia. Crucially, Aβ oligomers are central to this complex process, linking vascular dysfunction to AD pathology (Fig. 1).[23]

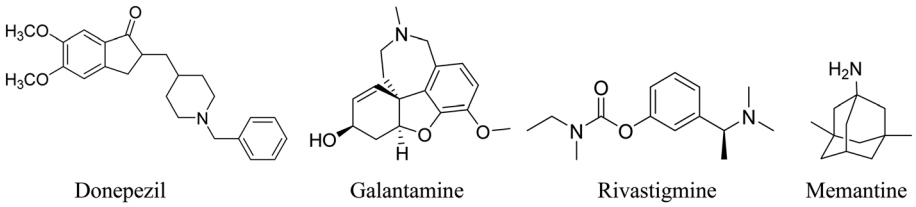


Fig. 6 USFDA-approved therapy for improving cognitive symptoms.[35]

M. Histamine and its receptors role in neuroinflammation in AD

In Alzheimer's disease patients, neurofibrillary tangles, the buildup of neuroinflammatory mediators in microglia, and extracellular amyloid plaques are commonly observed. Neuroinflammation is a persistent feature and plays a vital role in the disease's progression. While histamine is generally thought to trigger inflammatory responses in the peripheral system, increasing evidence suggests that it has a dual role in modulating microglial inflammatory responses in the central nervous system. H1R activation stimulates microglial activation and pro-inflammatory effects, whereas H2R activation produces inhibitory and anti-inflammatory outcomes. H3R is prominently expressed in both microglia and astrocytes. Acute to moderate microglial activation enhances the anti-inflammatory responses of M2 microglia, while chronic microglial activation contributes to neuroinflammation in Alzheimer's disease. The activation of microglia and astrocytes is considered a central driver of neuroinflammatory processes. When microglia are excessively activated, they produce high levels of cytotoxic factors, such as nitrogen oxides and prostaglandins, which damage neurons, leading to degeneration and cell death.[24]

N. Glycogen synthase kinase-3β and tau: an essential pair in AD

GSK-3β is a ubiquitous serine/threonine kinase initially recognized for its role in phosphorylating and inhibiting glycogen synthase. As a key regulator of numerous cellular processes, GSK-3β is central to cell metabolism and signaling, playing significant roles in both healthy and disease states. It has been implicated in various human disorders, including neurodegenerative diseases like AD. GSK-3β is thought to serve as a molecular link between Aβ and tau in

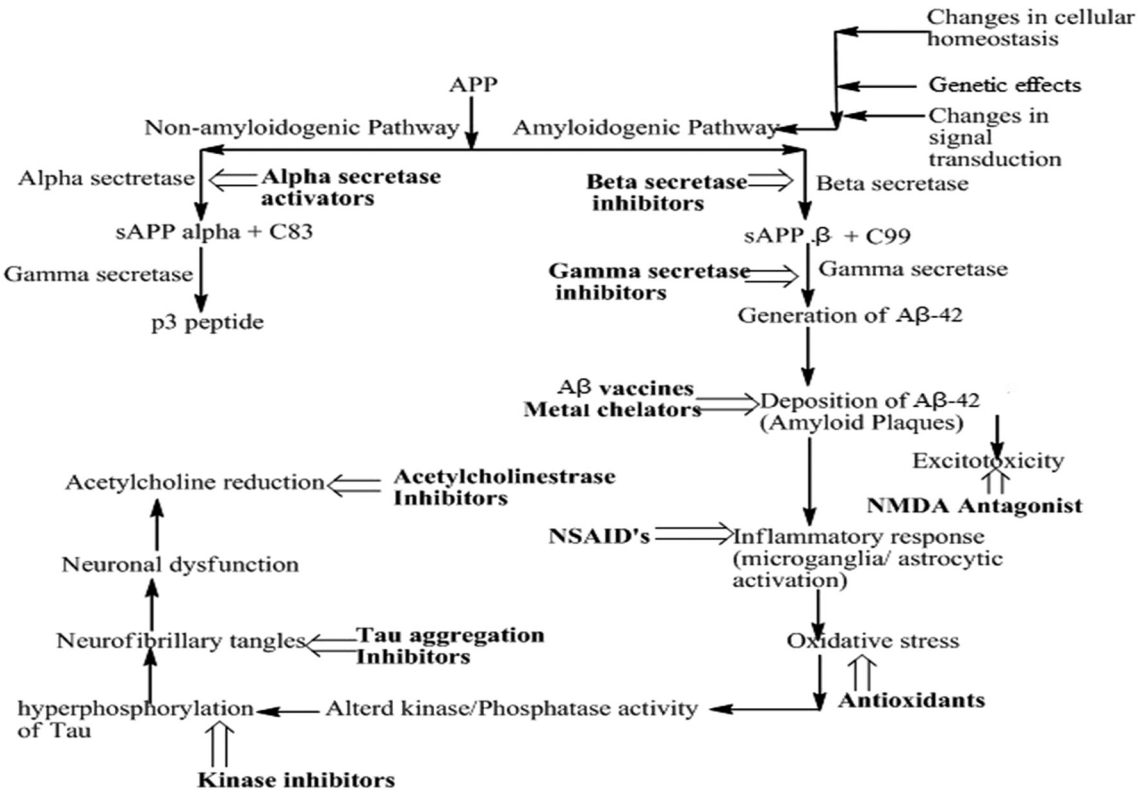


Fig. 7 Downstream events of APP cleavage and therapeutic options being explored.

Table 2 Aβ-Targeting small molecules in clinical trials (**https://clinicaltrials.gov/**)

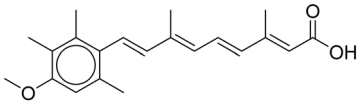
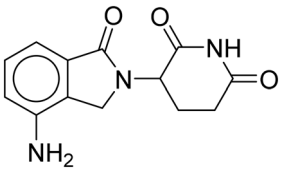
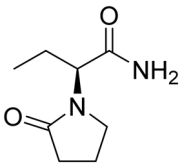
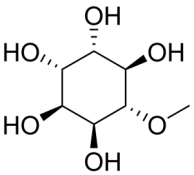
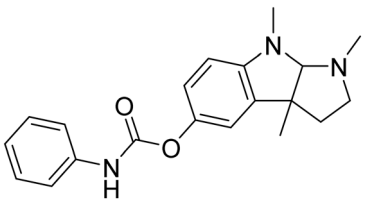
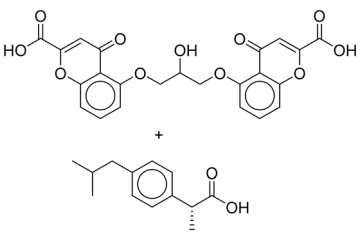
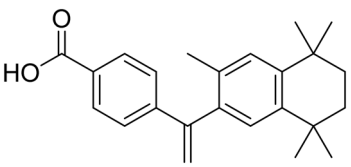
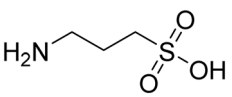
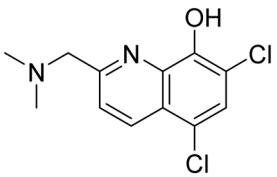
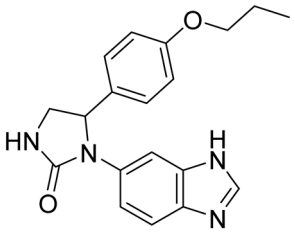
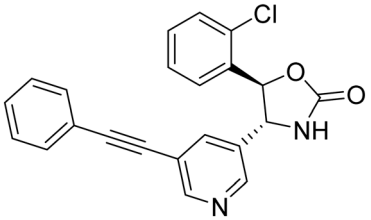
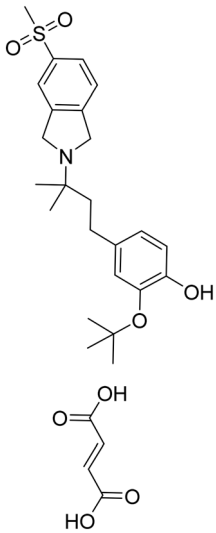
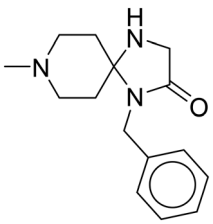
Drug name	Structure	Mode of action	Route	Status	Ref.
Acitretin		Reduces Aβ generation	Oral	Phase II	41
Lenalidomide		BACE1 inhibitor	Oral	Phase II	42
Levetiracetam		Reduce Aβ generation	Oral	Phase II	43
NIC5-15 (1*R*,2*S*,3*R*,4*S*,5*S*,6*S*)-6-methoxy cyclohexane-1,2,3,4,5-pentaol		Modulator of γ-secretase	Oral	Phase II	44
Posiphen		Hinders the translation of the APP	Oral	Phase II	20
ALZT-OP1 [cromolyn + (*R*)-ibuprofen]		Facilitate the elimination of Aβ or its aggregates	Oral	Phase III	45
Bexarotene		Facilitate the elimination of Aβ or its aggregates	Oral	Phase II	46
ALZ-801 3-aminopropane-1-sulfonic acid		Disrupt or hinder the formation of Aβ aggregates	Oral	Phase II	47
Contraloid	Peptide (all D enantiomeric) sequence: PTLHTHNRRRRR	Terminates toxic and replicating amyloid beta (Aβ) oligomer prions by disassembling aggregates into non-toxic Aβ monomers	Oral	Phase I	48
PBT2 5,7-dichloro-2-((dimethylamino)methyl) quinolin-8-ol		Decreasing metal-facilitated Aβ aggregation	Oral	Phase II	49

Table 2 *(continued)*

Drug name	Structure	Mode of action	Route	Status	Ref.
Varoglutamstat		Prevents the formation of a particularly toxic and aggregation-prone variant of Aβ known as pGlu-Aβ	Oral	Phase II	50
ALX-001 (4*R*,5*R*)-5-(2-chlorophenyl)-4-(5-(phenylethynyl)pyridin-3-yl) oxazolidin-2-one		Designed to block the pathogenic binding of toxic amyloid-β oligomers and cellular prion protein to glutamate receptor	Oral	Phase II	51
CT1812 2-(*tert*-butoxy)-4-(3-methyl-3-(5-(methylsulfonyl) isoindolin-2-yl)butyl)phenol fumarate		Prevents the interaction between oligomeric Aβ and its receptors, leading to a reduction in synaptic toxicity caused by Aβ	Oral	Phase I	52
Nasal insulin	Restructuring of synapses and utilization of glucose		Intranasal	Phase III	53
Simufilam		Diminishes tau buildup, decreases neuroinflammation	Oral	Phase III	54

the development of AD. Aβ activates GSK-3β, which then phosphorylates tau. Additionally, GSK-3β promotes the production of β-amyloid by upregulating β-amyloid cleaving enzyme-1 (BACE1) and presenilin-1 (PS1) and contributes to Aβ toxicity. The upregulation of GSK-3β also induces tau hyperphosphorylation, disrupts neuronal synaptic plasticity, and plays a role in the early onset of AD symptoms. Recent studies have shown that tau has acetyltransferase activity, enabling it to self-acetylate. This process also acetylates β-catenin, stabilizing it and allowing tau to exert its anti-apoptotic effects. These findings suggest that tau may directly acetylate GSK-3β, enhancing its activity and triggering a vicious cycle that contributes to chronic neurodegeneration, as seen in the progression of AD.[25]

O. Role of serotonin in AD

Serotonin (5-HT), also known as 5-hydroxytryptamine, is a biogenic amine that acts as a neurotransmitter. It functions at neuronal synapses, influencing cognition, mood, and sleep by binding to receptors on both

neuronal and non-neuronal cell membranes. The 5-HT receptors involved in regulating physiological signaling pathways are classified into two main types: G-protein coupled receptors and ligand-gated ion channels. These receptors are further divided into seven groups: 5-HT1 (including 5-HT1A, 5-HT1B, 5-HT1D, 5-HT1E, and 5-HT1F), 5-HT2 (including 5-HT2A, 5-HT2B, and 5-HT2C), 5-HT3, 5-HT4, 5-HT5 (including 5-HT5A and 5-HT5B), 5-HT6, and 5-HT7. Since the 5-HT7 receptor subtype is associated with neurogenesis and hippocampal neuronal function, its role in apoptosis and long-term potentiation in Alzheimer's disease has been investigated. Studies have shown that activating the 5-HT7 receptor can help alleviate synaptic dysfunction in Alzheimer's by reducing apoptosis in the hippocampus. However, this effect appears to be more linked to the treatment of psychotic symptoms in AD rather than cognitive enhancement. Hyperactivity of pyramidal neurons in the CA1 region of hippocampal circuit is an early sign of Alzheimer's disease. Abnormal serotonin signaling may contribute to this increased neural activity in the CA1 region of mice. Disruptions in 5-HT/5-HT3aR and/or 5-HT/5-HT1aR signaling have been found to cause heightened excitability of pyramidal neurons and a reduction in serotonin signaling in the hippocampus. This disrupted signaling could lead to cognitive impairment by promoting increased neural activity in the CA1 pyramidal neurons.[26]

P. Role of gamma-aminobutyric acid (GABA) in AD

GABA has been identified in 1950 and regarded as the main inhibitory neurotransmitter in the mammalian brain, essential for coordinating the activity of human cortical networks. Consequently, the GABAergic system has been linked to various behavioral and cognitive functions, including the regulation of alertness, anxiety, learned fear, and memory. The GABAergic system in the hippocampus is essential for preserving the excitatory/inhibitory (E/I) balance and synchronizing the activity of multiple populations of pyramidal neurons both within the hippocampus and across other regions of the brain. The alterations in the GABAergic system in Alzheimer's disease and normal aging have been extensively studied through animal models. Current literature indicates that GABA levels decline as part of the normal aging process. This decline is particularly evident in patients with AD and mild cognitive impairment (MCI), especially in the cingulate cortex and the medial parietal lobe. However, it remains unclear whether these changes can predict the onset of dementia in healthy older adults. Disruptions in neural networks have also been reported to emerge during the preclinical and mild stages of Alzheimer's disease. Although animal models offer compelling evidence that dysregulated GABAergic signaling, potentially influenced by APOEε4, contributes to hippocampal hyperactivity and subsequent memory impairments in aging animals, this mechanism has not been directly tested in humans, either cross-sectionally or longitudinally.[27]

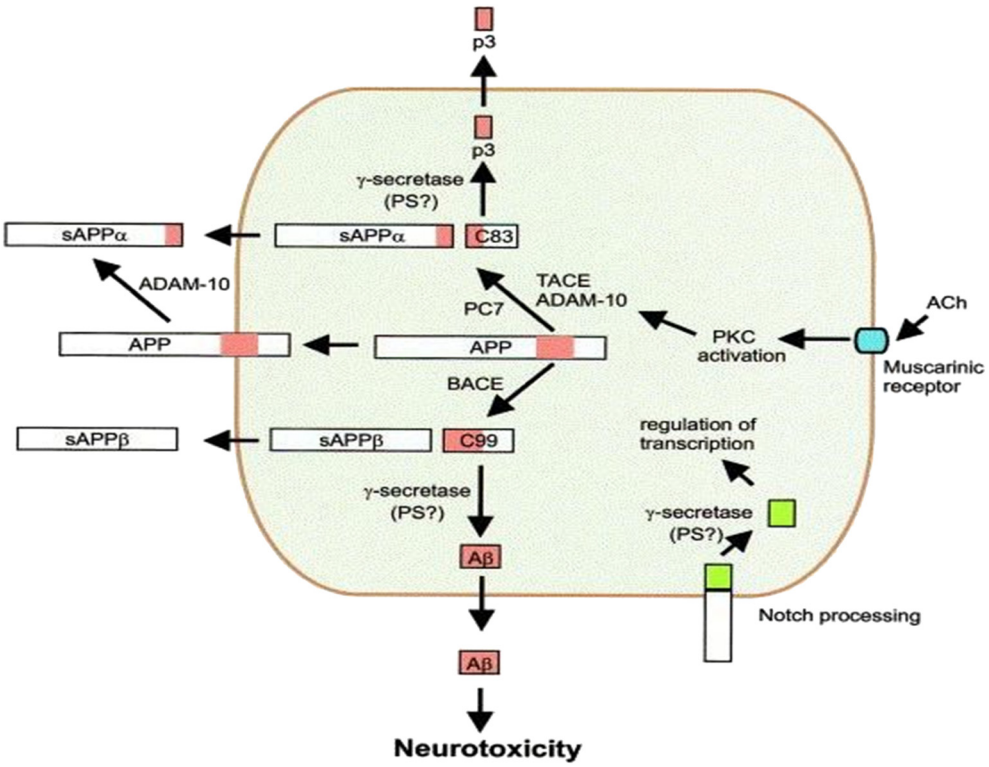


Fig. 8 APP processing by α-, β- and γ-secretases.

3. Therapeutic approaches for the treatment of AD

3.1 Current therapeutic strategies

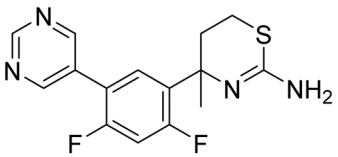
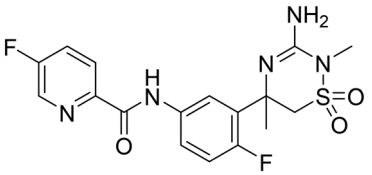
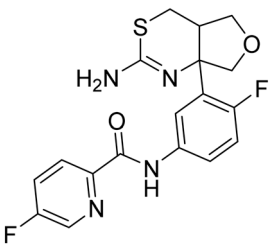
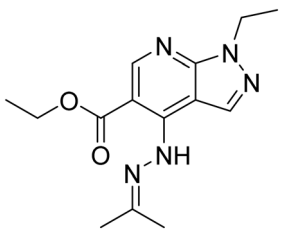
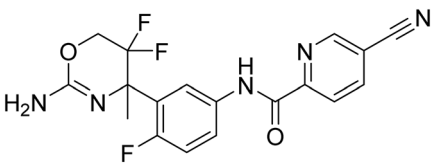
The current treatment options for AD are focused on preventing disease progression *via* monoclonal antibodies and on providing symptomatic relief to the patients.

3.1.1 Drugs that may change disease progression. Aducanumab, lecanemab and donanemab are anti-amyloid antibodies that remove amyloid plaques from the brain. Aducanumab was approved by the US-Food and Drug Administration (USFDA) in 2021 for mild cognitive impairment or mild dementia of Alzheimer's. However, it has not been approved in Europe due to a lack of strong evidence of its efficacy. It is an IgG1 antibody binding to the Aβ at amino acids 3–7. Lecanemab and donanemab also acts on amyloid plaques, albeit differently, by inhibiting aggregated soluble and insoluble forms of Aβ peptide with high selectivity to Aβ protofibrils. US-FDA approved it in July 2023 for patients with early Alzheimer's disease. The common side effects of these antibodies include amyloid-related imaging abnormalities (ARIA), which can lead to swelling and bleeding in the brain, as well as swelling of the face, headaches, infusion-related reactions, and vision changes.[28–31]

3.1.2 Drugs that may mitigate some of the symptoms of the disease

3.1.2.1 Cognitive symptoms. These alleviate memory and thinking symptoms without affecting the progression of the disease. They offer temporary relief by targeting neurotransmitters or receptors, enhancing patient comfort, dignity, and independence. These include cholinesterase inhibitors (donepezil, galantamine, and rivastigmine) and the NMDA receptor antagonist memantine (Fig. 6). Cholinesterase inhibitors preserve acetylcholine levels, which decline in AD and contribute to cognitive loss.[32] Memantine blocks excessive glutamate receptor activation, preventing neuronal death caused by glutamate excess. These

Table 3 List of α-secretase activators/enhancers in clinical trials[57]

Compound name	Structure	Status
LY2811376 4-(2,4-difluoro-5-(pyrimidin-5-yl)phenyl)-4-methyl-5,6-dihydro-4*H*-1,3-thiazin-2-amine		Phase I
MK-8931 *N*-(3-(3-amino-2,5-dimethyl-1,1-dioxido-5,6-dihydro-2*H*-1,2,4-thiadiazin-5-yl)-4-fluorophenyl)-5-fluoropicolinamide		Phase I
LY2886721 *N*-(3-(2-amino-4*a*,5-dihydro-4*H*-furo[3,4-*d*][1,3]thiazin-7*a*(7*H*)-yl)-4-fluorophenyl)-5-fluoropicolinamide		Phase I
Etazolate		Phase II
AZ-4217 *N*-(3-(2-amino-5,5-difluoro-4-methyl-5,6-dihydro-4*H*-1,3-oxazin-4-yl)-4-fluorophenyl)-5-cyanopicolinamide		Phase II
APH1105	A bryostatin analog	Phase II

medications address cognitive symptoms and temporarily improve AD patients' quality of life. The cholinesterase inhibitors have been approved for use in mild to severe dementia due to Alzheimer's, whereas memantine is approved for moderate to severe dementia. A combination of donepezil with memantine is also approved for moderate to severe dementia due to Alzheimer's.[33,34]

3.1.2.2 Non-cognitive (behavioral and psychological) symptoms. In AD patients, sleep changes such as difficulty in sleeping, taking longer daytime naps, changes in sleep cycle, *etc.*, may aggravate mood swings. Suvorexant, a potent dual orexin receptor (OXR1 and OXR2) antagonist, is recommended for treating sleep changes in AD patients. It promotes sleep by binding to the receptors and blocking the binding of orexin A and B, neuropeptides that promote wakefulness, to the receptors. Recently, suvorexant has been found to decrease tau phosphorylation and Aβ in humans.[36]

3.2 Therapeutic strategies based on hypotheses proposed

AD drug development aims at disease modification or symptom management by targeting Aβ and tau protein.[37] Developing new central nervous system (CNS) drugs is challenging but vital to finding more effective AD treatments.[38] Most of the drugs that reached phase II trials failed to show promising results in phase III, like BIIB092, crenezumab, TRx0237, azeliragon, verubecestat, atabecestat, BI 409306, *etc.*[39] The following section discusses various therapeutic options based on the understanding of proposed hypotheses and also lists developmental candidates, particularly in clinical trials.

3.2.1 Aβ-Based approach. Targeting Aβ with vaccines and antibodies is a promising approach for halting AD progression, exemplified by the recent entry of monoclonal antibodies into the market and ongoing clinical trials.[40] Fig. 7 illustrates the downstream events of APP processing and the possible therapeutic interventions being considered for drug development. Some small molecules targeting Aβ peptide for AD treatment are in clinical trials (Table 2).

3.2.2 Secretase inhibitors. Secretases are a group of proteolytic enzymes responsible for processing APP. Three key secretases, namely α-secretase, γ-secretase, and β-secretase, are involved in this process. In healthy conditions, APP undergoes cleavage by α- and γ-secretases. However, the cleavage pattern in AD involves β- and γ-secretases [Fig. 8].[55]

α-Secretase. Activation of α-secretase is represented by the metalloprotease ADAM10, which cleaves APP within the Aβ domain, inhibiting Aβ generation and yielding neuroprotective APP fragments. Therefore, α-secretase cleavage of APP is beneficial by impeding the formation of Aβ peptides and protecting against neurotoxic agents. It has led to the proposal of enhancing α-secretase activity as a treatment strategy to shift the balance towards the

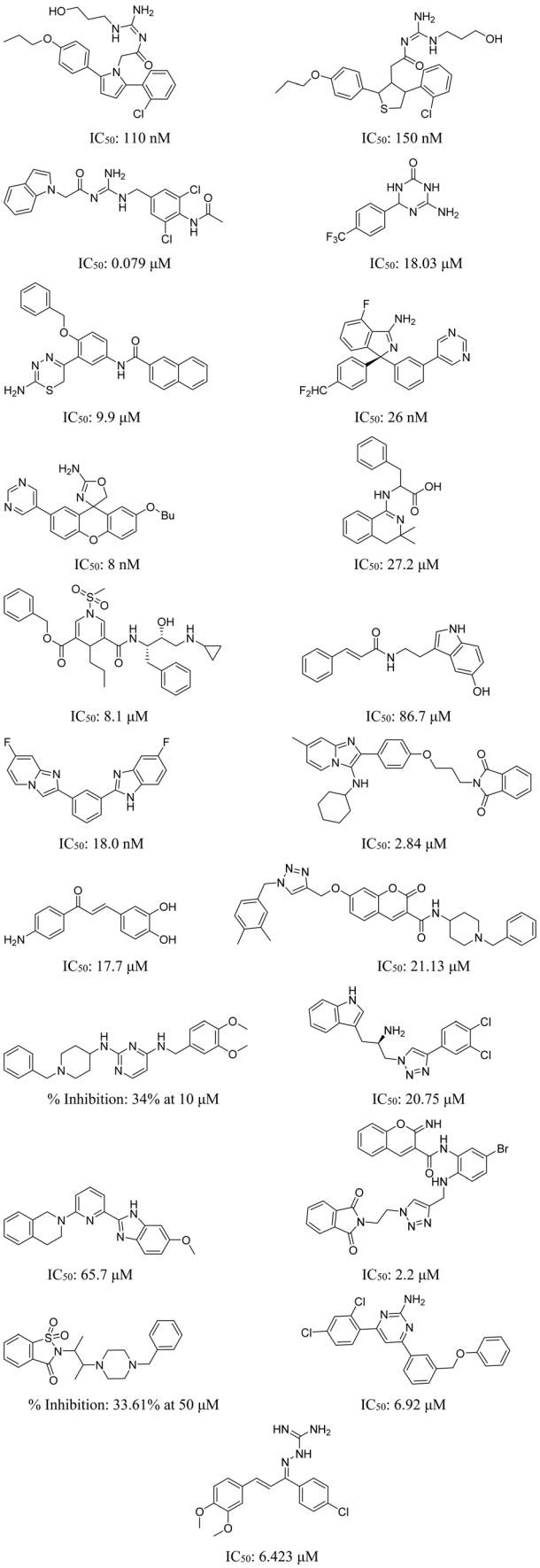


Fig. 9 A few representative β-secretase inhibitors for AD.[62,63]

Table 4 γ-Secretase inhibitors for AD in clinical trials

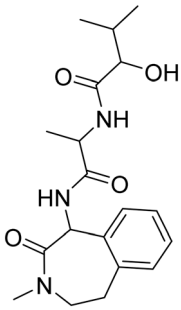
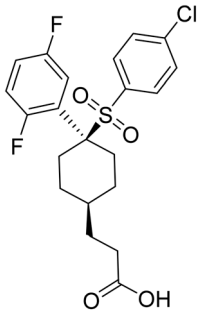
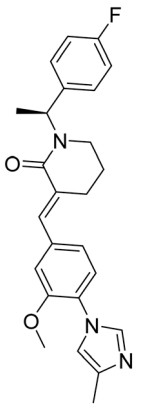
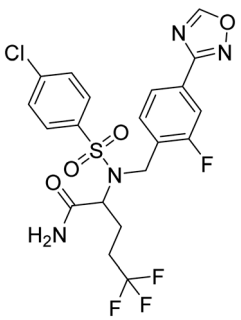
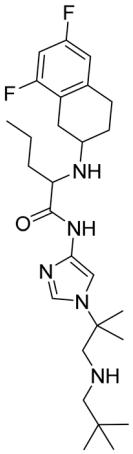
Drug name	Structure	Mode of action	Remarks	Status	Ref.
Semagacestat		Reduces Aβ levels in AD and induces changes in the peptidome of human cerebrospinal fluid	In phase III trials, the outcome was inferior to placebo	Terminated in phase III	67
MK-0752 3-((1*s*,4*r*)-4-((4-chlorophenyl)sulfonyl)-4-(2,5-difluorophenyl)cyclohexyl) propanoic acid		Lowers Aβ1-40 levels in healthy participants, and currently undergoing testing for its potential in cancer treatment	The medication was linked to gastrointestinal discomfort and feelings of fatigue	Terminated in phase I	68
E 2012 (*S*,*E*)-1-(1-(4-fluorophenyl) ethyl)-3-(3-methoxy-4-(4-methyl-1*H*-imidazol-1-yl)benzylidene)piperidin-2-one		A gamma-secretase inhibitor/modulator that preserves notch function without impacting notch processing	Lenticular opacity	Terminated in phase I	69
Avagacestat, BMS-708163, 2-((4-chloro-*N*-(2-fluoro-4-(1,2,4-oxadiazol-3-yl)benzyl)phenyl) sulfonamido)-5,5,5-trifluoropentanamide		Preserving notch function leads to a reduction in Aβ levels in the cerebrospinal fluid of healthy participants	Amyloid-related imaging abnormalities (ARIA)	Terminated in phase II	69

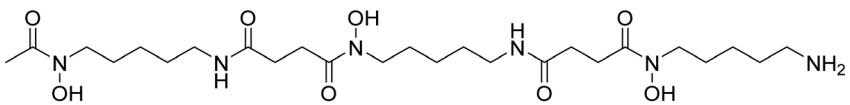
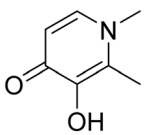
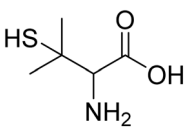
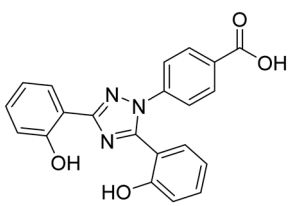
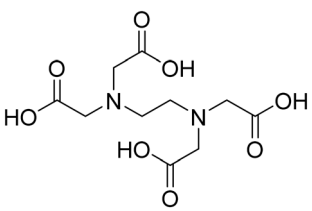
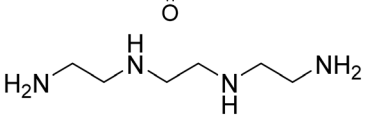
Table 4 *(continued)*

Drug name	Structure	Mode of action	Remarks	Status	Ref.
Nirogacestat, PF-3084014 2-((6,8-difluoro-1,2,3,4-tetrahydronaphthalen-2-yl)amino)-*N*-(1-(2-methyl-1-(neopentylamino) propan-2-yl)-1*H*-imidazol-4-yl) pentanamide		Reversible, orally bioavailable, noncompetitive, and selective γ-secretase inhibitor	Aβ1-40 levels show no decline in the cerebrospinal fluid of patients with AD	US FDA has approved its use for desmoid tumors. Terminated in phase II for AD patients	69

nonamyloidogenic pathway, potentially influencing the progression of AD (Table 3).[56]

β-Secretase. The 1999 discovery of β-secretase (BACE) was pivotal in AD research, identified independently by five research groups using various names like BACE, β-secretase, Asp2, or memapsin 2.[58] BACE, a type 1 transmembrane aspartic protease with 501 amino acids, functions optimally under low pH conditions in intracellular compartments. It is predominantly expressed in brain neurons, and modulating its expression directly impacts Aβ production.[59] BACE's

Table 5 Clinically approved small molecule-based chelating agents in metal chelation therapy

Name	Structure
Deferoxamine	
Deferiprone	
D-Penicillamine	
Deferasirox	
Ethylenediaminetetraacetic acid	
Triethylenetetramine (TETA)	

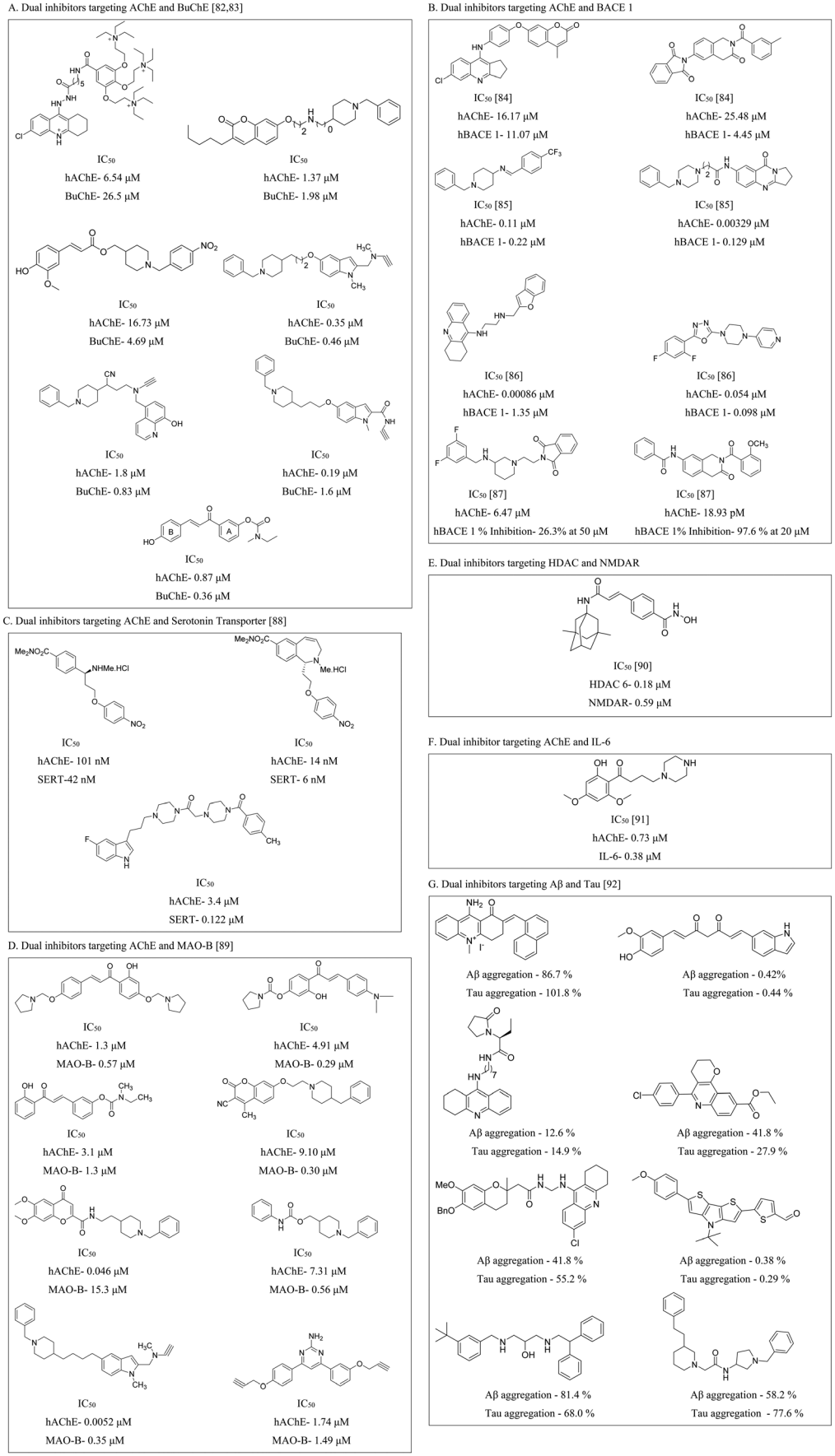


Fig. 10 Structures of some of the representative dual inhibitors.[82–92]

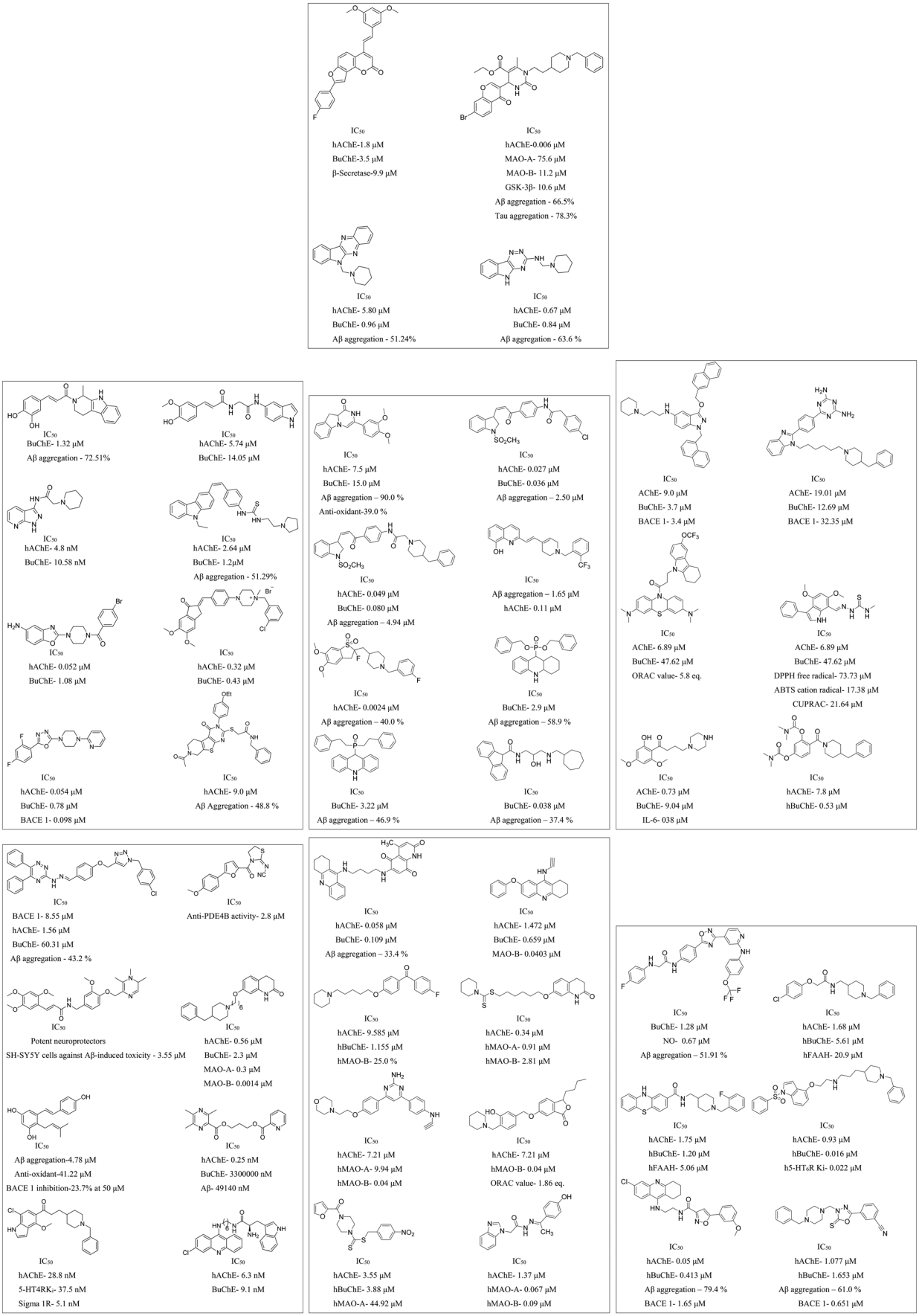


Fig. 11 Structures of some of the representative multi-target-directed ligands.[86,96,97]

Table 6 Drugs under clinical trial for AD treatment

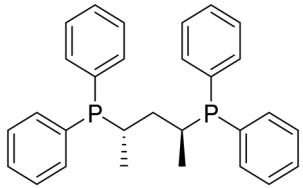
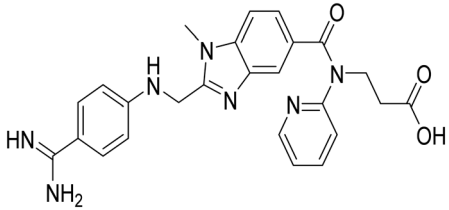
Drug name	Structure	Mode of action	Class	National Clinical Trial number
Phase I				
Disease-modifying biologicals				
		Mode of action		
MK-2214		Anti-tau monoclonal antibody	Tau	NCT05466422
SHR-1707		Prevent Aβ plaque and activate microglia to phagocytize various forms of Aβ	Amyloid	NCT06199037
NIO752		Antisense oligonucleotide to tau, decreasing the abundance of tau aggregates at neuromuscular junction	Tau	NCT06372821
IBC-Ab002		Humanized IgG1 antibody inhibits an immune checkpoint protein (PD-L1), stimulating the immune system	Inflammation/immunity	NCT05551741
ALN-APP		Small interfering RNA targeting the amyloid precursor protein mRNA	Amyloid	NCT05231785
CpG1018		Immune adjuvant made up of short, unmethylated cytosine–phosphate–guanine oligodeoxynucleotides, stimulate clearance of amyloid pathology	Inflammation/immunity	NCT05606341
AL003		Monoclonal antibody (MAb) targeting SIGLEC-3 (CD33), reactivates microglia and immune cells in the brain, improves microglial clearance of toxic proteins	Inflammation	NCT03822208
AAV-hTERT		Extending telomeres may benefit AD, reduce Aβ-induced neurotoxicity, and effects on multiple cellular pathways	Epigenetic	NCT04133454
Lu AF87908		MAb to reduce tau	Tau	NCT04149860
LY3372993		MAb to reduce amyloid (N3pG-AB)	Amyloid	NCT06653153
AAVrh.10hAPOE2		MAb targeting SIGLEC-3 (CD33), reactivates microglia and immune cells in the brain, improves microglial clearance of toxic proteins	Epigenetic	NCT05400330
XPro1595		TNF inhibitor, reduces neuroinflammation	Inflammation	NCT05318976
GSK933776		MAb against N-terminus of Aβ	Amyloid	NCT00459550
ALZ-101		Vaccine against soluble Aβ oligomers	Amyloid	NCT05328115
VT301		Regulatory T-cells (Tregs)	Inflammation	NCT05016427
CAD106		CAD106 combines multiple copies of Aβ1-6 peptide derived from the N-terminal B cell epitope of Aβ, coupled to a Qβ virus-like particle. In animals, CAD106 induced Aβ-antibody titers without activating Aβ-reactive T cells	Amyloid	NCT01097096
KHK6640		MAb that consists of anti-Aβ-peptide	Amyloid	NCT02377713
NPT088		An Ig-fusion general amyloid interaction motif (GAIM) based dimer	Amyloid	NCT03008161
Disease-modifying drugs				
BDPP (2*S*,4*S*)-(−)-2,4-bis(diphenylphosphino)pentane		Prevents Aβ and tau aggregation	Proteostasis/proteinopathies	NCT02502253
BEY2153		Aβ and tau aggregation inhibitor, inhibits neuronal death	Proteostasis/proteinopathies	NCT04476303
Dabigatran		Direct thrombin inhibitor, reduce neurovascular damage	Vasculature	NCT03752294

Table 6 *(continued)*

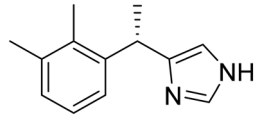
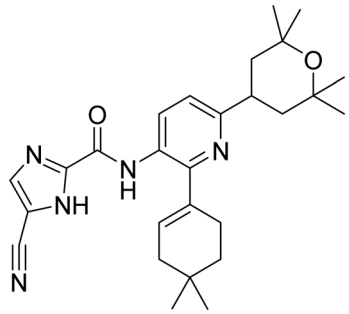
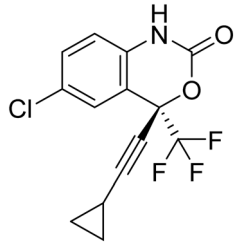
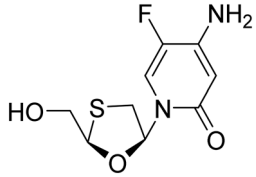
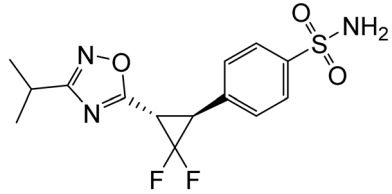
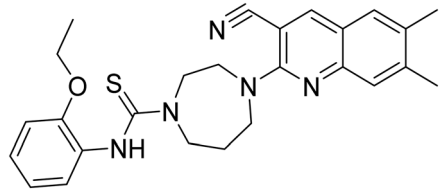
Drug name	Structure	Mode of action	Class	National Clinical Trial number
Dexmedetomidine		Selective α2-adrenergic receptor agonist, neuroprotection	Circadian rhythm	NCT06052254
Edicotinib		CSF-1R antagonist, attenuates microglial proliferation and neurodegeneration	Inflammation	NCT04121208
Efavirenz		NNRTI, promotes cholesterol removal, enhances amyloid reduction	Epigenetics	NCT03706885
Emtricitabine		NRTI, reduces neuroinflammation	Inflammation	NCT04500847
MK-4334		Positive allosteric modulators of α7 nAChR	Growth factors and hormones	NCT03740178
NNI-3624-(3-cyano-6,7-dimethylquinolin-2-yl)-*N*-(2-ethoxyphenyl)-1,4-diazepane-1-carbothioamide		Enhance neurogenesis, activates progenitor cells	Neurogenesis	NCT04074837

Table 6 *(continued)*

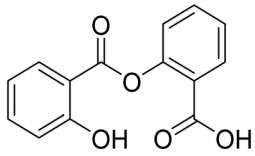
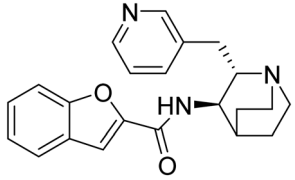
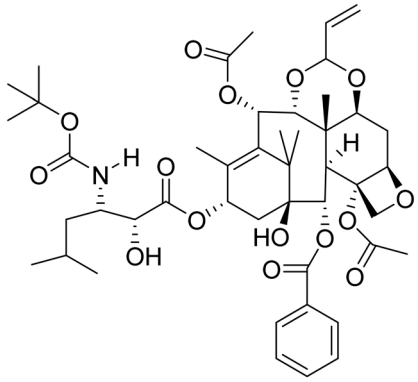
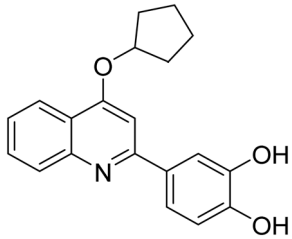
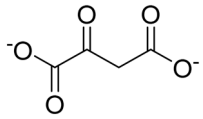
Drug name	Structure	Mode of action	Class	National Clinical Trial number
REM0046127	Regulates calcium dyshomeostasis, tau and Aβ reduction		Synaptic plasticity/neuroprotection	NCT04672135
Salsalate		NSAID to reduce inflammation	Inflammation	NCT03277573
TC-5619 *N*-((2*S*,3*R*)-2-(pyridin-3-ylmethyl) quinuclidin-3-yl)benzofuran-2-carboxamide		Partial agonist at the α7 subtype of the neural nicotinic acetylcholine receptors	Cognition enhancement	NCT01254448
TPI-287 (1*S*,4*S*,7*S*,7*aR*,7*a*1*S*,10*aS*,11*aR*,13*aS*,13*bR*)-1-(benzoyloxy)-4-(((2*R*,3*S*)-3-((*tert*-butoxycarbonyl)amino)-2-hydroxy-5-methylhexanoyl)oxy)-2-hydroxy-5,7*a*1,14,14-tetramethyl-9-vinyl-1,3,4,7,7*a*,7*a*1,10*a*,11,11*a*,13*b*-decahydro-2*H*-8,10,12-trioxa-2,6-methanocyclobuta[*b*] cyclodeca[*de*]naphthalene-7,13*a*(13*H*)-diyl diacetate		Stabilization of microtubule	Tau	NCT01966666
CMS121 4-(4-(cyclopentyloxy)quinolin-2-yl) benzene-1,2-diol		Fatty acid synthase inhibitor it protects against excess lipid peroxidation and inflammation and alleviates cognition	Inflammation	NCT05318040
Oxaloacetate		Improves mitochondrial function	Bioenergetics	NCT02593318
Telmisartan		Angiotensin II receptor blocker	Vasculature	NCT02471833

Table 6 *(continued)*

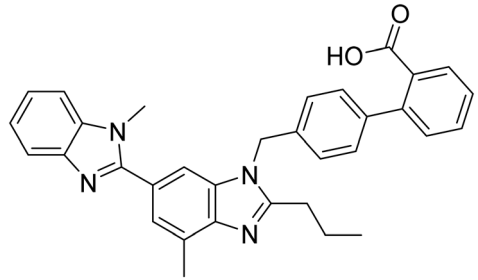
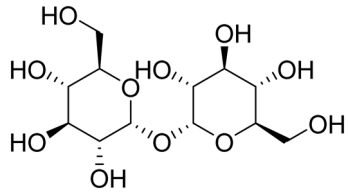
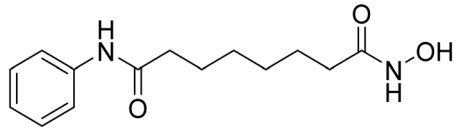
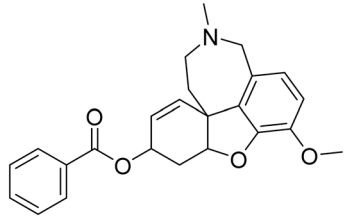
Drug name	Structure	Mode of action	Class	National Clinical Trial number
				
Trehalose		Induces autophagy and promotes clearance of aggregated proteins	Cell death	NCT05332678
Vorinostat		Histone deacetylase (HDAC) inhibitor, enhanced synaptic plasticity	Epigenetics	NCT03056495
Symptom-reducing small molecules				
MK-1942	Improves mitochondrial structure and function		Neurotransmitter receptors	NCT04308304
MK-8189	Phosphodiesterase 10A inhibitor		Behavioural changes	NCT05227118
Memogain		AChE/BuChE MTDL	Neurotransmitter receptors	—
Phase II				
Disease-modifying biologicals				
AL002	MAb targeting TREM2 receptors to promote microglial clearance of Aβ		Inflammation	NCT05744401
ACI-35	Active immunotherapy targeting tau		Tau	NCT04445831
ABvac40	Active immunotherapy to remove Aβ		Amyloid	NCT03461276
AADvac1	This is an active vaccine designed to elicit an immune response against pathologically modified forms of tau protein		Tau	NCT01850238
BCG vaccine	Vaccination against tuberculosis infection, immunomodulator		Inflammation	NCT05004688
Bryostatin 1	Protein kinase C inhibitor, facilitates synaptogenesis		Synaptic plasticity/neuroprotection	NCT04538066
Daratumumab	MAb targeting CD38, regulates microglial activity		Inflammation/immunity	NCT04070378
Etanercept	Inhibits the function of a pro-inflammatory cytokine called tumor necrosis factor alpha (TNF-α)		Inflammation	NCT01068353

Table 6 *(continued)*

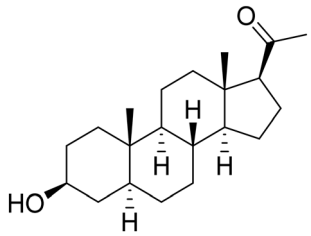
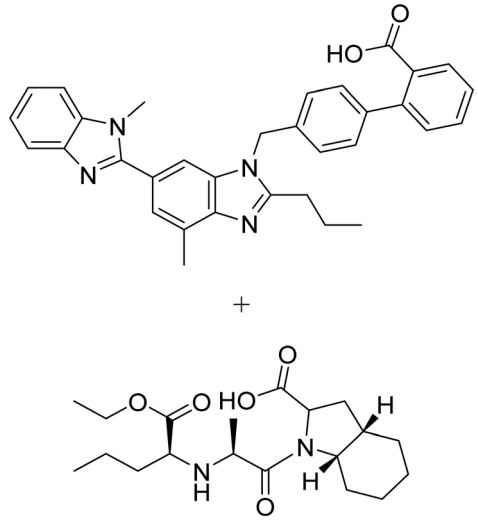
Drug name	Structure	Mode of action	Class	National Clinical Trial number
Crenezumab	MAb targeting soluble Aβ oligomers		Amyloid	NCT01723826
Gosuranemab	MAb targeting truncated form of tau		Tau	NCT03352557
Gantenerumab	Human IgG1 Ab against Aβ fibrils		Amyloid	NCT01760005
Pepinemab	MAb directed at semaphorin 4D to reduce inflammation		Inflammation	NCT04381468
GV1001	hTERT peptide vaccine, mimics extra-telomeric functions to inhibit neurotoxicity, apoptosis, and reactive oxygen species		Epigenetic	NCT05303701
GB301	Regulatory T cells, reduce neuroinflammation		Inflammation/immunity	NCT04468659
IVIG	Polyclonal antibody, remove amyloid		Amyloid	NCT01300728
JNJ-63733657	MAb targeting soluble tau		Tau	NCT04619420
IONIS MAPTRx	Antisense oligonucleotide targeting tau expression, MAPT RNA inhibitor		Tau	NCT03186989
R07126209	Anti-Aβ MAb with enhanced BBB penetration		Amyloid	NCT04639050
Semorinemab	MAb to remove extracellular tau		Tau	NCT03828747
Tilavonemab	MAb to remove tau and prevent propagation		Tau	NCT02880956
Zagotenemab	MAb to remove tau and reduce tau propagation		Tau	NCT03518073
Disease-modifying drugs				
Allopregnanolone		GABA-A receptor modulator, promote neurogenesis and reduce inflammation	Growth factors/hormones	NCT04838301
Telmisartan + perindopril		Telmisartan: angiotensin II receptor blocker Perindopril: angiotensin converting enzyme inhibitor	Vasculature	NCT02085265
Empagliflozin		SGLT2 inhibitor, improve glycemic control, enhance neuronal function	Metabolism and bioenergetics	NCT05081219

Table 6 *(continued)*

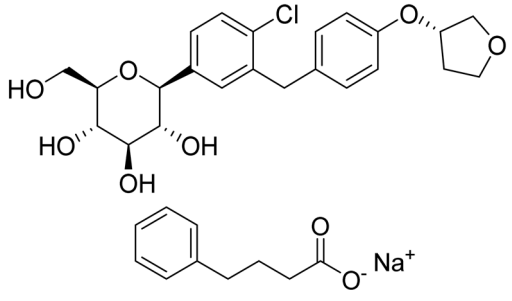
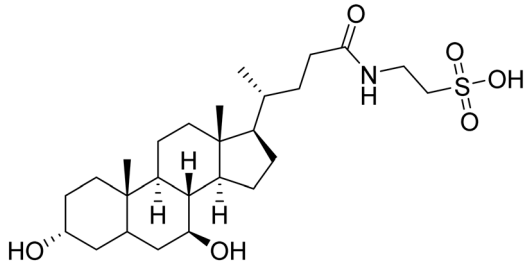
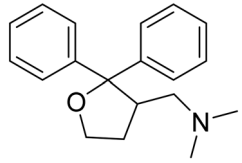
Drug name	Structure	Mode of action	Class	National Clinical Trial number
Sodium phenylbutyrate + tauroursodeoxycholic acid		Reduce cell death associated with mitochondrial dysfunction, modulate neuroinflammation	Cell death	NCT03533257
Fosgonimeton		Activates signalling *via* the hepatocyte growth factor system to regenerate neurons and enhance synaptic plasticity	Synaptic plasticity/neuroprotection	NCT04488419
AR1001	PDE-5 inhibitor it improves synaptic plasticity		Synaptic plasticity/neuroprotection	NCT05531526
Blarcamesine		Sigma-1 receptor agonist, M2 antagonist, ameliorate oxidative stress, protein misfolding, mitochondrial dysfunction and inflammation	Synaptic plasticity/neuroprotection	NCT04314934
Zatolmilast		PDE-4 inhibitor, prolongs cAMP activity and improves neuronal plasticity	Synaptic plasticity/neuroprotection	NCT03817684

Table 6 *(continued)*

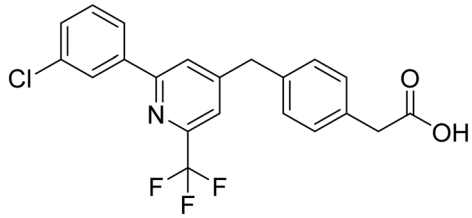
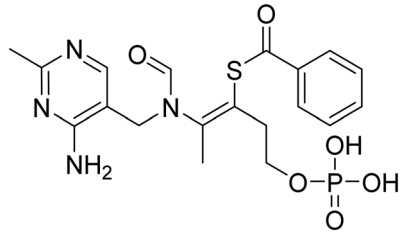
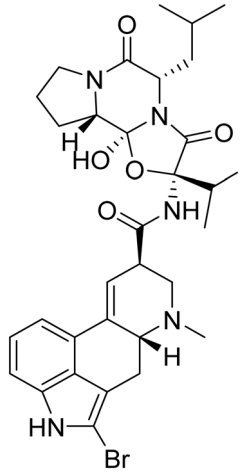
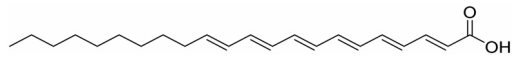
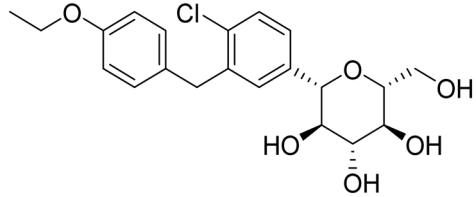
Drug name	Structure	Mode of action	Class	National Clinical Trial number
				
Benfotiamine		Synthetic thiamine to improve neuronal function	Metabolism and bioenergetics	NCT06223360
Bromocriptine		Dopamine agonist with anti-Aβ effects	Neurotransmitter receptors	NCT04413344
DHA (docosahexanoic acid)		Omega 3 fatty acid, improve synaptic function, antioxidant	Oxidative stress	NCT00440050
Dapagliflozin		SGLT2 inhibitor, to improve insulin sensitivity and CNS glucose metabolism	Metabolism and bioenergetics	NCT03801642
Elayta		Sigma-2 receptor antagonist, competes	Synaptic	NCT05531656

Table 6 *(continued)*

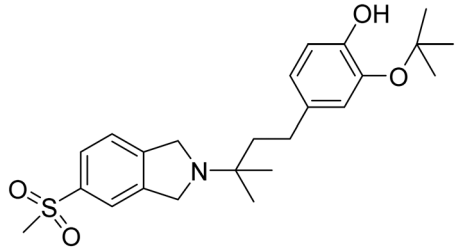
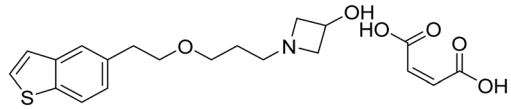
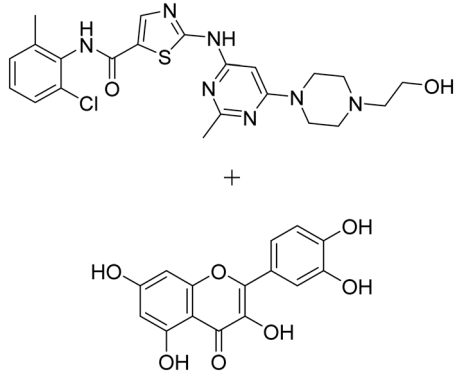
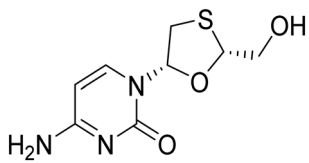
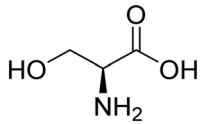
Drug name	Structure	Mode of action	Class	National Clinical Trial number
		with oligomeric Aβ binding, protect against Aβ-induced synaptic toxicity	plasticity/neuroprotection	
Edonerpic acid		Neurotrophic agent, activates sigma receptors to preserve synaptic plasticity, protect against Aβ toxicity	Synaptic plasticity/neuroprotection	NCT00663936
Dasatinib + quercetin		Dasatinib: tyrosine kinase inhibitor Quercetin: flavonoid, senolytic therapy approach to reduce senescent cells and tau aggregation	Inflammation/immunity	NCT05422885
Lamivudine		Nucleoside reverse transcriptase inhibitor, reduces genetic rearrangements	Epigenetic	NCT04552795
L-Serine		Dietary amino acid, reduce brain inflammation and preserve nerve cells	Inflammation	NCT05331144
Liraglutide		Glucagon-like peptide 1 receptor agonist, improve CNS glucose metabolism	Metabolism and bioenergetics	NCT01469351

Table 6 *(continued)*

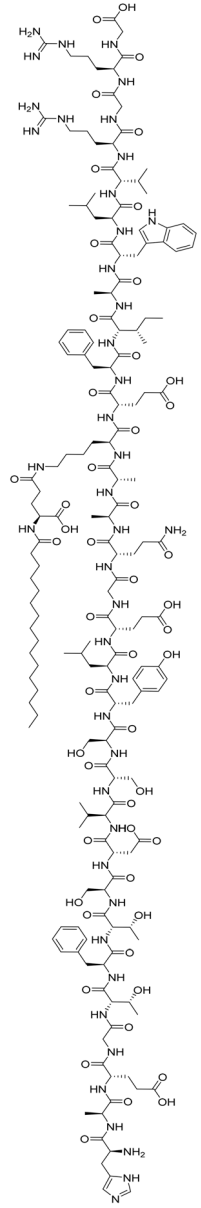
Drug name	Structure	Mode of action	Class	National Clinical Trial number
				

Table 6 *(continued)*

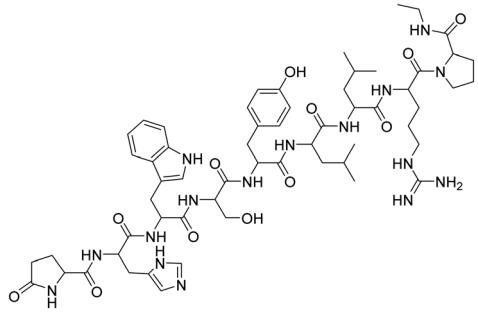
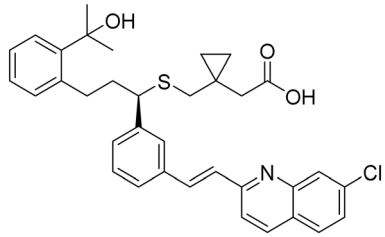
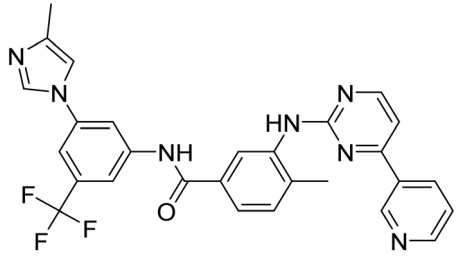
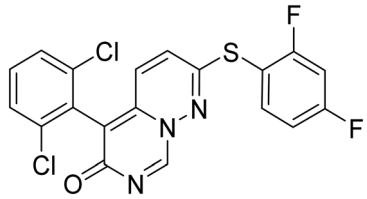
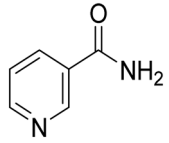
Drug name	Structure	Mode of action	Class	National Clinical Trial number
Lupron		GnRH receptor agonist, reduce effects of elevated GnRH and gonadotropins on the brain	Growth factors and hormones	NCT00063310
Montelukast		Cysteinyl leukotriene type 1 (cysLT-1) receptor antagonist, effects on inflammatory processes, neuronal injury, blood–brain-barrier integrity, and Aβ protein accumulation	Inflammation	NCT03991988
Nilotinib		Tyrosine kinase inhibitor, autophagy enhancer, promotes clearance of Aβ and tau	Proteostasis/proteinopathies	NCT05143528
Neflamapimod		p38 MAPK-α inhibitor, enhance endolysosomal function to reduce synaptic dysfunction	Synaptic plasticity/neuroprotection	NCT03402659
Nicotinamide		HDAC inhibitor, reduce tau-induced microtubule depolymerization and tau phosphorylation	Tau	NCT00580931
Tacrolimus		Calcineurin inhibitor, prevent Aβ-induced dendritic spine loss and	Synaptic plasticity/neuroprotection	NCT04263519

Table 6 *(continued)*

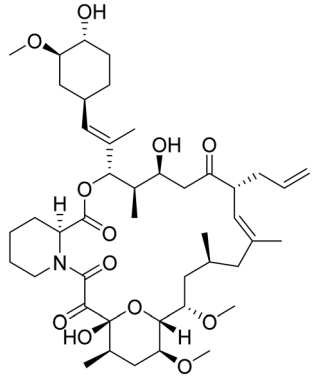
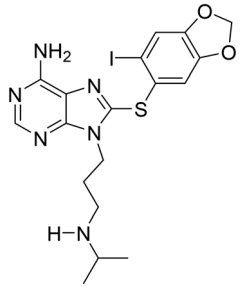
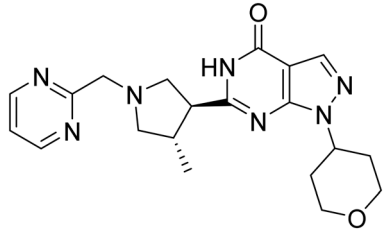
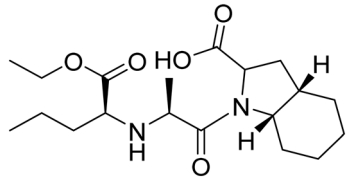
Drug name	Structure	Mode of action	Class	National Clinical Trial number
		synaptic dysfunction		
PU-AD8-((6-iodobenzo[*d*][1,3]dioxol-5-yl) thio)-9-(3-(isopropylamino)propyl)-9*H*-purin-6-amine		Heat shock protein 90 inhibitor, prevent aggregation and hyperphosphorylation of tau	Tau	NCT03935568
PF-044479436-((3*S*,4*S*)-4-methyl-1-(pyrimidin-2-ylmethyl)pyrrolidin-3-yl)-1-(tetrahydro-2*H*-pyran-4-yl)-1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-one		Selective phosphodiesterase 9 (PDE9) inhibitor	Cognition enhancement	NCT00988598
Perindopril		Angiotensin converting enzyme inhibitor	Vasculature	NCT02085265

Table 6 *(continued)*

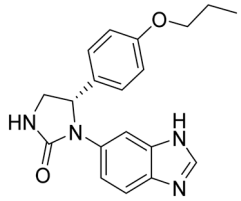
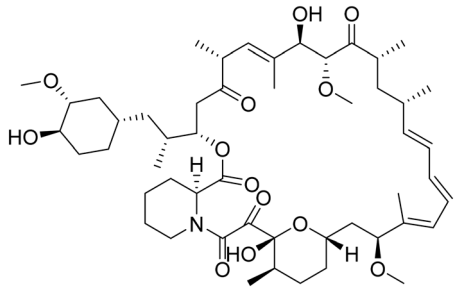
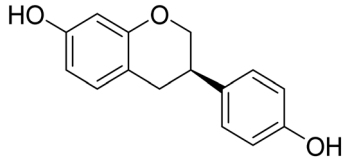
Drug name	Structure	Mode of action	Class	National Clinical Trial number
PQ912(*S*)-1-(1*H*-benzo[*d*]imidazol-6-yl)-5-(4-propoxyphenyl)imidazolidin-2-one		Glutaminyl cyclase (QC) enzyme inhibitor to reduce pyroglutamate Aβ (pGlu-Aβ) production	Amyloid	NCT02389413
Rapamycin		mTOR inhibitor, ameliorate metabolic and vascular effects of aging	Proteostasis/proteinopathies	NCT04629495
S-Equol		Agonist of non-hormonal estrogen receptor B located on mitochondria to potentiate mitochondrial function	Metabolism and bioenergetics	NCT03101085

Table 6 *(continued)*

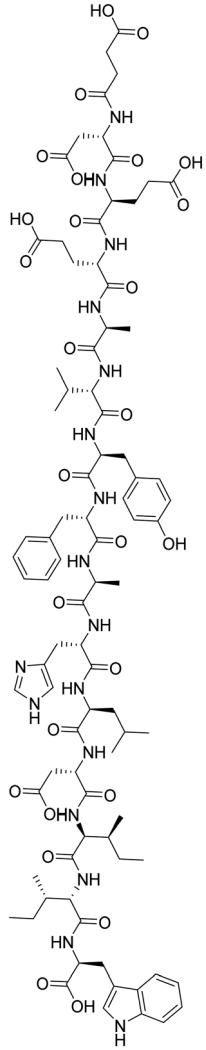
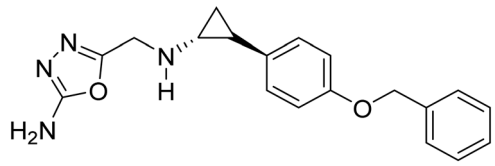
Drug name	Structure	Mode of action	Class	National Clinical Trial number
Sovateltide		Endothelin B receptor agonist, augments activity of neuronal progenitor cells	Neurogenesis	NCT04052737
Vafidemstat		HDAC demethylase inhibitor and MAO-B inhibitor, neuroprotective	Synaptic plasticity/neuroprotection	NCT03867253

Table 6 *(continued)*

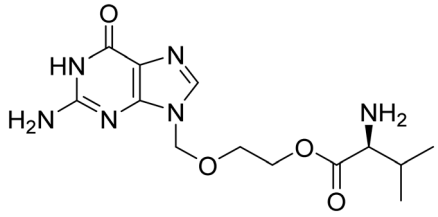
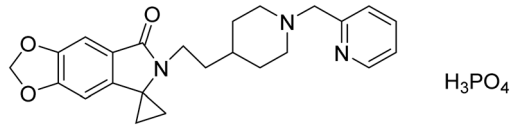
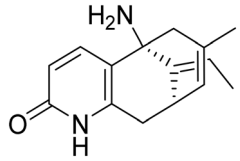
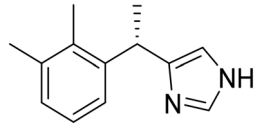
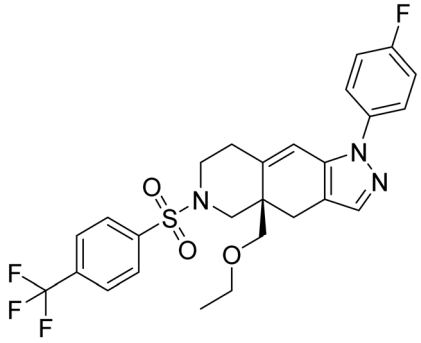
Drug name	Structure	Mode of action	Class	National Clinical Trial number
Valacyclovir		Antiviral against HSV-1 and -2 infection, prevent Aβ aggregation and plaque deposition	Infection/immunity	NCT03282916
Symptom-reducing small molecules				
AD-35phosphenoperoxoic acid compound with 6′-(2-(1-(pyridin-2-ylmethyl)piperidin-4-yl)ethyl)spiro[cyclopropane-1,5′-[1,3]dioxolo[4,5-*f*]isoindol]-7′(6′*H*)-one		Acetylcholinesterase inhibitor	Neurotransmitter receptors	NCT03625401
Huperzine A		NMDA receptor antagonist and AChE inhibitor (MTDL)	Neurotransmitter receptors	NCT00083590
Dexmedetomidine		Sublingual dexmedetomidine, selective α2-adrenergic receptor agonist	Neurotransmitter receptors	NCT06052254
CORT108297(*R*)-4*a*-(ethoxymethyl)-1-(4-fluorophenyl)-6-((4-(trifluoromethyl)phenyl)sulfonyl)-4,4*a*,5,6,7,8-hexahydro-1*H*-pyrazolo[3,4-*g*]isoquinoline		Selective glucocorticoid receptor antagonist, reduce neuroendocrine stress responses	Hormone (cognition enhancement)	NCT04601038

Table 6 *(continued)*

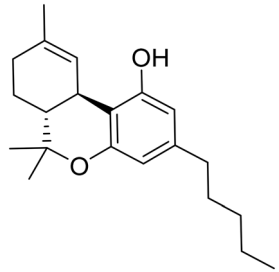
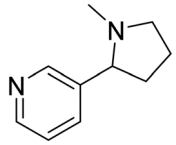
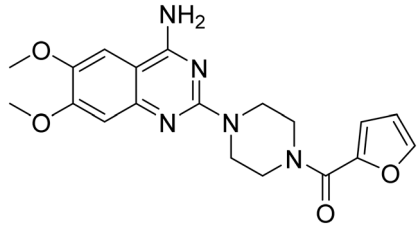
Drug name	Structure	Mode of action	Class	National Clinical Trial number
Dronabinol		CB1 and CB2 endocannabinoid receptor partial agonist	Neurotransmitter receptors	NCT02792257
Nicotine		Nicotinic acetylcholine receptor agonist enhances cognition	Neurotransmitter receptors	NCT02720445
Prazosin		α-1 adrenoreceptor antagonist	Neurotransmitter receptors	NCT01126099
SAGE-718	First-in-class, oxysterol-based positive allosteric modulator (PAM) of *N*-methyl-D-aspartate (NMDA) receptors		Neurotransmitter receptors	NCT05619692
Phase III				
Disease-modifying biologicals				
Donanemab	MAb specific for pyroglutamate form of Aβ		Amyloid	NCT06566170
Gantenerumab	MAb directed at Aβ plaques and oligomers		Aβ	NCT01760005
Lecanemab	MAb directed at Aβ protofibrils		Aβ	NCT05269394
UB311	Vaccine that stimulates a T-helper type 2 regulatory immune response over a T-helper type 1 pro-inflammatory response, and to avoid cross-reactivity with similar endogenous antigens, *i.e.*, autoimmune responses		Amyloid	NCT02551809

Table 6 *(continued)*

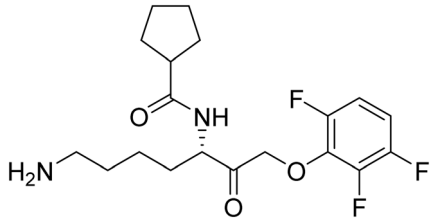
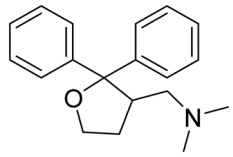
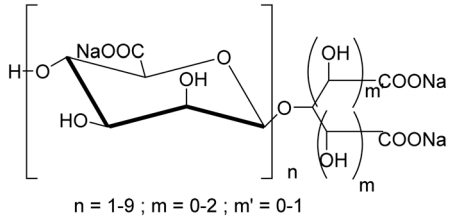
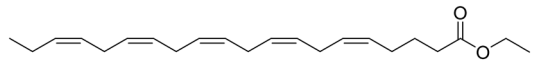
Drug name	Structure	Mode of action	Class	National Clinical Trial number
Disease-modifying drugs				
Atuzaginstat		It reduces neuroinflammation and hippocampal degeneration	Inflammation/infection due to *P. gingivalis*	NCT03823404
Blarcamesine		Sigma-1 receptor agonist, M2 autoreceptor antagonist. It ameliorates oxidative stress, protein misfolding, mitochondrial dysfunction, and inflammation	Synaptic plasticity	NCT04314934
GV-971sodium (2*S*,3*S*,4*S*,5*S*,6*R*)-6-((1-carboxylato-2,4-dihydroxyhexan-3-yl)oxy)-3,4,5-trihydroxytetrahydro-2*H*-pyran-2-carboxylate oxo-l3-methanolate		Algae-derived acidic oligosaccharides, changes microbiome to reduce peripheral and central inflammation	Inflammation	NCT04520412
Icosapent ethyl		Purified form of the omega-3 fatty acid EPA. It improves synaptic function and reduces inflammation	Oxidative stress	NCT02719327

Table 6 *(continued)*

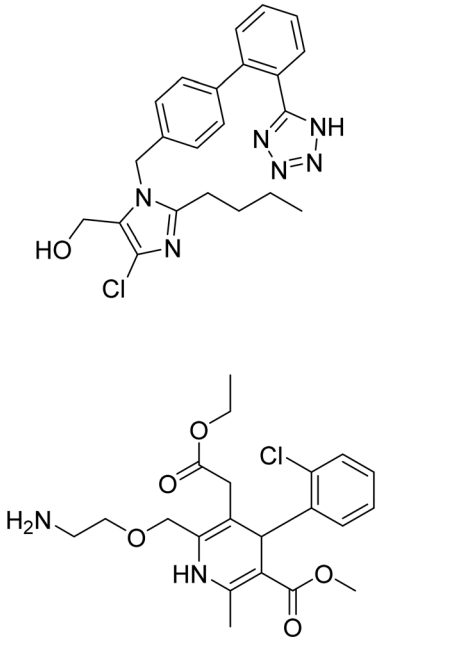
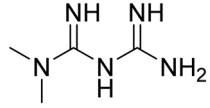
Drug name	Structure	Mode of action	Class	National Clinical Trial number
Losartan + amlodipine + atorvastatin		Losartan: angiotensin II receptor blocker Amlodipine: calcium channel blocker Atorvastatin: anti-hyperlipidemic (HMG--CoA reductase inhibitor)	Vasculature	NCT02913664
Metformin		Insulin sensitizer to improve CNS glucose metabolism	Metabolism and bioenergetics	NCT04098666
Omega-3 fatty acids		Antioxidant	Oxidative stress	NCT01058941

Table 6 *(continued)*

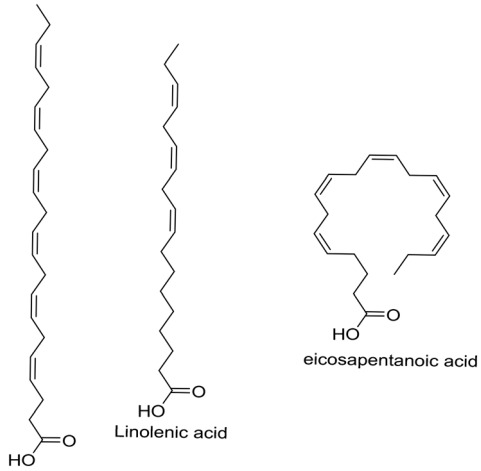
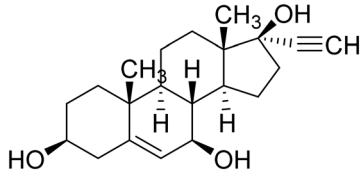
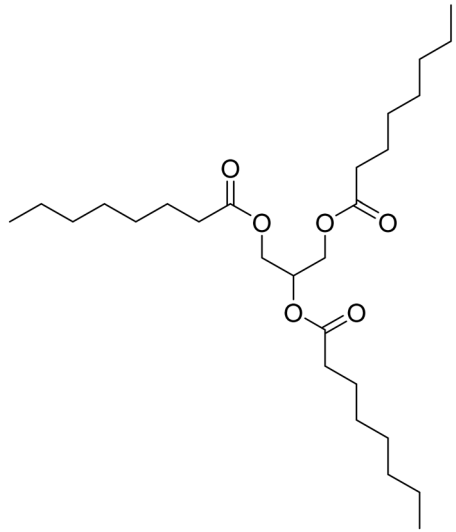
Drug name	Structure	Mode of action	Class	National Clinical Trial number
				
NE3107		MAPK-1/3 inhibitor. It reduces pro-inflammatory NFκB activation	Inflammation	NCT04669028
Tricaprilin		Caprylic triglyceride. It induces ketosis and improves mitochondrial and neuronal function	Metabolism and bioenergetics	NCT05809908

Table 6 *(continued)*

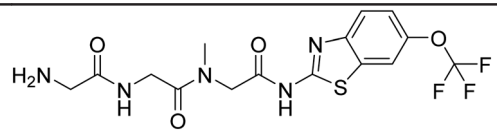
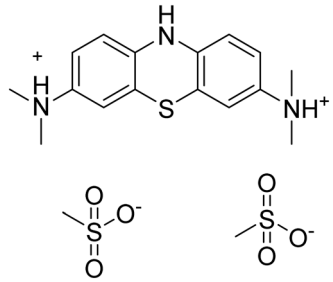
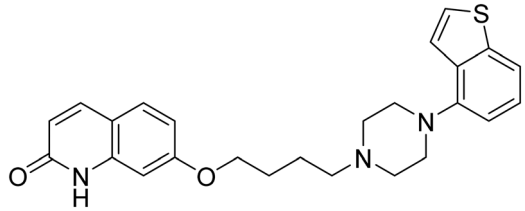
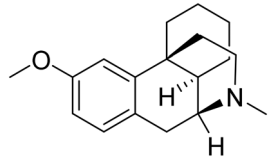
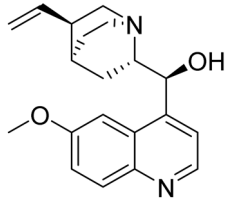
Drug name	Structure	Mode of action	Class	National Clinical Trial number
Troriluzole		Glutamate modulator; prodrug of riluzole. It improves synaptic function	Synaptic plasticity/neuroprotection	NCT03605667
Leuco-methylthioninium (LMTX) mesylate		Tau protein aggregation inhibitor	Tau	NCT03539380
Symptom-reducing small molecules				
Brexpiprazole		Atypical antipsychotic, D2 receptor partial agonist	Neurotransmitter receptors	NCT03548584
Dextromethorphan + quinidine	 	Sigma1 receptor agonist, NMDA receptor antagonist	Neurotransmitter receptors	NCT01584440
Donepezil + memantine		Donepezil: binds to AChE and reversibly inactivates it Memantine: blocks current flow through NMDA receptor channels	Cognition enhancement	NCT02580305

Table 6 *(continued)*

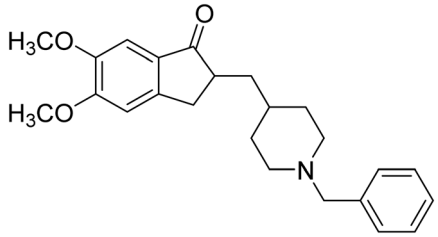
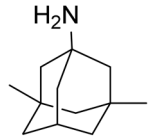
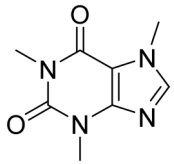
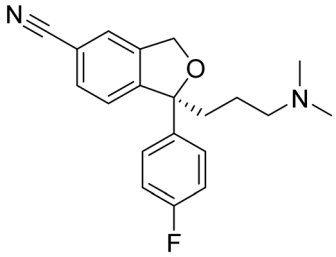
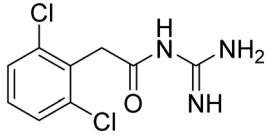
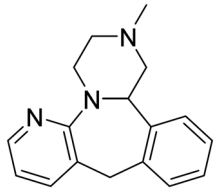
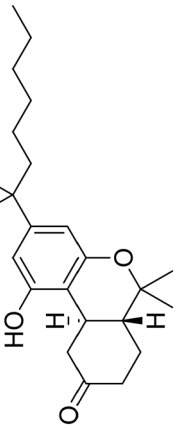
Drug name	Structure	Mode of action	Class	National Clinical Trial number
				
				
Caffeine		Pleiotropic effect on CNS	Metabolism and bioenergetic, cognition enhancement	NCT00692510
Escitalopram		Selective serotonin reuptake inhibitor	Neurotransmitter receptors	NCT05004987
Guanfacine		α-2 adrenergic agonist	Cognition enhancement	NCT03116126
Mirtazapine		α-1 antagonist	Neurotransmitter receptors	NCT01505504

Table 6 *(continued)*

Drug name	Structure	Mode of action	Class	National Clinical Trial number
Nabilone		Synthetic cannabinoid, CB1 and CB2 receptor agonist. It suppresses neuronal excitability and neurotransmitter release	Neurotransmitter receptors	NCT04516057
Octohydroamino-acridine succinate		AChE inhibitor	Cognition enhancement	NCT01569516

discovery led to the identification of its homolog, BACE2. Still, due to its low expression in brain neurons and distinct APP cleavage activity, BACE1 remains the main β-secretase, a potential therapeutic target to reduce cerebral Aβ levels in AD.[60]

Despite several drugs developed to inhibit BACE activity, such as elenbecestat, atabecestat, lanabecestat, and verubecestat, failing to reach the market, researchers remain committed to the pursuit of BACE-inhibitory drugs due to the critical role it has in the disease development.[61] The structures of some of the representative β-secretase inhibitors are given in Fig. 9, indicating the use of various scaffolds.

γ-Secretase. γ-Secretase, composed of presenilin-I (PS-I), nicastrin, anterior pharynx-I, and presenilin enhancer-2, plays a pivotal role in AD as it executes the final intramembrane cleavage of APP.[64] γ-Secretase cleavage, which follows cleavage by α-secretase, yields the C99 fragment, leading to a minor fraction of Aβ-42. Mutations in presenilins, the catalytic core of γ-secretase, contribute to elevated Aβ-42 levels in familial AD (FAD). However, γ-secretase influences other substrates like notch, delta, and tumor necrosis factor-alpha converting enzyme (TACE).[65] Targeting γ-secretase to reduce Aβ formation is challenging due to the potential disruption of vital functions of these substrates.[66] As a result, drugs designed as γ-secretase modulators (such as avagacestat, semagacestat, and flurizan) have faced setbacks during clinical trials.[67] The status of different γ-secretase inhibitors is shown in Table 4.

3.2.3 Metal chelators. Metal ions, such as Zn^{2+}, Cu^{2+}, and Fe^{3+}, promote the aggregation of β-amyloid. Zn^{2+} can lead to aggregation even at low physiological concentrations, while Cu^{2+} and Fe^{3+} enhance aggregation under mildly acidic conditions. Elevated Cu^{2+} and Zn^{2+} levels have been linked to developing the apoE4 allele associated with AD. β-Amyloid also participates in redox reactions mediated by metal ions, generating ROS.[70] To counteract metal interactions with Aβ, strategies like using iron-chelating agents are under investigation (Table 5).[71]

3.2.4 Acetylcholinesterase inhibitors. The cholinergic hypothesis in AD focused on the loss of cholinergic neurons. It reduced acetyltransferase (ChAT) activity, primarily in the nucleus basalis of Meynert, a vital source of cholinergic input to the neocortex.[72] This degeneration is associated with cognitive decline, impacting memory, attention, and learning-related brain regions such as the hippocampus and frontal cortex. Issues encompass impaired choline uptake, compromised acetylcholine release, receptor imbalances, disrupted neurotrophin support, and axonal transport deficits. Reduced ChAT and increased AChE activity result in acetylcholine depletion, impairing cognitive function.[73] Treatment primarily relies on acetylcholinesterase inhibitors (AChEIs) to restore acetylcholine levels. Some approved AChEIs include tacrine, donepezil, rivastigmine, galantamine, *etc.*, of which tacrine has been withdrawn.[74]

AD's complexity involves various pathological factors, including Aβ plaques, neurofibrillary tangles, elevated AChE

and MAO activity, and increased reactive oxygen species and metal ions. Single-target drugs often prove insufficient due to AD's multifaceted pathology. Many drugs failed in phase three clinical trials due to inadequate target interaction, toxic side effects, or a lack of differentiation from placebos.[75] FDA-approved treatments offer symptomatic relief but do not halt disease progression. Addressing AD's multifaceted nature demands a comprehensive approach. Combination therapy has limitations, including drug interactions and pharmacokinetic challenges.[76] Multi-target directed ligands (MTDLs) and dual inhibitors are emerging as a promising strategy, targeting multiple disease-related pathways with a single molecule. MTDLs often focus on AChE, MAO enzymes, and the Aβ cascade pathway, offering potential for more effective and streamlined AD treatment by addressing the intricate network of pathological factors involved.[77]

3.3 Dual inhibitors

Given the intricate nature of AD and the multitude of factors contributing to its progression, addressing a single causative aspect is unlikely to yield a complete cure or effectively slow down the disease's advancement.[78] Therefore, recent reports involve the development of molecules capable of targeting two distinct factors concurrently. This innovative strategy offers the potential to diminish required dosage concentrations, enhancing the likelihood of effective treatment and disease progression attenuation. Moreover, it could result in cost savings and alleviate the financial burden on patients.[79–81] Examples of such dual inhibitors are given in Fig. 10.

3.4 Multi-target-directed ligands

Similar to dual inhibitors, multi-target-directed ligands (MTDLs), often termed "dirty drugs", offer promise for AD treatment.[93] These compounds combine pharmacophore moieties from different bioactive compounds, enhancing therapeutic safety and efficacy compared to single-target drugs.[94] MTDLs offer a comprehensive approach to addressing the intricate network of factors contributing to AD pathogenesis (Fig. 11).[95]

4. Candidates under clinical investigation for AD

Despite recent clinical trial failures, several promising candidates are in the AD drug development pipeline. Table 6 collates the available information (updated as of Nov 2024) on various developmental candidates in clinical trials, phase-wise and by category. The list is in addition to the candidates mentioned in the above sections (**https://clinicaltrials.gov/**).

Future perspective

Given the complexity of the condition and the numerous potential risk factors involved, current research is concentrated on various causative factors of AD. Many molecules in the developmental stage are designed to disrupt AD progression by targeting one or multiple agents linked to the condition. These potential targets encompass the accumulation of beta-amyloid and tau proteins (distinctive signs of Alzheimer's), neuroinflammation, immune reactions, metabolic alterations, and various other elements. Recent basic and clinical research has generated extensive insights into the biological mechanisms underlying Alzheimer's disease. Despite advances in understanding the molecular basis of Alzheimer's disease, efforts to develop effective drugs or non-pharmacological interventions to prevent, halt, or slow its progression have remained largely unsuccessful. Extensive pharmaceutical studies and clinical trials, whether successful or not, are invaluable as they help identify promising drugs or eliminate ineffective ones, guiding the way forward in the fight against Alzheimer's disease. The outcomes of "failed" clinical trials should be leveraged to refine and adjust future approaches. Priority should be given to preventing or slowing neurodegeneration, especially in individuals at risk, as treating advanced Alzheimer's such as restoring damaged neurons and synapses will likely remain a challenging task, at least in the near term. Non-pharmacological approaches that utilize modern technologies, such as non-invasive or minimally invasive surgical procedures, should be actively integrated into the strategies for combating Alzheimer's disease. Maintaining a healthy lifestyle through diet, sleep, and exercise can be beneficial and may help delay the onset of Alzheimer's symptoms, potentially through mechanisms like neurogenesis. If a significant delay of one to two decades or more can be achieved, it could effectively equate to the eradication of Alzheimer's disease for many elderly individuals. It is anticipated that the forthcoming treatments will entail a combination of drugs or devices targeting multiple objectives, accompanied by risk reduction approaches akin to those employed in current therapies for numerous cancer and AIDS cases. In clinical studies on donanemab, a trend toward slower Tau accumulation was noted. Therefore, future research should focus on exploring the relationship between reduced Aβ plaques and Tau levels to achieve meaningful benefits for Alzheimer's patients. The accelerated FDA approval of aducanumab, donanemab and lecanemab has brought new hope for Alzheimer's drug development, and we anticipate more effective and affordable treatments for patients in the future.

Conclusion

Single-target drugs often prove insufficient due to AD's multifaceted pathology. Many drugs have failed in clinical trials due to inadequate target interaction, toxic side effects, or a lack of differentiation from placebos. FDA-approved treatments offer symptomatic relief but do not halt disease progression. Addressing AD's multifaceted nature demands a

comprehensive approach. Therefore, this review aims to emphasize recent progress in exploring innovative AD treatments from the perspective of medicinal chemistry. Various aspects of addressing AD have been consolidated, such as multiple hypotheses, single targets, and MTDLs. Aβ aggregation inhibitors, metal chelators, and neuroprotective mechanisms appear to hold promise, and MTDLs are expected to play a crucial role in the management of AD. In conclusion, although a cure for Alzheimer's disease through drug therapy has not yet been found, significant progress is being made. It is anticipated that new treatments with high efficacy, low adverse effects, and economic viability will be developed soon. This review may serve as a valuable resource for the medicinal chemistry community for exploring strategies to manage AD.

Data availability

The authors confirm that the data supporting the findings of this study are available within the article and/or its ESI.†

Author contributions

Amit Sharma: data curation, formal analysis, investigation, writing original draft. Santosh Rudrawar: conceptualization, validation, formal analysis, supervision, writing – review & editing. Hemant R. Jadhav: conceptualization, validation, formal analysis, supervision, writing – review & editing.

Conflicts of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

1 J. V. Shanmugam, B. Duraisamy, B. C. Simon and P. Bhaskaran, Alzheimer's disease classification using pre-trained deep networks, *Biomed. Signal Process. Control*, 2022, **71**, 103217, DOI: **10.1016/j.bspc.2021.103217**.
2 **https://www.alz.org/alzheimers-dementia/facts-figures**, accessed (07 May 2024).
3 M. Domico and V. Hill, *What You Need to Know about Alzheimer's Disease*, Bloomsbury Publishing USA, 2022, DOI: **10.1016/S0002-9343(97)00262-3**.
4 S. A. Galle, I. K. Geraedts, J. B. Deijen, M. V. Milders and M. L. Drent, The interrelationship between insulin-like growth factor 1, apolipoprotein E ε4, lifestyle factors, and the aging body and brain, *J. Prev. Alzheimers Dis.*, 2020, **7**, 265–273, DOI: **10.14283/jpad.2020.11**.
5 K. J. Olczak, V. Taylor-Bateman, H. L. Nicholls, M. Traylor, C. P. Cabrera and P. B. Munroe, Hypertension genetics past, present and future applications, *J. Intern. Med.*, 2021, **290**, 1130–1152, DOI: **10.1111/joim.13352**.
6 I. Z. Sadiq, Free radicals and oxidative stress: Signaling mechanisms, redox basis for human diseases, and cell cycle regulation, *Curr. Mol. Med.*, 2023, **23**, 13–35, DOI: **10.2174/1566524022666211222161637**.
7 E. S. Thoe, A. Fauzi, Y. Q. Tang, S. Chamyuang and A. Y. Y. Chia, A review on advances of treatment modalities for Alzheimer's disease, *Life Sci.*, 2021, **276**, 119129, DOI: **10.1016/j.lfs.2021.119129**.
8 T. E. Golde, Disease-modifying therapies for Alzheimer's disease: More questions than answers, *Neurotherapeutics*, 2022, **19**, 209–227, DOI: **10.1007/s13311-022-01201-2**.
9 N. G. Regier, N. A. Hodgson and L. N. Gitlin, Characteristics of activities for persons with dementia at the mild, moderate, and severe stages, *Gerontologist*, 2017, **57**, 987–997, DOI: **10.1093/geront/gnw133**.
10 G. E. Vitek, B. Decourt and M. N. Sabbagh, Lecanemab (BAN2401): an anti–beta-amyloid monoclonal antibody for the treatment of Alzheimer disease, *Expert Opin. Invest. Drugs*, 2023, **32**, 89–94, DOI: **10.1080/13543784.2023.2178414**.
11 M. Nasb, W. Tao and N. Chen, Alzheimer's Disease Puzzle: Delving into Pathogenesis Hypotheses, *Aging Dis.*, 2024, **15**(1), 43–73, DOI: **10.14336/AD.2023.0608**.
12 G. Lee and C. J. Leugers, Tau and tauopathies, *Prog. Mol. Biol. Transl. Sci.*, 2012, **107**, 263–293, DOI: **10.1016/B978-0-12-385883-2.00004-7**.
13 L. A. Craig, N. S. Hong and R. J. McDonald, Revisiting the cholinergic hypothesis in the development of Alzheimer's disease, *Neurosci. Biobehav. Rev.*, 2011, **35**, 1397–1409, DOI: **10.1016/j.neubiorev.2011.03.001**.
14 S. Li, The β-adrenergic hypothesis of synaptic and microglial impairment in Alzheimer's disease, *J. Neurochem.*, 2023, **165**, 289–302, DOI: **10.1111/jnc.15782**.
15 Y.-J. Cheng, C.-H. Lin and H.-Y. Lane, Involvement of cholinergic, adrenergic, and glutamatergic network modulation with cognitive dysfunction in Alzheimer's disease, *Int. J. Mol. Sci.*, 2021, **22**, 2283, DOI: **10.3390/ijms22052283**.
16 K. Honarnejad and J. Herms, Presenilins: role in calcium homeostasis, *Int. J. Biochem. Cell Biol.*, 2012, **44**, 1983–1986, DOI: **10.1016/j.biocel.2012.07.019**.
17 M. F. Khan and G. Wang, Environmental agents, oxidative stress and autoimmunity, *Curr. Opin. Toxicol.*, 2018, **7**, 22–27, DOI: **10.1016/j.cotox.2017.10.012**.
18 D. V. Hansen, J. E. Hanson and M. Sheng, Microglia in Alzheimer's disease, *J. Cell Biol.*, 2018, **217**, 459–472, DOI: **10.1083/jcb.201709069**.
19 L.-L. Chen, Y.-G. Fan, L.-X. Zhao, Q. Zhang and Z.-Y. Wang, The metal ion hypothesis of Alzheimer's disease and the anti-neuroinflammatory effect of metal chelators, *Bioorg. Chem.*, 2023, **131**, 106301, DOI: **10.1016/j.bioorg.2022.106301**.
20 M. L. Maccecchini, M. Y. Chang, C. Pan, V. John, H. Zetterberg and N. H. Greig, Posiphen as a candidate drug to lower CSF amyloid precursor protein, amyloid-β peptide and τ levels: target engagement, tolerability and pharmacokinetics in humans, *J. Neurol., Neurosurg. Psychiatry*, 2012, **83**, 894–902, DOI: **10.1136/jnnp-2012-302589**.

21 A. Traikapi and N. Konstantinou, Gamma oscillations in Alzheimer's disease and their potential therapeutic role, *Front. Syst. Neurosci.*, 2021, **15**, 782399, DOI: **10.3389/fnsys.2021.782399**.
22 C. Condello, G. E. Merz, A. Aoyagi, W. F. DeGrado and S. B. Prusiner, Aβ and Tau Prions Causing Alzheimer's Disease, in *Alzheimer's Disease: Methods and Protocols*, Springer US, New York, NY, 2022, pp. 293–337.
23 L. Fan, C. Mao, H. Xinchao, S. Zhang, Z. Yang, H. Zhengwei and H. Sun, New insights into the pathogenesis of Alzheimer's disease, *Front. Neurol.*, 2020, **10**, 1312, DOI: **10.3389/fneur.2019.01312**.
24 Z. Zhou, Q. An, W. Zhang, Y. Li, Q. Zhang and H. Yan, Histamine and Receptors in Neuroinflammation: Their Roles on Neurodegenerative Diseases, *Behav. Brain Res.*, 2024, **465**, 114964, DOI: **10.1016/j.bbr.2024.114964**.
25 Q. Zhou, S. Li, M. Li, D. Ke, Q. Wang, Y. Yang, G.-P. Liu, X.-C. Wang, E. Liu and J.-Z. Wang, Human tau accumulation promotes glycogen synthase kinase-3β acetylation and thus upregulates the kinase: a vicious cycle in Alzheimer neurodegeneration, *EBioMedicine*, 2022, **78**, 103970, DOI: **10.1016/j.ebiom.2022.103970**.
26 E. Aaldijk and Y. Vermeiren, The Role of Serotonin within the Microbiota-gut-brain Axis in the Development of Alzheimer'S Disease: A Narrative Review, *Ageing Res. Rev.*, 2022, **75**, 101556, DOI: **10.1016/j.arr.2021.101556**.
27 J. Jiménez-Balado and T. S. Eich, GABAergic Dysfunction, Neural Network Hyperactivity and Memory Impairments in Human Aging and Alzheimer's Disease, *Semin. Cell Dev. Biol.*, 2021, **116**, 146–159, DOI: **10.1016/j.semcdb.2021.01.005**.
28 N. Korte, R. Nortley and D. Attwell, Cerebral blood flow decrease as an early pathological mechanism in Alzheimer's disease, *Acta Neuropathol.*, 2020, **140**, 793–810, DOI: **10.1007/s00401-020-02215-w**.
29 T. Pardo-Moreno, A. González-Acedo, A. Rivas-Domínguez, V. García-Morales, F. J. García-Cozar, J. J. Ramos-Rodríguez and L. Melguizo-Rodríguez, Therapeutic approach to Alzheimer's disease: Current treatments and new perspectives, *Pharmaceutics*, 2022, **14**, 1117, DOI: **10.3390/pharmaceutics14061117**.
30 R. Perneczky, F. Jessen, T. Grimmer, J. Levin, A. Flöel, O. Peters and L. Froelich, Anti-amyloid antibody therapies in Alzheimer's disease, *Brain*, 2023, **146**, 842–849, DOI: **10.1093/brain/awad005**.
31 G. C. Alexander, S. Emerson and A. S. Kesselheim, Evaluation of aducanumab for Alzheimer disease: scientific evidence and regulatory review involving efficacy, safety, and futility, *JAMA, J. Am. Med. Assoc.*, 2021, **325**, 1717–1718, DOI: **10.1001/jama.2021.3854**.
32 Z. Breijyeh and R. Karaman, Comprehensive review on Alzheimer's disease: Causes and treatment, *Molecules*, 2020, **25**, 5789, DOI: **10.3390/molecules25245789**.
33 H. Sugimoto, Y. Yamanish, Y. Iimura and Y. Kawakami, Donepezil hydrochloride (E2020) and other acetylcholinesterase inhibitors, *Curr. Med. Chem.*, 2000, **7**, 303–339, DOI: **10.2174/0929867003375191**.
34 J. Marco-Contelles, M. do Carmo Carreiras, C. Rodríguez, M. Villarroya and A. G. García, Synthesis and pharmacology of galantamine, *Chem. Rev.*, 2006, **106**, 116–133, DOI: **10.1021/cr040415t**.
35 P. Anand and B. Singh, A review on cholinesterase inhibitors for Alzheimer's disease, *Arch. Pharmacal Res.*, 2013, **36**, 375–399, DOI: **10.1007/s12272-013-0036-3**.
36 B. P. Lucey, H. Liu, C. D. Toedebusch, D. Freund, T. Redrick, S. L. Chahin and K. G. Mawuenyega, Suvorexant acutely decreases tau phosphorylation and Aβ in the human CNS, *Ann. Neurol.*, 2023, **94**, 27–40, DOI: **10.1002/ana.26641**.
37 L. S. Schneider, F. Mangialasche, N. Andreasen, H. Feldman, E. Giacobini, R. Jones and V. Mantua, Clinical trials and late-stage drug development for A lzheimer's disease: an appraisal from 1984 to 2014, *J. Intern. Med.*, 2014, **275**, 251–283, DOI: **10.1111/joim.12191**.
38 D. Jeremic, L. Jiménez-Díaz and J. D. Navarro-López, Past, present and future of therapeutic strategies against amyloid-β peptides in Alzheimer's disease: A systematic review, *Ageing Res. Rev.*, 2021, **72**, 101496, DOI: **10.1016/j.arr.2021.101496**.
39 J. M. Kim, H. Jeon, H. Y. Kim and Y. S. Kim, Failure, Success, and Future Direction of Alzheimer Drugs Targeting Amyloid-β Cascade: Pros and Cons of Chemical and Biological Modalities, *ChemBioChem*, 2023, **24**, e202300328, DOI: **10.1002/cbic.202300328**.
40 S. Ghosh, R. Ali and S. Verma, Aβ-oligomers: A potential therapeutic target for Alzheimer's disease, *Int. J. Biol. Macromol.*, 2023, 124231, DOI: **10.1016/j.ijbiomac.2023.124231**.
41 T. Athar, K. Al Balushi and S. A. Khan, Recent advances on drug development and emerging therapeutic agents for Alzheimer's disease, *Mol. Biol. Rep.*, 2021, **48**(7), 5629–5645, DOI: **10.1007/s11033-021-06512-9**.
42 B. Decourt, J. Wilson, A. Ritter, C. Dardis, F. P. DiFilippo, X. Zhuang, D. Cordes, G. Lee, N. D. Fulkerson, T. St Rose, K. Hartley and M. N. Sabbagh, MCLENA-1: A Phase II Clinical Trial for the Assessment of Safety, Tolerability, and Efficacy of Lenalidomide in Patients with Mild Cognitive Impairment Due to Alzheimer's Disease, *Open Access J. Clin. Trials*, 2020, **12**, 1–13, DOI: **10.2147/oajct.s221914**.
43 K. Vossel, K. G. Ranasinghe, A. J. Beagle, A. La, K. Ah Pook, M. Castro, D. Mizuiri, S. M. Honma, N. Venkateswaran, M. Koestler, W. Zhang, L. Mucke, M. J. Howell, K. L. Possin, J. H. Kramer, A. L. Boxer, B. L. Miller, S. S. Nagarajan and H. E. Kirsch, Effect of Levetiracetam on Cognition in Patients With Alzheimer Disease With and Without Epileptiform Activity: A Randomized Clinical Trial, *JAMA Neurol.*, 2021, **78**(11), 1345–1354, DOI: **10.1001/jamaneurol.2021.3310**.
44 W. Yao, H. Yang and J. Yang, Small-molecule drugs development for Alzheimer's disease, *Front. Aging Neurosci.*, 2022, **14**, 1019412, DOI: **10.3389/fnagi.2022.1019412**.
45 **https://www.alz.org/**, (accessed 30 May 2024).
46 J. L. Cummings, K. Zhong, J. W. Kinney, C. Heaney, J. Moll-Tudla, A. Joshi, M. Pontecorvo, M. Devous, A. Tang and J.

Bena, Double-blind, placebo-controlled, proof-of-concept trial of bexarotene in moderate Alzheimer's disease, *Alzheimers Res. Ther.*, 2016, **8**, 1–9, DOI: **10.1186/s13195-016-0173-2**.

47 J. A. Hey, J. Y. Yu, M. Versavel, S. Abushakra, P. Kocis, A. Power, P. L. Kaplan, J. Amedio and M. Tolar, Clinical pharmacokinetics and safety of ALZ-801, a novel prodrug of tramiprosate in development for the treatment of Alzheimer's disease, *Clin. Pharmacokinet.*, 2018, **57**, 315–333, DOI: **10.1007/s40262-017-0608-3**.

48 J. Kutzsche, D. Jürgens, A. Willuweit, K. Adermann, C. Fuchs, S. Simons, M. Windisch, M. Hümpel, W. Rossberg, M. Wolzt and D. Willbold, Safety and pharmacokinetics of the orally available antiprionic compound PRI-002: A single and multiple ascending dose phase I study, *Alzheimers Dement.*, 2020, **6**, e12001, DOI: **10.1002/trc2.12001**.

49 L. Lannfelt, K. Blennow, H. Zetterberg, S. Batsman, D. Ames, J. Harrison, C. L. Masters, S. Targum, A. I. Bush, R. Murdoch and J. Wilson, Ritchie CW; PBT2-201-EURO study group. Safety, efficacy, and biomarker findings of PBT2 in targeting Abeta as a modifying therapy for Alzheimer's disease: a phase IIa, double-blind, randomised, placebo-controlled trial, *Lancet Neurol.*, 2008, **7**(9), 779–786, DOI: **10.1016/S1474-4422(08)70167-4**.

50 P. Scheltens, M. Hallikainen, T. Grimmer, T. Duning, A. A. Gouw, C. E. Teunissen and A. M. Wink, Safety, tolerability and efficacy of the glutaminyl cyclase inhibitor PQ912 in Alzheimer's disease: results of a randomized, double-blind, placebo-controlled phase 2a study, *Alzheimers Res. Ther.*, 2018, **10**, 1–14, DOI: **10.1186/s13195-018-0431-6**.

51 J. Spurrier, L. S. Nicholson, X. T. Fang, A. J. Stoner, T. Toyonaga, D. Holden and T. R. Siegert, Reversal of synapse loss in Alzheimer mouse models by targeting mGluR5 to prevent synaptic tagging by C1Q, *Sci. Transl. Med.*, 2022, **14**, eabi8593, DOI: **10.1126/scitranslmed.abi8593**.

52 N. J. Izzo, C. M. Yuede, K. M. LaBarbera, C. S. Limegrover, C. Rehak, R. Yurko and L. Waybright, Preclinical and clinical biomarker studies of CT1812: A novel approach to Alzheimer's disease modification, *Alzheimer's Dementia*, 2021, **17**, 1365–1382, DOI: **10.1002/alz.12302**.

53 D. Kellar, T. Register, S. N. Lockhart, P. Aisen, R. Raman, R. A. Rissman, J. Brewer and S. Craft, Intranasal insulin modulates cerebrospinal fluid markers of neuroinflammation in mild cognitive impairment and Alzheimer's disease: A randomized trial, *Sci. Rep.*, 2022, **12**, 1346, DOI: **10.1038/s41598-022-05165-3**.

54 H.-Y. Wang, Z. Pei, K.-C. Lee, E. Lopez-Brignoni, B. Nikolov, C. A. Crowley, M. R. Marsman, R. Barbier, N. Friedmann and L. H. Burns, PTI-125 reduces biomarkers of Alzheimer's disease in patients, *J. Prev. Alzheimers Dis.*, 2020, **7**, 256–264, DOI: **10.14283/jpad.2020.6**.

55 T. Iwatsubo, Molecular pathogenesis and disease-modifying therapies of Alzheimer's disease and related disorders, *JMA J.*, 2022, **5**, 307–313, DOI: **10.31662/jmaj.2022-0079**.

56 M. R. Khezri, M. Mohebalizadeh and M. Ghasemnejad-Berenji, Therapeutic potential of ADAM10 modulation in Alzheimer's disease: a review of the current evidence, *Cell Commun. Signaling*, 2023, **21**, 60, DOI: **10.1186/s12964-023-01072-w**.

57 A. Miranda, E. Montiel, H. Ulrich and C. Paz, Selective Secretase Targeting for Alzheimer's Disease Therapy, *J. Alzheimer's Dis.*, 2021, **81**(1), 1–17, DOI: **10.3233/JAD-201027**, PMID: 33749645.

58 Y. Zhang, H. Chen, R. Li, K. Sterling and W. Song, Amyloid β-based therapy for Alzheimer's disease: Challenges, successes and future, *Signal Transduct. Target. Ther.*, 2023, **8**, 248, DOI: **10.1038/s41392-023-01484-7**.

59 S. Roselli, T. M. Satir, R. Camacho, S. Fruhwürth, P. Bergström, H. Zetterberg and L. Agholme, APP-BACE1 Interaction and Intracellular Localization Regulate Aβ Production in iPSC-Derived Cortical Neurons, *Cell. Mol. Neurobiol.*, 2023, 1–16, DOI: **10.1007/s10571-023-01374-0**.

60 Y. C. Yen, A. M. Kammeyer, J. Tirlangi, A. K. Ghosh and A. D. Mesecar, A Structure-Based Discovery Platform for BACE2 and the Development of Selective BACE Inhibitors, *ACS Chem. Neurosci.*, 2021, **12**(4), 581–588, DOI: **10.1021/acschemneuro.0c00629**.

61 G. Evin, Future Therapeutics in Alzheimer's Disease: Development Status of BACE Inhibitors, *BioDrugs*, 2016, **30**(3), 173–194, DOI: **10.1007/s40259-016-0168-3**, PMID: 27023706.

62 A. Iraji, M. Khoshneviszadeh, O. Firuzi, M. Khoshneviszadeh and N. Edraki, Novel small molecule therapeutic agents for Alzheimer disease: Focusing on BACE1 and multi-target directed ligands, *Bioorg. Chem.*, 2020, **97**, 103649, DOI: **10.1016/j.bioorg.2020.103649**.

63 P. Gehlot, S. Kumar, V. K. Vyas, B. S. Choudhary, M. Sharma and R. Malik, Guanidine-based β amyloid precursor protein cleavage enzyme 1 (BACE 1) inhibitors for the Alzheimer's disease (AD): A Review, *Bioorg. Med. Chem.*, 2022, 117047, DOI: **10.1016/j.bmc.2022.117047**.

64 C. Haass, C. Kaether, G. Thinakaran and S. Sisodia, Trafficking and proteolytic processing of APP, *Cold Spring Harbor Perspect. Med.*, 2012, **2**, a006270, DOI: **10.1101/cshperspect.a006270**.

65 P. Nie, A. Vartak and Y. M. Li, γ-Secretase inhibitors and modulators: Mechanistic insights into the function and regulation of γ-Secretase, *Semin. Cell Dev. Biol.*, 2020, **105**, 43–53, DOI: **10.1016/j.semcdb.2020.03.002**.

66 J. Y. Hur, γ-Secretase in Alzheimer's disease, *Exp. Mol. Med.*, 2022, **54**(4), 433–446, DOI: **10.1038/s12276-022-00754-8**.

67 D. B. Henley, K. L. Sundell, G. Sethuraman, S. A. Dowsett and P. C. May, Safety profile of semagacestat, a gamma-secretase inhibitor: IDENTITY trial findings, *Curr. Med. Res. Opin.*, 2014, 2021–2032, DOI: **10.1185/03007995.2014.939167**.

68 D. Wang, J. Xu, B. Liu, X. He, L. Zhou, X. Hu, F. Qiao, A. Zhang, X. Xu, H. Zhang, M. S. Wicha, L. Zhang, Z. M. Shao and S. Liu, IL6 blockade potentiates the anti-tumor effects of γ-secretase inhibitors in Notch3-expressing breast cancer, *Cell Death Differ.*, 2018, **25**(2), 330–339, DOI: **10.1038/cdd.2017.162**.

69 G. Nordvall, J. Lundkvist and J. Sandin, Gamma-secretase modulators: a promising route for the treatment of Alzheimer's disease, *Front. Mol. Neurosci.*, 2023, **16**, 1279740, DOI: **10.3389/fnmol.2023.1279740**.

70 A. I. Bush and R. E. Tanzi, Therapeutics for Alzheimer's disease based on the metal hypothesis, *Neurotherapeutics*, 2008, **5**, 421–432, DOI: **10.1016/j.nurt.2008.05.001**.

71 A. Gucký and S. Hamuľaková, Targeting Biometals in Alzheimer's Disease with Metal Chelating Agents Including Coumarin Derivatives, *CNS Drugs*, 2024, **38**, 507–532, DOI: **10.1007/s40263-024-01093-0**.

72 E. Siemers, Drug Development in AD: Point of View from the Industry, *J. Prev. Alzheimers Dis.*, 2015, **2**, 216–218, DOI: **10.14283/jpad.2015.80**.

73 D. B. Henley, K. L. Sundell, G. Sethuraman, S. A. Dowsett and P. C. May, Safety profile of semagacestat, a gamma-secretase inhibitor: IDENTITY trial findings, *Curr. Med. Res. Opin.*, 2014, **30**, 2021–2032, DOI: **10.1185/03007995.2014.939167**.

74 R. E. Becker and N. H. Greig, Increasing the success rate for Alzheimer's disease drug discovery and development, *Expert Opin. Drug Discovery*, 2012, **7**, 367–370, DOI: **10.1517/17460441.2012.672409**.

75 A. Atri, J. L. Molinuevo, O. Lemming, Y. Wirth, I. Pulte and D. Wilkinson, Memantine in patients with Alzheimer's disease receiving donepezil: new analyses of efficacy and safety for combination therapy, *Alzheimers Res. Ther.*, 2013, **5**, 1–11, DOI: **10.1186/alzrt160**.

76 A.-L. Barabási, N. Gulbahce and J. Loscalzo, Network medicine: a network-based approach to human disease, *Nat. Rev. Genet.*, 2011, **12**, 56–68, DOI: **10.1038/nrg2918**.

77 C. Albertini, A. Salerno, P. de Sena, M. Pinheiro and M. L. Bolognesi, From combinations to multitarget-directed ligands: A continuum in Alzheimer's disease polypharmacology, *Med. Res. Rev.*, 2021, **41**, 2606–2633, DOI: **10.1002/med.21699**.

78 F. Li, C. Zhao and L. Wang, Molecular-targeted agents combination therapy for cancer: developments and potentials, *Int. J. Cancer*, 2014, **134**, 1257–1269, DOI: **10.1002/ijc.28261**.

79 S. Maramai, M. Benchekroun, M. T. Gabr and S. Yahiaoui, Multitarget therapeutic strategies for Alzheimer's disease: Review on emerging target combinations, *Biomed. Res. Int.*, 2020, 5120230, DOI: **10.1155/2020/5120230**.

80 R. R. Ramsay, M. R. Popovic-Nikolic, K. Nikolic, E. Uliassi and M. L. Bolognesi, A perspective on multi-target drug discovery and design for complex diseases, *Clin. Transl. Med.*, 2018, **7**, 1–14, DOI: **10.1186/s40169-017-0181-2**.

81 J. Zhou, X. Jiang, S. He, H. Jiang, F. Feng, W. Liu, Q. Wei and H. Sun, Rational design of multitarget-directed ligands: strategies and emerging paradigms, *J. Med. Chem.*, 2019, **62**, 8881–8914, DOI: **10.1021/acs.jmedchem.9b00017**.

82 D. Malafaia, H. M. T. Albuquerque and A. M. S. Silva, Amyloid-β and tau aggregation dual-inhibitors: A synthetic and structure-activity relationship focused review, *Eur. J. Med. Chem.*, 2021, **214**, 113209, DOI: **10.1016/j.ejmech.2021.113209**.

83 P. Mishra, A. Kumar and G. Panda, Anti-cholinesterase hybrids as multi-target-directed ligands against Alzheimer's disease (1998–2018), *Bioorg. Med. Chem.*, 2019, **27**, 895–930, DOI: **10.1016/j.bmc.2019.01.025**.

84 Z. Najafi, M. Saeedi, M. Mahdavi, R. Sabourian, M. Khanavi, M. B. Tehrani and F. H. Moghadam, Design and synthesis of novel anti-Alzheimer's agents: Acridine-chromenone and quinoline-chromenone hybrids, *Bioorg. Chem.*, 2016, **67**, 84–94, DOI: **10.1016/j.bioorg.2016.06.001**.

85 Y. Deng, Y. Jiang, X. Zhao and J. Wang, Design, Synthesize and Bio-Evaluate 1, 2-Dihydroisoquinolin-3 (4H)-One Derivates as Acetylcholinesterase and β-Secretase Dual Inhibitors in Treatment with Alzheimer's Disease, *J. Biosci. Med.*, 2016, **4**, 112, DOI: **10.4236/jbm.2016.41014**.

86 N. Kumar, V. Kumar, P. Anand, V. Kumar, A. R. Dwivedi and V. Kumar, Advancements in the development of multi-target directed ligands for the treatment of Alzheimer's disease, *Bioorg. Med. Chem.*, 2022, **61**, 116742, DOI: **10.1016/j.bmc.2022.116742**.

87 Z. Sang, K. Wang, J. Dong and L. Tang, Alzheimer's disease: updated multi-targets therapeutics are in clinical and in progress, *Eur. J. Med. Chem.*, 2022, **238**, 114464, DOI: **10.1016/j.ejmech.2022.114464**.

88 H. Kogen, N. Toda, K. Tago, S. Marumoto, K. Takami, M. Ori and N. Yamada, Design and synthesis of dual inhibitors of acetylcholinesterase and serotonin transporter targeting potential agents for Alzheimer's disease, *Org. Lett.*, 2002, **20**, 3359–3362, DOI: **10.1021/ol026418e**.

89 F. He, Y. Ran, X. Li, D. Wang, Q. Zhang, J. Lv and Y. Chenggong, Design, synthesis and biological evaluation of dual-function inhibitors targeting NMDAR and HDAC for Alzheimer's disease, *Bioorg. Chem.*, 2020, **103**, 104109, DOI: **10.1016/j.bioorg.2020.104109**.

90 S. Kaur and Y. Bansal, Design, molecular Docking, synthesis and evaluation of xanthoxylin hybrids as dual inhibitors of IL-6 and acetylcholinesterase for Alzheimer's disease, *Bioorg. Chem.*, 2022, **121**, 105670, DOI: **10.1016/j.bioorg.2022.105670**.

91 P. Lv, C.-L. Xia, N. Wang, Z.-Q. Liu, Z.-S. Huang and S.-L. Huang, Synthesis and evaluation of 1, 2, 3, 4-tetrahydro-1-acridone analogues as potential dual inhibitors for amyloid-beta and tau aggregation, *Bioorg. Med. Chem.*, 2018, **26**, 4693–4705, DOI: **10.1016/j.bmc.2018.08.007**.

92 A. Iraji, M. Khoshneviszadeh, O. Firuzi, M. Khoshneviszadeh and N. Edraki, Novel small molecule therapeutic agents for Alzheimer disease: Focusing on BACE1 and multi-target directed ligands, *Bioorg. Chem.*, 2020, **97**, 103649, DOI: **10.1016/j.bioorg.2020.103649**.

93 Z. Luo, J. Sheng, Y. Sun, L. Chuanjun, J. Yan, A. Liu, H.-b. Luo, L. Huang and X. Li, Synthesis and evaluation of multi-target-directed ligands against Alzheimer's disease based on the fusion of donepezil and ebselen, *J. Med. Chem.*, 2013, **56**, 9089–9099, DOI: **10.1021/jm401047q**.

94 D. A. Rodríguez-Soacha, M. Scheiner and M. Decker, Multi-target-directed-ligands acting as enzyme inhibitors and receptor ligands, *Eur. J. Med. Chem.*, 2019, **180**, 690–706, DOI: **10.1016/j.ejmech.2019.07.040**.

95 R. Leon, A. G. Garcia and J. Marco-Contelles, Recent advances in the multitarget-directed ligands approach for the treatment of Alzheimer's disease, *Med. Res. Rev.*, 2013, 139–189, DOI: **10.1002/med.20248**.

96 A. Dorababu, Promising heterocycle-based scaffolds in recent (2019–2021) anti-Alzheimer's drug design and discovery, *Eur. J. Pharmacol.*, 2022, **920**, 174847, DOI: **10.1016/j.ejphar.2022.174847**.

97 C. Pathak and U. D. Kabra, A comprehensive review of multi-target directed ligands in the treatment of Alzheimer's disease, *Bioorg. Chem.*, 2024, 107152, DOI: **10.1016/j.bioorg.2024.107152**.