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Review Article

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Small Molecule Therapeutics Targeting Amyloid-β in Alzheimer's Disease: Mechanisms, Clinical Progress, and Future Strategies

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Alzheimer's disease (AD) imposes a growing burden on global healthcare systems. Current therapeutic interventions primarily alleviate cognitive and functional symptoms but have limited impact on the underlying neurodegenerative processes driving disease progression. This underscores the urgent need for treatments that target the pathogenic mechanisms of the disease. Advances in monoclonal antibody therapies against amyloid-β (Aβ) provide encouraging evidence for disease modification, though challenges related to dosing, cost, and safety constrain their broader application. Small molecule therapeutics represent a compelling alternative owing to advantageous properties such as enhanced brain penetration, oral bioavailability, and suitability for long-term administration in elderly patients. Building on these attributes, this review evaluates small molecule therapeutics as promising candidates for AD treatment. It summarizes small molecule compounds targeting Aβ across mechanisms that include modulating production, inhibiting aggregation, disassembling aggregates, enhancing clearance, and mitigating neurotoxicity. A comprehensive assessment of current data emphasizes the importance of continued research to overcome ongoing challenges and fully leverage the potential of small molecules. The limited number of candidates in late-stage clinical trials indicates that substantial efforts are still required to identify and refine effective agents. Continued investigation into their mechanisms and optimization of compound profiles will advance the development of small molecule-based therapies for AD.

Key words: Alzheimer disease, Amyloid beta-peptides, Drug therapy, Clinical trials as topic, Protein aggregation, pathological

INTRODUCTION

Alzheimer's disease (AD), the most common cause of dementia, remains a major global health challenge with no available therapy capable of halting or reversing its progressive neurodegenerative course [1]. Approved pharmacologic options to date have been limited to the cholinesterase inhibitors, including donepezil (Aricept), rivastigmine (Exelon), and galantamine (Razadyne), which enhance cholinergic neurotransmission by increasing synaptic acetylcholine levels [2, 3], and to the N-methyl-D-aspartic acid (NMDA) receptor antagonist memantine (Namenda), which mitigates excitotoxicity by regulating excessive NMDA receptor activity [4]. These agents provide only symptomatic relief without altering the underlying disease progression [5], leading to intensive efforts to develop disease-modifying therapies. In recent years, the U.S. Food and Drug Administration (FDA) has approved mono-

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clonal antibody treatments against amyloid-β (Aβ) [6, 7]. Agents such as lecanemab and donanemab have demonstrated that reducing cerebral amyloid burden can slow cognitive decline in patients with early AD, thereby providing clinical validation of the amyloid hypothesis as a disease-modifying strategy [8, 9]. This achievement marks an important advance, yet antibody-based therapies are constrained by practical limitations, including low blood-brain barrier (BBB) penetration, repeated intravenous administration, high treatment cost, and amyloid-related imaging abnormalities (ARIA) [10]. These considerations underscore the need for alternative therapeutic modalities.

Small molecule therapeutics represent such an alternative to biologic agents for AD. These compounds possess notable advantages in brain penetration, oral bioavailability, scalable manufacturing, chemical stability, and reduced immunogenicity [11], all of which are particularly relevant for chronic disease that primarily affects the elderly populations [12]. Beyond these pharmacokinetic and practical benefits, small molecules exhibit considerable structural versatility, enabling the rational design of agents that can modulate diverse aspects of Aβ pathology at multiple mechanistic levels. Despite these strengths, the successful clinical translation of small molecule candidates has been hampered by persistent challenges such as suboptimal target engagement, off-target toxicity, and issues with data reproducibility. Advances in drug discovery methodologies, including multi-target ligand design, artificial intelligence (AI)-based modeling, and refined screening platforms, are beginning to address these longstanding obstacles and are expanding the opportunities for small molecule drug development in AD.

Here, we provide a comprehensive overview to date of small molecules targeting Aβ. This review is based on 43 compounds selected from the 438 compounds listed in the Alzforum Therapeutics database (as of September 10, 2025). These Aβ-targeting compounds are subsequently categorized into five mechanistic classes: modulation of production, inhibition of aggregation, dissociation of aggregates, enhancement of clearance, and attenuation of neurotoxicity (Fig. 1). Although numerous programs have been launched over the past several decades, only a few have progressed to late-stage clinical testing with limited evidence of efficacy. This trajectory reflects both the evolving understanding of AD biology and the ongoing refinement of therapeutic strategies. Given the current challenges, small molecules, particularly targeting Aβ aggregates, may represent a new strategy and provide the basis for next-generation AD therapeutics.

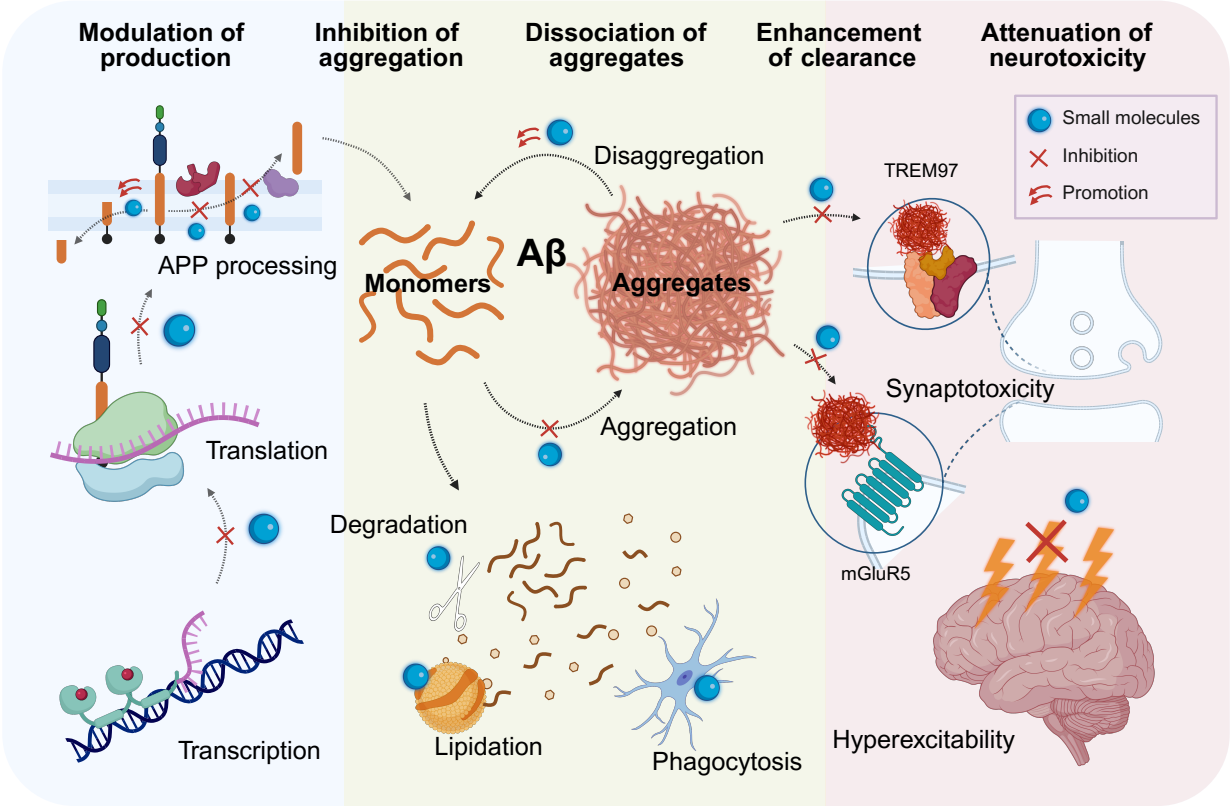

Fig. 1. Schematic illustration of small molecule mechanisms targeting Aβ pathology.

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Aβ PRODUCTION

APP undergoes proteolytic processing through two main pathways: the non-amyloidogenic route, which precludes Aβ formation, and the amyloidogenic pathway, which generates Aβ peptides, notably Aβ42, that are strongly linked to AD pathogenesis [13, 14]. The balance between these pathways is determined by the activity of key enzymes, including α-secretase, β-secretase (BACE1), and γ-secretases. Therapeutic strategies have focused on modulating these enzymes to shift APP processing away from pathogenic Aβ production [15]. Early approaches targeted the major secretases directly, either by enhancing α-secretase activity to promote non-amyloidogenic processing or by inhibiting BACE1 or γ-secretase to block Aβ production. Beyond direct secretase modulation, additional strategies include inhibition of APP translation, regulation of cholesterol metabolism, and selective modulation of enzymatic activity to reduce generation of more toxic Aβ isoforms such as Aβ42 or pyroglutamate-modified Aβ (pE3-Aβ) [16-19]. These approaches aim to reduce the production or toxicity of Aβ by intervening at multiple points in APP metabolism (Table 1). The following subsections review small molecules developed for each of these mechanistic classes: APP mRNA translation inhibitors, α-secretase upregulators, BACE1 inhibitors, γ-secretase inhibitors (GSIs) and modulators (GSMs), glutaminyl cyclase (QC) inhibitors, and cholesterol metabolism modulators.

APP mRNA translation inhibitors

Buntanetap (Posiphen, ANVS-401), the (+)-enantiomer of phenserine, is an APP mRNA translation inhibitor that targets the 5′-untranslated region (5′-UTR) iron-responsive element, thereby reducing APP protein expression without acetylcholinesterase inhibition [16, 20]. To date, no conclusive clinical biomarker data, particularly regarding Aβ levels, have been reported for buntanetap, although recent trials have begun to show promising biomarker changes associated with neuroinflammatory and neuronal health markers. Comprehensive amyloid data from plasma and cerebrospinal fluid (CSF) are still pending from ongoing and future studies. This distinguishes it from phenserine, which inhibits both APP expression and acetylcholinesterase. A phase 2/3 trial (NCT05686044) did not demonstrate significant benefit in cognition in the overall population. Exploratory analyses indicated a significant and dose-dependent Alzheimer's Disease Assessment Scale-Cognitive Subscale 11 (ADAS-Cog11) improvement in the mild AD subgroup (Mini-Mental State Examination, MMSE 21-24) with plasma biomarker positivity (pTau217/total tau ratio ≥4.2%), but these findings require confirmation as they were not prespecified. Based on these subgroup observations, a pivotal phase 3 trial in early AD was initiated in 2025 (NCT06709014). Buntanetap remains the only clinical example of APP translation inhibitor, positioning this mechanism as a distinctive upstream approach under active evaluation.

α-secretase upregulators

Acitretin is a second-generation retinoid that has been investigated as a repurposed therapeutic agent in AD. The rationale relies on the presence of retinoic acid-responsive elements (RARE) within the promoter region of a disintegrin and metalloproteinase domain-containing protein 10 (ADAM10). By interacting with cellular retinoic acid-binding proteins (CRABP), acitretin activates retinoic acid receptor (RAR) and retinoid X receptor (RXR) heterodimers, which induce ADAM10 transcription and shift APP metabolism toward the non-amyloidogenic α-secretase pathway. Upregulated ADAM10 expression facilitates α-secretase mediated cleavage of APP, leading to increased generation of soluble APPα (sAPPα) and reduced substrate availability for amyloidogenic Aβ production [21]. In the phase 2 trial (EUCTR 2009-011881-27), CSF sAPPα significantly increased from baseline, providing the first human evidence of ADAM10 upregulation *in vivo*. However, this effect was not accompanied by significant changes in other CSF biomarkers nor cognitive improvement. Treatment was generally tolerated, but the long-term use of systemic retinoids raises concerns about cumulative toxicities in elderly patients, warranting further investigation of their safety profile in chronic administration. [22, 23]. Overall, acitretin demonstrated target engagement but did not influence downstream amyloid biomarkers or cognition, and development was not advanced beyond the proof-of-mechanism stage.

BACE1 inhibitors

BACE1 is the aspartyl protease that cleaves APP at the β-site, initiating the amyloidogenic cascade by generating the C99 fragment, which is subsequently processed by γ-secretase to produce Aβ peptides [24]. Because this step lies upstream of Aβ formation, inhibition of BACE1 was considered an attractive strategy to suppress Aβ production at its source [25]. In both preclinical studies and early-phase human trials, small molecule BACE1 inhibitors consistently produced marked reductions of Aβ in CSF and brain, confirming pharmacodynamic target engagement. However, these biomarker effects did not translate into clinical benefit, and several trials even reported signals of cognitive worsening, leading to the termination of multiple phase 2 and 3 programs for futility or adverse events [26]. Several BACE1 inhibitors failed in late-stage clinical trials due to lack of cognitive benefit or worsening, including verubecestat, lanabecestat, atabecestat, elenbecestat, and

Table 1. Small molecules modulating Aβ production

Name (alternative name)	Mechanism of action	Clinical phase (current status)	Pathological biomarker	Cognition	Ref
APP mRNA translation inhibitors					
Buntanetap (Posiphen, ANVS-401)	APP mRNA translation inhibitor (via 5'-UTR)	Phase 2/3 (completed); Phase 3 (ongoing)	No Aβ biomarker data available	No benefit overall; *Mild AD (MMSE 21-24) with pTau217/total tau Ratio ≥4.2% ↑ (ADAS-Cog11)	[16, 20]
α-secretase upregulators					
Acitretin	ADAM10 upregulator	Phase 2 (completed)	*CSF sAPPα ↑ CSF Aβ42 (-)	No benefit	[21, 22]
BACE1 inhibitors					
Verubecestat (MK-8931)	BACE1 inhibitor	Phase 2/3 (EPOCH, terminated for futility); Phase 3 (APECS, terminated for futility)	Amyloid PET ↓ CSF Aβ40 & Aβ42, sAPPβ ↓	No benefit (in EPOCH), *Worsened (in APECS)	[27, 37, 38]
Lanabecestat (AZD3293, LY3314814)	BACE1 inhibitor	Phase 2/3 (AMARANTH, terminated for futility); Phase 3 (DAYBREAK-ALZ, terminated for futility)	*CSF Aβ40 & Aβ42 ↓ (in AMARANTH) *Amyloid PET ↓ (in AMARANTH)	No benefit	[28, 32]
Atabecestat (JNJ-54861911)	BACE1 inhibitor	Phase 2b/3 (EARLY, terminated for liver enzyme elevations)	No Aβ biomarker data	*Worsened (25 mg), No benefit (5 mg)	[29, 40]
Elenbecestat (E2609)	BACE1 inhibitor	Phase 3 (MissionAD1/AD2, terminated for unfavorable risk-benefit)	*Amyloid PET ↓	No benefit	
Umibecestat (CNP520)	BACE1 inhibitor	Phase 2/3 (Generation S1/S2, terminated for cognitive worsening)	*Plasma Aβ40 ↓	*Worsened (reversible after washout)	[30]
LY2886721	BACE1 inhibitor	Phase 2 (terminated for hepatic AEs)	*Plasma/CSF Aβ40, Aβ42 ↓ *CSF sAPPβ ↓ CSF sAPPα ↑	No data available	[42]
LY3202626	BACE1 inhibitor	Phase 2 (NAVIGATE-AD, terminated for futility)	Plasma Aβ40, Aβ42 ↓ Amyloid PET (-)	No benefit	[44]
PF-06751979	BACE1 inhibitor	Phase 1 (completed, development discontinued for sponsor decision, 2018)	CSF Aβ fragments ↓, sAPPα ↑, sAPPβ ↓	No data available	[45]
BI 1181181	BACE1 inhibitor	Phase 1 (terminated for skin reactions)	No data available	No data available	
RG7129 (RO5508887)	BACE1 inhibitor	Phase 1 (terminated for sponsor decision)	No data available	No data available	
Thalidomide	BACE1 suppressor (TNFα-inhibitor)	Phase 2a (terminated for poor tolerability and safety profile)	Not assessed (dose-limiting toxicity)	No benefit	[48]
Lenalidomide (Revlimid)	Thalidomide analog	Phase 2 (MCLENA-1, completed, results not published); Phase 2 (MCLENA-2, not yet recruiting)	No data available	No data available	
γ-secretase inhibitors/modulators					
Semagacestat (LY450139)	γ-secretase inhibitor	Phase 3 (IDENTITY/IDENTITY-2, terminated for cognitive worsening and safety such as skin cancer, other AEs)	*Plasma Aβ42, Aβ40 ↓ CSF Aβ42, Aβ40 (-) Amyloid PET (-)	*Worsened (140 mg) No benefit (100 mg)	[50]
Avagacestat (BMS-708163)	γ-secretase inhibitor	Phase 2 (terminated for lack of efficacy and unfavorable risk-benefit profile)	CSF Aβ40, Aβ42 ↓	No benefit	[51]
Ibuprofen	γ-secretase modulator	Phase 2 (completed)	No data available	No benefit overall (ADAS-Cog); 18-mo ↑ (MMSE, iADL, GDS, CDR-SB) APOE4 carrier ↑ (ADAS-Cog)	[58]
Tarenflurbil (R-flurbiprofen, Flurizan™, MPC-7869)	γ-secretase modulator	Phase 3 (completed)	No data available	No benefit (primary endpoints, ADAS-Cog, ADCS-ADL) Worsened (secondary endpoints, CDR-SB, NPI)	[60]
CHF 5074	γ-secretase modulator	Phase 2a (completed)	CSF Aβ42 (-) *Amnestic/multidomain MCI ↓	No benefit overall; APOE4 carriers ↑ (Trail Making Test-B)	[61]
EVP-0962	γ-secretase modulator	Phase 2 (completed)	No data available	No data available	
PF-06648671	γ-secretase modulator	Phase 1 (completed, further development status unknown)	CSF Aβ42, Aβ40 ↓ CSF Aβ37, Aβ38 ↑ total CSF Aβ unchanged	No data available	[63]
Nivegacetor (RG6289, RO7269162)	γ-secretase modulator	Phase 2a (ongoing)	CSF Aβ42, Aβ40 ↓ CSF Aβ37, Aβ38 ↑	No data available	[64]
NIC5-15 (D-Pinitol)	γ-secretase modulator	Phase 2 (completed)	No data available	↑ (MMSE, ADAS-Cog)	
QC inhibitors					
Varoglutamstat (PQ912)	Glutaminyl cyclase inhibitor	Phase 2b (VIVAD, completed); Phase 2 (VIVA-MIND, terminated for sponsor decision)	No data available	No benefit	[68]
Cholesterol metabolism modulators					
Efavirenz	CYP46A1 allosteric activator	Phase 2a (ongoing)	No data available	No data available	

*Asterisks indicate statistically significant differences. Arrows indicate the direction of change: for cognitive outcomes, ↑ and ↓ represent improvement or worsening, respectively; for pathological biomarkers, ↑ and ↓ indicate numerical increase or decrease. (-) indicates no change.

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umibecestat [26]. For example, verubecestat was associated with cognitive worsening in the APECS trial [27], lanabecestat showed no benefit in the AMARANTH trial [28], and atabecestat led to cognitive worsening at high dose [29]. Elenbecestat and umibecestat also failed to show benefit, with umibecestat showing reversible cognitive worsening [30]. This lack of efficacy may be attributable to several factors. Preclinical studies suggested that a substantial reduction of Aβ was necessary to influence plaque dynamics, and short-term dosing in transgenic rodent models appeared to reduce amyloid pathology and improve cognition [31-33]. Achieving comparable suppression in humans likely required sustained and intensive inhibition, which may have disrupted processing of other BACE1 substrates such as neuregulin-1, seizure-related 6 (SEZ6), and L1 cell adhesion molecule (L1CAM), all crucial for synaptic and cognitive function [34-36]. As a result, establishing a therapeutic window was challenging, as higher doses were associated with adverse effects, including cognitive decline or hepatic toxicity, whereas lower doses failed to achieve efficacy. Across disease stages, from mild-to-moderate to prodromal and even prevention cohorts, trials uniformly failed to demonstrate benefit, suggesting that the timing of intervention alone did not determine the outcome [27-30, 37]. Collectively, these findings underscore that robust Aβ lowering in biomarkers has not yielded clinical efficacy, leading to broad discontinuation of this class and prompting re-evaluation of amyloid-targeting strategies.

Verubecestat (MK-8931) was the first BACE1 inhibitor to advance to phase 3 trials [38]. Preclinical evidence confirmed robust target engagement in plasma, CSF, and brain [33]. The phase 2/3 EPOCH trial (NCT01739348) in mild-to-moderate AD was terminated early after an interim futility analysis. The co-primary endpoints, including ADAS-Cog and Alzheimer's Disease Cooperative Study-Activities of Daily Living (ADCS-ADL), showed no significant difference from placebo. The phase 3 APECS trial (NCT01953601) in prodromal AD was also terminated for the same reason. The primary endpoint, Clinical Dementia Rating-Sum of Boxes (CDR-SB), showed no significant benefit. Notably, higher-dose groups demonstrated significant cognitive worsening. Although reductions in amyloid positron emission tomography (PET) and CSF Aβ were observed, these biomarker changes were reported mainly in descriptive analyses or small subsets without statistical testing [27, 37]. In summary, verubecestat demonstrated that substantial suppression of Aβ production in humans does not translate into clinical benefit and may be associated with adverse outcomes. Its discontinuation set the precedent for the class-wide failure of BACE1 inhibitors.

Lanabecestat (AZD3294, LY3314814) is characterized by a slow off-rate binding profile, supporting sustained target engagement [32]. Preclinical and early clinical studies confirmed potent target engagement with dose-dependent reductions of plasma and CSF Aβ [32, 39]. The development program progressed to two late-stage trials, the phase 2/3 AMARANTH trial (NCT02245737) in early AD and the phase 3 DAYBREAK-ALZ trial (NCT02783573) in mild AD. Both trials were terminated for futility, as cognitive and functional outcomes, including ADAS-Cog, Alzheimer's Disease Cooperative Study-instrumental Activities of Daily Living (ADCS-iADL), and CDR-SB, showed no significant differences between lanabecestat and placebo. In AMARANTH, lanabecestat caused significant, dose-dependent reductions of Aβ40 and Aβ42 in CSF and amyloid PET signal [28]. Overall, lanabecestat provided validated biomarker evidence in CSF but failed to demonstrate clinical efficacy in early and mild AD populations.

Atabecestat (JNJ-54861911) demonstrated substantial Aβ lowering in early-phase studies, supporting progression to late-stage trials [40, 41]. The phase 2b/3 EARLY trial (NCT02569398) enrolled cognitively normal older adults (CDR=0) with biomarker-confirmed preclinical AD, defined by amyloid positivity on CSF or PET. The trial was terminated due to elevated liver enzymes, and the primary endpoint (Preclinical Alzheimer Cognitive Composite, PACC) showed significant cognitive worsening in the high-dose group [29]. Together, atabecestat advanced BACE inhibition into a preclinical AD prevention trial, but safety concerns precluded further development.

Elenbecestat (E2609) advanced to two phase 3 trials, MissionAD1 (NCT02956486) and MissionAD2 (NCT03036280) in patients with early AD. Treatment produced significant reductions in amyloid PET signal, but across multiple clinical endpoints, such as Alzheimer's Disease Composite Score (ADCOMS), CDR-SB, and ADAS-Cog14, there was no significant benefit compared with placebo. Moreover, adverse events consistent with other BACE1 inhibitors were more frequent in the treatment group, leading to trial termination for an unfavorable risk-benefit profile.

Umibecestat (CNP520) advanced to two phase 2/3 prevention trials Generation S1 (NCT02565511) and Generation S2 (NCT03131453) in cognitively unimpaired, amyloid-positive apolipoprotein E4 (APOE4) carriers. Patients in Generation S1 (GS1) were exclusively APOE4 homozygotes, representing a higher-risk cohort. In contrast, Generation S2 (GS2) included a broader population comprising both APOE4 homozygotes and heterozygotes with elevated brain amyloid levels confirmed by CSF biomarkers or amyloid PET. Thus, GS2 encompassed amyloid-positive heterozygotes alongside the higher-risk homozygous individuals in GS1. Interim analyses confirmed target engagement through significant plasma Aβ40 lowering. Unexpected cognitive worsening on the Repeatable Battery for the Assessment of Neuropsychological

Status (RBANS), along with brain volume loss, was observed in treatment groups relative to placebo. The trials were terminated due to cognitive worsening. However, the cognitive worsening reversed after a median 3.5-month washout, suggesting that the decline reflected a pharmacologically reversible effect rather than irreversible neurodegeneration [30]. Thus, umibecestat extended BACE1 inhibition into the preclinical prevention setting, but its discontinuation underscored both cognitive worsening and the lack of a viable therapeutic window for this approach.

Two Eli Lilly compounds advanced into phase 2 development but were discontinued without progression to phase 3. LY2886721 showed robust biomarker effects, lowering CSF and plasma Aβ40 and Aβ42, but development was halted due to elevations in liver enzymes [42]. LY3202626 was evaluated in the NAVIGATE-AD trial (NCT02791191), a biomarker-driven study enrolling patients with mild AD (MMSE 20-26) and confirmed amyloid pathology by florbetapir PET. The trial selected tau PET as the primary endpoint. This reflected the rationale that while amyloid pathology initiates the disease process, downstream tau accumulation more directly mediates neurodegeneration and cognitive decline [43]. However, treatment showed no significant effect on tau accumulation, nor did it improve cognition. Despite clear reductions in plasma Aβ species, no cognitive benefit was observed, and the trial was terminated for futility [44].

Several other BACE1 inhibitors were halted in early clinical stages. PF-06751979, developed by Pfizer, showed potent target engagement with dose-dependent reductions of several CSF Aβ species in phase 1 [45]. However, development was discontinued in 2018 when the company exited AD research despite robust biomarker data. BI 1181181 from Boehringer Ingelheim reached phase 1 but was stopped due to skin-related adverse events. RG7129 (RO5508887) from Roche also entered phase 1 but was terminated for strategic reasons without efficacy data. Collectively, these compounds underscore the consistent trajectory of early biomarker success followed by discontinuation due to safety issues, futility, or sponsor reprioritization.

In contrast to direct enzymatic inhibitors, another line of investigation has examined immunomodulatory agents that indirectly suppress BACE1 expression. Thalidomide and its derivative lenalidomide, originally developed for oncology and hematology, were repurposed for AD based on their ability to inhibit TNF-α-mediated upregulation of BACE1 and Aβ production [46, 47]. Thalidomide advanced to early clinical evaluation in AD, but was halted due to dose-limiting toxicity and poor tolerability (NCT01094340) [48]. Lenalidomide, a second-generation analogue with a more favorable safety profile, was subsequently investigated as an alternative. A phase 2 study (NCT04032626) in amnestic mild cognitive impairment (aMCI) has been completed, with topline results not yet peer-reviewed, and further clinical testing is in preparation (NCT06177028). While these agents represent a repurposing strategy distinct from direct enzymatic inhibition, their clinical potential remains uncertain.

γ-secretase inhibitors/modulators

The γ-secretase complex is an intramembrane protease that cleaves C99, the membrane-bound fragment generated by BACE1. The enzyme performs a series of stepwise trimming events on longer intermediates such as Aβ49 or Aβ48, producing a range of Aβ species. Longer peptides, including Aβ42 and Aβ43, are more prone to aggregation and are strongly implicated in AD pathogenesis. In contrast, shorter forms such as Aβ37 and Aβ38 are less amyloidogenic [14]. This trimming property established γ-secretase not only as the final step of Aβ generation but also as a potential point for modulating the balance between toxic and benign Aβ species. Early therapeutic strategies focused on GSIs aimed at completely blocking Aβ production. However, γ-secretase processes numerous other substrates, notably the Notch receptor, essential for cell differentiation and immune regulation [49]. Consequently, GSI treatment led to severe adverse effects, including dermatologic and gastrointestinal toxicity, as well as cognitive worsening, leading to the discontinuation of clinical programs [50, 51]. These limitations shifted attention toward GSMs, which differ from inhibitors by not blocking the cleavage activity entirely. Instead, GSMs subtly alter the trimming process of the enzyme to selectively decrease the production of aggregation-prone Aβ42 and Aβ43 peptides, while increasing the formation of shorter, less toxic peptides such as Aβ37 and Aβ38 [18]. Thus, GSMs represent a refined therapeutic strategy that addresses the safety issues associated with GSIs, while enabling modulation of Aβ production.

Semagacestat (LY450139) was the first GSI to reach phase 3 in AD. Early studies confirmed target engagement with reductions of plasma Aβ, providing the rationale for subsequent pivotal trials [52]. Despite early concerns about off-target toxicity related to Notch signaling [53], two large phase 3 programs, IDENTITY (NCT00594568) and IDENTITY-2 (NCT00762411), were launched. IDENTITY enrolled patients with mild-to-moderate AD. Interim analyses revealed that semagacestat failed to improve cognition, as measured by ADAS-Cog. Additionally, significant cognitive worsening was observed at higher dose across multiple endpoints, including ADCS-ADL, CDR-SB, Neuropsychiatric Inventory (NPI), and MMSE. Biomarker analyses demonstrated significant reductions in plasma Aβ40 and Aβ42 but showed no significant changes in CSF Aβ or amyloid PET. Adverse events were frequent, including dermatologic and gastrointestinal com-

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plications, increased risk of skin cancer, and infections, consistent with Notch inhibition. Due to cognitive worsening and dose-limiting Notch-related toxicity, the phase 3 trials were terminated early [50]. Overall, semagacestat demonstrated that broad-spectrum γ-secretase inhibition effectively lowers peripheral Aβ but disrupts multiple physiological pathways essential for cellular and immune homeostasis.

Avagacestat (BMS-708163) was developed as a second-generation GSI with improved selectivity for APP over Notch substrates. This aimed to reduce dose-limiting toxicities observed with earlier GSIs, such as semagacestat [54]. Phase 2 trials (NCT00890890) enrolled patients with prodromal AD, defined as mild cognitive impairment (MCI) with positive CSF biomarkers (CSF Aβ42 <200 pg/mL or total tau/Aβ42 ratio ≥0.39). However, cognitive endpoints showed no evidence of clinical benefit. CSF analyses showed small, non-significant reductions in both Aβ40 and Aβ42. Adverse events observed were consistent with residual Notch inhibition despite improved selectivity. Consequently, development was halted due to lack of efficacy and an unfavorable risk-benefit profile [51]. In summary, avagacestat demonstrated that even partial selectivity for APP over Notch could not overcome safety liabilities or lack of clinical efficacy, underscoring the shift toward GSMs as a more viable therapeutic approach.

Epidemiological studies suggested that long-term use of nonsteroidal anti-inflammatory drugs (NSAIDs) reduced AD incidence [55, 56]. Preclinical research indicated that certain NSAIDs, including ibuprofen, could act as GSMs by selectively lowering Aβ42 while increasing shorter Aβ species, particularly Aβ38, without affecting Notch processing [57]. Based on this, ibuprofen was evaluated in a phase 2 trial involving patients with mild-to-moderate AD. After 12 months, treatment showed no significant differences from placebo on ADAS-Cog. In a subgroup followed for 18 months, ADAS-Cog similarly showed no benefit. However, several secondary measures, including MMSE, ADCS-iADL, Geriatric Depression Scale (GDS), and CDR-SB, suggested small trends indicating slower decline. These exploratory findings lacked statistical significance due to limited sample size, but aligned with epidemiological evidence suggesting benefits from long-term NSAID use [56]. Exploratory analyses also indicated less cognitive worsening in APOE4 carriers, although this was not statistically significant. Gastrointestinal side effects were manageable with esomeprazole but limited the doses that could be tested, thereby constraining further development [58]. This prompted development of tarenflurbil (R-flurbiprofen, Flurizan™, MPC-7869), the R-enantiomer of the NSAID flurbiprofen, designed to enhance GSM activity while minimizing cyclooxygenase (COX) inhibition [59]. However, in a large phase 3 trial (NCT00105547) involving patients with mild AD, tarenflurbil failed to show benefits on primary cognitive endpoints such as ADAS-Cog and ADCS-ADL. Furthermore, secondary outcomes, including CDR-SB and NPI, suggested cognitive worsening compared with placebo. The lack of efficacy was largely attributed to limited brain penetration [60]. Together, ibuprofen and tarenflurbil represent the initial clinical exploration of NSAIDs as GSMs. Despite intriguing epidemiological and preclinical rationale, both agents failed to demonstrate clinical benefit, which has limited further development of this therapeutic approach.

CHF5074 is a flurbiprofen-derived GSM designed to selectively lower Aβ42 while sparing Notch processing. Early clinical trials confirmed its safety and demonstrated dose-dependent reductions in inflammatory markers, such as sCD40L and TNF-α, in CSF and plasma. While no overall effects on cognition or CSF Aβ were observed, reductions in CSF Aβ42 reached statistical significance within the amnestic/multidomain MCI subgroup. Exploratory analyses also suggested a possible cognitive benefit in APOE4 carriers based on Trail Making Test-B results, but this did not reach statistical significance [61]. EVP-0962 (EVP-0015962) is a GSM exhibiting NSAID-like properties. It selectively reduces Aβ42 while increasing shorter Aβ species, without affecting Notch signaling. Preclinical studies demonstrated its efficacy in reducing amyloid plaque and rescuing cognitive function in animal models [62]. Although phase 1 and 2 trials have been completed, no formal data have been published, and clinical development has since ceased. PF-06648671 was developed by Pfizer as a potent GSM. In phase 1 studies, PF-06648671 produced favorable biomarker changes [63], but development was discontinued following the strategic decision by Pfizer to exit AD research, and no further efficacy trials were pursued. Nivegacetor (RG6289, RO7269162) remains under active development and is currently being tested in patients with prodromal AD (NCT06402838). Early-phase studies confirmed a dose-dependent shift in CSF Aβ species consistent with GSM activity [64]. While earlier GSMs failed to progress beyond early clinical trials, nivegacetor stands as the only compound actively pursued, representing the leading effort to validate γ-secretase modulation as a therapeutic strategy.

NIC5-15 (D-pinitol) is a naturally occurring inositol derivative originally developed as an insulin sensitizer for diabetes and metabolic disorders. It was later repositioned for AD based on exploratory evidence of modulating Aβ processing similarly to GSMs. Small clinical studies (NCT00470418) in patients with mild AD showed trends toward improvement in MMSE and ADAS-Cog scores, but these were not statistically significant. Development has since been discontinued, and no further clinical trials are underway.

QC inhibitors

Varoglutamstat (PQ912) is a competitive inhibitor of QC, an enzyme upregulated in the brains of AD patients [65]. QC catalyzes the cyclization of the N-terminal glutamate in truncated Aβ peptides, generating pE3-Aβ. These peptides exhibit greater aggregation propensity, stability, and neurotoxicity compared with unmodified Aβ [66]. The high abundance of pE3-Aβ within amyloid plaques in AD brains [67] has positioned QC inhibition as a promising disease-modifying therapeutic strategy [68]. Preclinical studies supported this rationale [69]. An early phase 2 study (NCT02389413) confirmed QC inhibition in patients and showed exploratory signals in biomarker outcomes [70]. This led to the larger phase 2b VIVIAD trial (NCT04498650) in patients with MCI or mild AD. However, VIVIAD failed to meet its primary and key secondary cognitive endpoints. Subsequently, the sponsor terminated the parallel phase 2a VIVA-MIND trial (NCT03919162) and discontinued the development program. Although target engagement of varoglutamstat was demonstrated, these effects did not translate into clinical benefit.

Cholesterol metabolism modulators

Efavirenz is an anti-HIV drug repurposed for AD based on its ability to allosterically activate CYP46A1 [71], a brain-specific enzyme responsible for converting cholesterol to 24-hydroxycholesterol (24HC) [72]. Alterations in cholesterol metabolism influence APP processing and the activity of the enzyme that cleaves it. Cholesterol, a key component of neuronal membranes, organizes lipid rafts that serve as signaling platforms for secretases. Elevated cholesterol levels enhance the colocalization of APP with β- and γ-secretases, thereby favoring the amyloidogenic pathway and Aβ generation. Conversely, reducing cholesterol or enhancing its turnover shifts APP processing toward the non-amyloidogenic pathway [17]. In a transgenic AD mouse model, low-dose efavirenz enhanced cholesterol turnover and improved memory performance [71]. A phase 1 study in patients with early AD (NCT03706885) confirmed target engagement by showing dose-dependent increases in CSF and plasma 24HC consistent with preclinical findings [73]. Larger phase 2a trials (EUCTR 2023-509613-37-01) are currently ongoing to evaluate the pharmacological effects and safety of efavirenz in patients with early AD.

Aβ AGGREGATION

Aβ aggregation is a dynamic and interconnected process rather than a simple linear pathway. Monomeric Aβ species can nucleate and elongate into fibrils. They also undergo secondary processes such as fragmentation and surface-catalyzed nucleation, generating a spectrum of aggregates ranging from soluble oligomers to mature fibrils [74]. These aggregates exist in equilibrium, with fibrils not only representing an endpoint but also acting as catalytic surfaces that sustain ongoing oligomer production [75]. From a therapeutic perspective, the precise stage of aggregation is less critical than the overall principle that modulation at one or more points along the pathway can reduce the burden of pathogenic aggregates [76]. Based on their mode of action, therapeutic agents targeting this process can be broadly classified into two categories: direct inhibitors, which bind Aβ species to interfere with self-assembly, and indirect inhibitors, which modulate cofactors such as metal ions that facilitate aggregation [77]. In the following section, we introduce representative compounds from each category, emphasizing their mechanistic rationale and clinical experiences (Table 2).

Direct inhibitors

Tramiprosate (3APS, Alzhemed™) is a small molecule glycosaminoglycan (GAG) mimetic designed to interfere with the interaction between sulfated GAGs and Aβ [78]. In the brain, GAGs such as heparan sulfate accelerate Aβ aggregation by electrostatic binding between their negatively charged sulfate groups to basic residues within the Aβ sequence. This interaction promotes local clustering of Aβ monomers, accelerates β-sheet transition and enhances nucleation [79]. Tramiprosate retains the negatively charged sulfate moieties within a simplified molecular scaffold. Unlike natural GAGs, tramiprosate lacks the polysaccharide backbone needed to crosslink Aβ, and is thus thought to prevent aggregation rather than promote it [80]. Phase 2 studies suggested reductions in CSF Aβ42, providing the basis for progression to phase 3 trials [81]. However, two large phase 3 trials (NCT00217763, NCT00088673) in mild-to-moderate AD failed to demonstrate benefit on cognition or function compared with placebo, although a significant reduction in hippocampal atrophy was observed [82]. Post-hoc analyses, however, suggested a significant benefit on ADAS-Cog in APOE4 homozygous patients, particularly in the mild AD subgroup (MMSE 22-26), where improvements were also observed on CDR-SB and Disability Assessment for Dementia (DAD) [83, 84]. These exploratory findings do not alter the overall negative result but suggest that APOE genotype may critically influence the efficacy of aggregation inhibitors, underscoring the need for genotype-based patient stratification.

ALZ-801 (Valiltramiprosate) is an oral valyl prodrug of tramiprosate developed to build upon the exploratory efficacy signal previously observed in APOE4 homozygous patients with tramiprosate [83]. Tramiprosate was limited by substantial pharmacokinetic variability and gastrointestinal tolerability issues [81].

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Table 2. Small molecules inhibiting Aβ aggregation

Name (alternative name)	Mechanism of action	Clinical phase (current status)	Pathological biomarker	Cognition	Ref
Direct inhibitors					
Tramiprosate (3APS, Alzhemed™)	Aβ aggregation inhibitor	Phase 3 (North America, completed); Phase 3 (Europe, terminated for futility)	No data available	No benefit overall; *APOE4 homozygous overall ↑ (ADAS-Cog) *APOE4 homozygous mild AD (MMSE 22-26) ↑ (ADAS-Cog, CDR-SB, DAD)	[82, 83]
ALZ-801 (Valiltramiprosate)	Valyl-prodrug of tramiprosate	Phase 3 (APOLLOE4, completed)	No data available	No benefit overall; *prespecified MCI ↑	[85]
ALZT-OP1 (Cromolyn sodium+Ibuprofen)	Aβ aggregation inhibitor (cromolyn sodium)+NSAID (ibuprofen)	Phase 3 (COGNITE, completed)	No data available	No data available	[88, 89]
Indirect inhibitors					
Clioquinol (PBT1)	MPAC	Phase 2 (completed)	*Plasma Aβ42 ↓	No benefit overall; *Severe subgroup (ADAS-Cog ≥25) ↑ (ADAS-Cog)	[92, 93]
PBT2	Dimethylaminomethyl-substituted clioquinol	Phase 2 (completed)	Amyloid PET overall (-); *Baseline SUVR >2.5 ↓ (Amyloid PET) Plasma Aβ (-)	No benefit	[94, 95]

*Asterisks indicate statistically significant differences. Arrows indicate the direction of change: for cognitive outcomes, ↑ and ↓ represent improvement or worsening, respectively; for pathological biomarkers, ↑ and ↓ indicate numerical increase or decrease. (-) indicates no change.

Valylation was introduced to improve oral absorption and reduce variability. The prodrug is rapidly cleaved *in vivo* to release active tramiprosate, thereby maintaining the pharmacological activity of tramiprosate [85, 86]. In a phase 2 trial (NCT04693520), ALZ-801 demonstrated favorable changes in AD biomarkers, including CSF and plasma Aβ42/40 ratios and a reduction in hippocampal atrophy, accompanied by cognitive stabilization in patients with MCI [87]. A phase 3 APOLLOE4 trial (NCT04770220) in early AD has been completed, and according to company reports, prespecified MCI subgroups exhibited exploratory signals of cognitive benefit. Taken together with the subgroup signal observed for tramiprosate, these findings further emphasize the importance of genotype-based patient stratification in AD.

ALZT-OP1 is a combination therapeutic approach combining two FDA-approved agents with distinct mechanisms. ALZT-OP1 consists of cromolyn sodium (OP1b), an inhaled mast-cell stabilizer originally used for asthma, and ibuprofen (OP1a), an oral NSAID. Cromolyn emerged from preclinical data showing inhibition of Aβ aggregation *in vitro* and stimulation of microglial clearance of soluble Aβ *in vivo* [88]. Ibuprofen was selected for its extensive clinical use, favorable safety profile, and epidemiological and experimental evidence suggesting reduced AD risk and potential γ-secretase modulating activity [57, 89]. The combination advanced to a phase 3 COGNITE trial (NCT02547818) in early AD, but the study was terminated without reported results, and the program has since been discontinued.

Indirect inhibitors

Metal ions such as Cu^{2+} and Zn^{2+} bind to histidine residues within the Aβ sequence, stabilizing intermolecular interactions and promoting aggregation [90, 91]. Clioquinol (PBT1), an 8-hydroxyquinoline compound originally marketed as an antimicrobial, was later repurposed as one of the first metal-protein attenuating compounds (MPACs) due to its ability to bind Cu^{2+} and Zn^{2+} and thereby interfere with Aβ aggregation [92]. In a phase 2 trial, clioquinol significantly reduced plasma Aβ42 levels. Although no overall cognitive benefit was observed, an exploratory post-hoc analysis suggested a treatment effect on ADAS-Cog in the more severely affected subgroup (baseline ADAS-Cog ≥25) [93]. Further development was discontinued due to manufacturing challenges rather than clear safety concerns [77]. PBT2, a second-generation derivative, was subsequently developed to improve solubility, BBB penetration, and synthetic feasibility. Preclinical studies demonstrated that PBT2 reduced brain Aβ and rescued cognitive deficits in transgenic mice, supporting its proposed role as a metal ionophore that redistributes metals and normalizes synaptic function [94]. In phase 2 trials (ACTRN12611001008910), PBT2 failed to demonstrate significant changes in plasma Aβ biomarkers or overall effect on amyloid PET imaging. However, an exploratory analysis stratified by baseline amyloid burden revealed a significant within-group reduction in PiB (Pittsburgh compound B) standardized uptake value ratio (SUVR) among patients with high baseline SUVR values (≥2.5), consistent with more advanced amyloid deposition. Despite this biomarker signal, PBT2 did not show consistent benefits on cognitive endpoints, which led to discontinuation of its clinical development [95]. Together, clioquinol and PBT2 illustrate both the promise and the limitations of the MPAC approach, underscoring drug repurposing as a recurrent theme in

Table 3. Small molecules dissociating Aβ aggregates

Name (Alternative name)	Mechanism of action	Clinical phase (Current status)	Pathological biomarker	Cognition	Ref
Disaggregators					
ELND005 (Scyllo-inositol, AZD-103)	Aβ oligomer disaggregator	Phase 2 (terminated for safety)	CSF, plasma Aβ (-); *250 mg, 78 w ↓ (CSF Aβ42)	No benefit overall; mild AD ↑ (NTB)	[99]
PRI-002 (RD2)	Aβ oligomer disaggregator	Phase 2 (ongoing)	No change overall; *Aβ oligomer slope ↓	↑ (CERAD word list learning)	[105]
Epigallocatechin gallate (EGCG)	Aβ oligomer disaggregator	Phase 2/3 (completed)	No data available	No data available	

*Asterisks indicate statistically significant differences. Arrows indicate the direction of change: for cognitive outcomes, ↑ and ↓ represent improvement or worsening, respectively; for pathological biomarkers, ↑ and ↓ indicate numerical increase or decrease. (-) indicates no change.

early AD drug discovery.

Aβ DISAGGREGATION

Disaggregation strategies arose from the recognition that inhibition of Aβ aggregation alone cannot address the substantial amyloid deposits already present in patients with AD [76]. In contrast to aggregation inhibitors, which primarily delay or block the formation of new assemblies, disaggregators are designed to destabilize pre-existing fibrils or remodel them into less toxic conformations [96]. Whereas antibody therapies achieve clearance through immune-mediated mechanisms [97], small molecules pursue a similar goal by directly disrupting fibrillar structures. In this way, disaggregation provides a small molecule route to reduce established amyloid pathology, complementing the clearance achieved with antibodies (Table 3).

Disaggregators

ELND005 (scyllo-inositol, AZD-103) was identified through small molecule library screening as one of the earliest agents proposed to act as an Aβ disaggregator. Preclinical studies showed that scyllo-inositol bound to preformed Aβ fibrils, promoted their destabilization and remodeling, reduced soluble oligomer levels, and improved cognitive performance in transgenic AD models [98]. In a phase 2 trial in mild-to-moderate AD, ELND005 did not produce significant effects on cognition or Aβ-related biomarkers. However, exploratory analyses suggested a potential cognitive benefit in the mild AD subgroup on the Neuropsychological Test Battery (NTB) and a significant reduction in CSF Aβ42 at 78 weeks in the high-dose group. These findings were not sufficient to change the overall result. High-dose exposure led to increased mortality and serious infections, ultimately resulting in termination of the program [99]. Collectively, these clinical outcomes underscore the challenge of balancing efficacy and safety when developing small molecule disaggregators for AD.

PRI-002 (RD2) is a rationally designed D-enantiomeric peptide developed as an Aβ disaggregator. It was discovered through screening of peptide libraries for fibril-binding motifs, followed by optimization of sequence and stereochemistry to enhance stability and activity [100, 101]. PRI-002 directly binds to preformed amyloid fibrils and oligomers, thereby destabilizing and disaggregating them into non-toxic species [102]. Its D-amino acid composition confers resistance to proteolytic degradation, enabling oral administration with favorable pharmacokinetics [103]. Preclinical studies demonstrated that PRI-002 reduced fibrillar plaque burden and improved cognition in transgenic AD models, supporting its disease-modifying potential [104]. In the phase 1b trial (NCT04711486), no significant changes were observed in global biomarkers or cognition overall. However, biomarker analyses demonstrated that higher plasma exposure of PRI-002 was significantly associated with a slower rate of increase in CSF Aβ oligomers, indicating *in vivo* target engagement. In line with this, exploratory cognitive assessments suggested a positive signal in the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) word list memory test [105]. Phase 2 is currently ongoing to further evaluate safety and efficacy in a larger cohort, positioning PRI-002 as a promising peptide-based strategy for targeting established amyloid pathology.

Epigallocatechin gallate (EGCG), the major catechin in green tea, emerged as a candidate for amyloid-targeted therapy from natural product screening [106]. *In vitro* studies demonstrated that EGCG interacts with preformed Aβ fibrils, inducing structural remodeling into off-pathway, non-toxic aggregates [96, 107]. These findings support its classification as an Aβ disaggregator. Multiple preclinical studies have reported that EGCG mitigates spatial memory deficits and reduces hippocampal Aβ42 accumulation, although variability among models and experimental protocols should be considered [108, 109]. Clinical evaluation in early-stage AD has been limited to a small exploratory study (NCT00951834), from which no conclusive efficacy or biomarker results have been reported to date. One of the main obstacles to clinical translation is the low oral bioavailability and rapid metabolic clearance of EGCG, which limit consistent brain exposure [110]. EGCG illustrates the potential of natural products to act as amyloid disag-

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gregators, as well as the practical barriers that have thus far limited their clinical translation.

Aβ CLEARANCE

Beyond efforts to reduce Aβ production, several approaches have focused on enhancing its removal from the brain. Circulating Aβ can cross into the central nervous system (CNS) through interaction with the receptor for advanced glycation end-products (RAGE) at the BBB [111]. Once within the brain, lipidation pathways mediated by ApoE facilitate Aβ clearance, while microglial phagocytosis and enzymatic degradation serve as additional routes for its removal [112-115]. Together, these mechanisms maintain amyloid homeostasis, and impairment of these pathways can shift the balance toward pathological accumulation [116]. Therefore, modulation of Aβ clearance has emerged as an attractive therapeutic target in AD (Table 4).

RAGE antagonists

Azeliragon (TPP488) is an antagonist of RAGE, a receptor that mediates the influx of circulating Aβ into the brain [111]. Early phase 2a studies confirmed safety and tolerability, but efficacy signals were inconsistent [117], prompting progression to the larger phase 3 STEADFAST trials (NCT02080364) in patients with mild AD. Azeliragon remained safe in phase 3, but the trials failed to meet their co-primary endpoints (ADAS-Cog11 and CDR-SB), and secondary clinical measures likewise showed no benefit. However, exploratory post-hoc analyses suggested that participants with HbA1c ≥6.5% experienced significantly less decline in ADAS-Cog11. Although not prespecified, this finding aligns with the hypothesis that RAGE may serve as a mechanistic link between diabetes and AD, reflecting its activation by advanced glycation end-products (AGEs) that accumulate in metabolic dysfunction [118].

ApoE lipidation enhancers

ApoE is a major apolipoprotein in the CNS, acting as the principal lipid carrier that supports cholesterol and phospholipid transport from glia to neurons [119]. Initially, ApoE is secreted from astrocytes and microglia in a lipid-poor state. Its lipidation depends on the membrane transporter ATP binding cassette subfamily A member 1 (ABCA1), which mediates the efflux of phospholipids and unesterified cholesterol to the extracellular space, thereby enabling the formation of high density lipoprotein (HDL)-like particles [120]. Once lipidated, ApoE can bind Aβ and facilitate its clearance through low-density lipoprotein receptor-related protein 1 and low-density lipoprotein receptor (LRP1/LDLR) pathways. These pathways include receptor-mediated uptake and degradation in neurons and glia, as well as efflux across the BBB into the periphery [121, 122]. In contrast, insufficient ApoE lipidation reduces the efficiency of Aβ transport and degradation, leading to greater cerebral accumulation. Notably, the ApoE4 isoform has been associated with reduced lipidation efficiency, which in turn impairs Aβ clearance and contributes to increased AD risk [123, 124].

Bexarotene is an RXR agonist originally approved for cutaneous T-cell lymphoma. It was repurposed for AD based on evidence that RXR activation induces expression of ApoE and its lipid

Table 4. Small molecules enhancing Aβ clearance

Name (alternative name)	Mechanism of action	Clinical phase (current status)	Pathological biomarker	Cognition	Ref
RAGE antagonists					
Azeliragon (TPP488)	RAGE antagonist	Phase 3 (STEADFAST, terminated for futility)	No data available	No benefit overall; *HbA1c ≥6.5% ↑ (ADAS-Cog11)	[118]
ApoE lipidation enhancers					
Bexarotene	RXR agonist	Phase 2 (completed)	Amyloid PET: No benefit overall; *APOE4 noncarrier ↓ (regional amyloid) *Serum Aβ42 ↑ (correlated with decreased cortical amyloid in treated APOE4 noncarrier)	No benefit overall *APOE4 noncarrier ↓ (MMSE)	[113, 126]
CS6253	ABCA1 modulator	Phase 1 (completed)	No data available	No data available	[127]
Microglia modulators					
GV-971	Gut-brain axis immunomodulator	Phase 3 (China, completed→ conditional approval in China) Phase 3 (GREEN MEMORY, suspended for COVID-19)	No data available	*↑ (ADAS-Cog12); *MMSE 11-14 ↑ (CIBIC+)	[129]
VG-3927	TREM2 agonist	Phase 1 (completed)	No data available	No data available	[133, 134]
IDE enhancers					
Nasal Insulin	IDE-mediated Aβ clearance[65]	Phase 2/3 (SNIFF, completed)	CSF Aβ42/Aβ40 and Aβ42/total tau ratios: No benefit overall; *Device 1 subgroup ↑	No benefit overall; *Device 1 subgroup ↑ (ADAS-Cog12, ADL-MCI)	[139]

*Asterisks indicate statistically significant differences. Arrows indicate the direction of change: for cognitive outcomes, ↑ and ↓ represent improvement or worsening, respectively; for pathological biomarkers, ↑ and ↓ indicate numerical increase or decrease. (-) indicates no change.

transporters such as ABCA1 and ATP-binding cassette subfamily G member 1 (ABCG1), thereby enhancing ApoE lipidation capacity. In transgenic mouse models, bexarotene treatment increased ApoE levels, reduced soluble Aβ, and improved cognitive performance, providing the basis for clinical trials [113, 125]. In a phase 2 proof-of-concept trial (NCT01782742) in patients with mild-to-moderate AD, no overall changes were observed in amyloid PET signal or cognitive outcomes across the cohort. In prespecified analyses, however, APOE4 noncarriers exhibited significant regional reductions in cortical amyloid burden, accompanied by elevations in serum Aβ42, consistent with enhanced Aβ efflux. Importantly, the nominal decline in MMSE observed among noncarriers was attributable to improvement in the placebo group and was not a drug-related effect. Adverse effects, including hyperlipidemia and hypothyroidism consistent with its oncologic use, posed further challenges for long-term application [126]. Taken together, RXR activation may promote Aβ clearance in certain genotypes but does not translate into cognitive benefit, and the combination of limited efficacy and safety concerns has curtailed further clinical development of bexarotene.

CS6253 is an ApoE-mimetic peptide that interacts with ABCA1 at the cell surface to stabilize the transporter and promote efflux of cholesterol and phospholipids [127]. Because ABCA1-mediated lipid efflux is the rate-limiting step in the formation of HDL-like ApoE particles [125], this mechanism enhances ApoE lipidation and thereby facilitates Aβ clearance through LRP1-dependent pathways [122]. Stabilization of ABCA1 may be particularly relevant for APOE4 carriers, in whom reduced lipidation efficiency has been linked to impaired Aβ clearance [124]. A first-in-human phase 1 study (NCT05965414) has been completed, although efficacy in AD remains to be established.

Microglia modulator

GV-971 is a marine-derived oligosaccharide composed of acidic linear chains ranging from dimers to decamers. It was developed as a first-in-class therapy targeting neuroinflammation via the gut-brain axis. Preclinical studies demonstrated that GV-971 reshapes gut microbiota, which in turn normalizes amino acid metabolites such as phenylalanine and isoleucine. These metabolic changes reduce peripheral Th1 cell infiltration into the brain and ultimately attenuate microglial overactivation. Collectively, these effects support restoration of immune homeostasis and may indirectly facilitate amyloid clearance [128]. In a phase 3 trial (NCT02293915) conducted in China, GV-971 produced a statistically significant improvement on the ADAS-Cog12 over 36 weeks in patients with mild-to-moderate AD. Exploratory subgroup analyses suggested that patients with more advanced impairment (MMSE 11-14) exhibited significant cognitive benefit on the Clinician's Interview-Based Impression of Change with caregiver input (CIBIC+) [129]. These findings led to regulatory approval in China. A confirmatory phase 4 study (NCT04520412) is ongoing, and further international trials are in progress to validate efficacy and safety across broader populations. While its approval has generated discussion, particularly regarding the need for validation outside China, GV-971 exemplifies a novel gut-brain axis-based immunomodulatory approach that may broaden the therapeutic landscape.

VG-3927 is an agonist of triggering receptor expressed on myeloid cells 2 (TREM2), which is a microglial surface receptor that senses lipoproteins such as ApoE and lipid debris surrounding amyloid plaques [130]. TREM2 signaling promotes the transition of microglia toward a disease-associated microglia (DAM) state. This phenotype is characterized by increased activation, clustering around plaques, and enhanced Aβ clearance [131]. Loss-of-function variants impair this response and increase the risk of AD [132]. By activating TREM2, VG-3927 is designed to restore DAM function and enhance Aβ uptake and degradation. Preclinical studies demonstrated reductions in pathological Aβ and neuroinflammatory markers in transgenic mouse models, along with pharmacodynamic evidence of target engagement [133, 134]. Clinical development has advanced through a completed phase 1 trial (NCT06343636), although efficacy in AD remains to be demonstrated.

IDE enhancers

Nasal insulin has been investigated as a strategy to enhance brain insulin signaling. This pathway is thought to promote Aβ degradation through insulin-degrading enzyme (IDE) [115]. Intranasal delivery enables direct access to the CNS via olfactory and trigeminal pathways while minimizing systemic exposure, thereby reducing the risk of hypoglycemia [135]. The rationale for this approach comes from evidence that brain insulin resistance contributes to AD pathogenesis. Reduced insulin receptor signaling lowers IDE activity and thereby impairs Aβ clearance [136]. Restoring insulin signaling in the brain may therefore provide therapeutic benefit in AD. Preclinical studies have shown that intranasal insulin improved memory performance in mouse models [137], and early pilot clinical trials also reported preserved cognition in patients with MCI or AD [138]. However, the phase 2/3 SNIFF trial (NCT01767909) did not meet its primary cognitive endpoint, and no overall CSF biomarker effects were observed. During the trial, the delivery device was switched from an electronic atomizer (Device 1) to an alternative device (Device 2), potentially differing in delivery efficiency and influencing the outcomes. In post-hoc analyses, participants treated with Device 1 showed nominally sig-

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nificant improvements in cognition, including ADAS-Cog12 and Activities of Daily Living for Mild Cognitive Impairment (ADL-MCI), accompanied by increases in CSF Aβ42/40 and Aβ42/total tau ratios [139]. However, clinical development has not advanced further, since the findings were preliminary and practical challenges have limited further clinical application.

Aβ NEUROTOXICITY

Accumulating evidence indicates that soluble Aβ oligomers are major contributors to neuronal dysfunction in AD. This approach differs from other therapeutic strategies that have primarily targeted Aβ burden itself. Instead, the focus here is on mitigating the functional consequences of oligomeric Aβ species at the synaptic and network levels. Experimental studies have suggested that Aβ oligomers disrupt synaptic communication and receptor signaling, impair plasticity and long-term potentiation, and alter cytoskeletal stability, all changes that converge on progressive synaptic failure [140-142]. In addition, Aβ exposure has been consistently linked to abnormal neuronal hyperexcitability in hippocampal and cortical circuits. This network dysfunction is thought to accelerate disease progression even in the absence of overt plaque pathology [143, 144]. Together, these insights provide the rationale for therapeutic strategies aimed at interfering with oligomer-driven synaptotoxicity or counteracting Aβ-associated hyperexcitability. The following section reviews pharmacologic agents that have been developed to address these pathogenic processes and their status in clinical development (Table 5).

Synaptotoxicity modulators

Zervimesine (CT1812, Elayta) is a sigma-2 receptor (Transmembrane protein 97, TMEM97) allosteric modulator identified through screening for compounds that displace Aβ oligomers from synaptic binding sites [145]. TMEM97 forms complexes with proteins such as progesterone receptor membrane component 1 (PGRMC1) and LRP/LDLR family members that mediate uptake of Aβ species [146]. Zervimesine has been proposed to modulate this complex in a way that lowers oligomer affinity, displacing them from synapses into the extracellular/CSF space and limiting their intracellular accumulation [147]. Rather than lowering amyloid burden, its rationale is instead to target the synaptic interface where oligomers are thought to exert their toxicity. In clinical studies, zervimesine has shown pharmacodynamic signals consistent with this mechanism. CSF proteomics demonstrated normalization of synapse- and inflammation-related proteins, together with significant reductions in neurofilament light chain at the high dose (NCT03493282; NCT03507790) [148, 149]. In phase 2 trials, no benefit overall was observed in cognition, although exploratory analyses showed a trend toward improvement in patients with low CSF p-tau217, defined by the median cutoff. These preliminary findings suggest potential efficacy in biologically defined patient populations [150]. Building on these observations, the phase 2 START trial (NCT05531656) is currently underway in patients with early AD to evaluate efficacy, safety, and tolerability over 18 months.

Simufilam (PTI-125) binds selectively to misfolded filamin A (FLNA), restoring its native conformation. FLNA is an actin-binding scaffold protein that organizes cytoskeletal structure and links membrane receptors with downstream signaling pathways under physiological conditions. In AD, soluble Aβ42 oligomers have been proposed to induce FLNA misfolding, which enables abnormal interactions with receptors such as α7 nicotinic acetylcholine receptors (α7nAChRs) and toll-like receptor 4 (TLR4) [151]. These complexes have been associated with tau hyperphosphorylation,

Table 5. Small molecules attenuating Aβ-induced neurotoxicity

Name (Alternative name)	Mechanism of action	Clinical phase (Current status)	Pathological biomarker	Cognition	Ref
Synaptotoxicity modulators					
Zervimesine (CT1812, Elayta)	TMEM97 modulator	Phase 2 (START, ongoing)	*CSF proteomics: synapse- and inflammation-related proteins normalized *CSF NfL ↓ (300 mg) *CSF Aβ42 ↓ (300 mg)	No benefit overall; Low p-tau217 subgroup ↑ (ADAS-Cog11)	[145, 147-150]
Simufilam (PTI-125)	Filamin A modulator (disrupts Aβ-α7nAChR interaction)	Phase 3 (ReThink-ALZ, completed) Phase 3 (ReFocus-ALZ, terminated for sponsor decision)	No benefit	No benefit	[152]
ALX-001 (BMS-984923)	mGluR5 SAM	Phase 1b (ongoing)	No data available	No data available	[156]
Hyperexcitability modulators					
Levetiracetam	SV2A modulator	Phase 2/3 (HOPE4MCI-AGB101, completed)	No data available	No benefit	[157]

*Asterisks indicate statistically significant differences. Arrows indicate the direction of change: for cognitive outcomes, ↑ and ↓ represent improvement or worsening, respectively; for pathological biomarkers, ↑ and ↓ indicate numerical increase or decrease. (-) indicates no change.

inflammatory activation, and synaptic dysfunction. By correcting FLNA conformation, simufilam was reported in preclinical studies to disrupt Aβ-α7nAChR binding and normalize related signaling pathways. This provides a distinctive mechanistic rationale for targeting Aβ neurotoxicity [152]. However, several key publications originally describing mechanism of simufilam were later retracted or flagged for data integrity concerns, and mid-stage clinical results were also criticized for inconsistency and lack of reproducibility. In the absence of convincing mechanistic support, the pivotal phase 3 ReThink-ALZ trial (NCT04994483) showed no benefit in cognition or biomarkers, and the companion ReFocus-ALZ trial (NCT05026177) was discontinued by sponsor decision amid ongoing controversy. Taken together, the case of simufilam illustrates the importance of rigorous validation. While an unconventional mechanistic hypothesis can stimulate rapid clinical progress, reproducible preclinical and early clinical evidence remain essential to sustain late-stage development.

ALX-001 (BMS-984923) is a selective silent allosteric modulator (SAM) of metabotropic glutamate receptor 5 (mGluR5), designed to block the pathogenic cellular prion protein (PrP^c)-mGluR5 signaling pathway initiated by soluble Aβ oligomers while preserving physiological glutamatergic transmission. Under pathological conditions, Aβ oligomers bind to PrP^c on the postsynaptic membrane, which leads to clustering of mGluR5 and activation of aberrant calcium signaling cascades. This cascade impairs long-term potentiation and contributes to synaptic dysfunction, independent of overall amyloid burden [153, 154]. By binding to an allosteric site on mGluR5, ALX-001 prevents oligomer-induced receptor clustering without interfering with glutamate binding or basal receptor activity [155]. Preclinical studies have shown that this mechanism normalizes intracellular Ca^{2+} transients, preserves synaptic plasticity, and mitigates synaptic protein loss in AD mouse models. Importantly, these effects were observed without altering total Aβ levels, underscoring that ALX-001 targets oligomer-driven neurotoxicity rather than Aβ burden itself [156]. Clinical development of ALX-001 remains at an early stage, with a phase 1b trial (NCT05804383) underway to assess safety, tolerability, and preliminary pharmacodynamic outcomes in patients with AD. No data are available yet for pathological biomarkers or cognition in humans. ALX-001 offers a mechanistically well-defined attempt to interfere with Aβ oligomer-driven synaptotoxicity via the PrP^c-mGluR5 pathway.

Hyperexcitability modulators

Levetiracetam, originally developed as an antiepileptic drug, exerts its pharmacologic effect through binding to synaptic vesicle protein 2A (SV2A), thereby modulating Ca^{2+}-dependent neurotransmitter release and reducing neuronal hyperexcitability [157]. Interest in repurposing arose from observations that hippocampal and cortical hyperactivity is a consistent feature in AD models and patients, and that low-dose levetiracetam can reduce aberrant activity and improve performance in specific memory tasks [158, 159]. Unlike approaches that target Aβ production, aggregation, or clearance, levetiracetam does not alter upstream amyloid burden but instead aims to mitigate downstream network dysfunction induced by Aβ exposure. Clinical development advanced with AGB101, a low-dose extended-release formulation, tested in the phase 2/3 HOPE4MCI trial (NCT03489044) in patients with mild cognitive impairment. The trial did not demonstrate cognitive benefit, and no data are available for pathological biomarkers. Nevertheless, exploratory studies (NCT02002819) suggest that subgroups characterized by subclinical epileptiform activity might be more responsive, highlighting the importance of precision in patient selection [160].

DISCUSSION

In this review, we examined a broad range of small molecules targeting Aβ, categorized by their mechanisms of action into modulation of production, inhibition of aggregation, dissociation of aggregates, enhancement of clearance, and attenuation of neurotoxicity. Our analysis reveals that although extensive efforts have been made in small molecule development, clinical translation has remained limited. This pattern reflects an exploratory and broadly dispersed portfolio of strategies to date, aimed at identifying effective therapeutic targets for AD, rather than intrinsic limitations of small molecules themselves, and now underscores the need to transition toward a more focused, target-validated approach.

Recent advances in biologics, particularly monoclonal antibodies, have demonstrated that reducing cerebral amyloid burden can modestly slow cognitive decline. These outcomes clinically validate amyloid aggregate clearance as a feasible and substantiated disease-modifying strategy in AD. However, among the 43 small molecules analyzed in this review, only three were designed to directly target amyloid aggregates as pathogenic species.

According to the 2025 Alzheimer's disease drug development pipeline, the current phase 1-3 AD portfolio contains a numerically greater proportion of small molecule disease-targeted therapies overall, yet the amyloid-focused late-stage programs are predominantly driven by antibody-based biologics, indicating that target validation in this domain has occurred mainly through biologic rather than small molecule approaches [161]. As consensus increasingly converges on amyloid aggregate clearance as a clinically relevant target, a more focused emphasis on clearance-

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Table 6. Comparative overview of biologics and small molecules

Category	Biologics (monoclonal antibodies)	Small molecules
Mechanistic focus	Aggregate-directed strategies	Diverse mechanisms, with relatively limited emphasis on aggregate-directed strategies
BBB penetration	Low	Generally higher
Route of administration	Intravenous	Oral (potential)
Risk of ARIA	High; class-specific safety concern	No ARIA-specific risk; adverse events are mechanism-dependent
Cost	High	Potentially lower
Accessibility	Limited by infrastructure and cost	Potentially broader accessibility
Implication for elderly populations	Requires hospital-based administration and monitoring	Potentially more convenient for long-term use in elderly patients

or disaggregation-oriented mechanisms may enhance the translational potential of future small molecules by more closely aligning them with this aggregate-directed therapeutic framework.

While biologics have established the therapeutic relevance of aggregate-directed strategies, their broader implementation occurs within the context of a rapidly aging global population, where long-term treatment feasibility and accessibility become increasingly important considerations [162]. In light of these demographic trends, small molecules may offer practical advantages related to delivery convenience and sustained administration, particularly for elderly patients (Table 6). Thus, strategically redirecting small molecule discovery toward aggregate-targeted mechanisms, while leveraging their inherent advantages in chronic, widely accessible treatment, could help achieve a more balanced contribution of biologics and small molecules within amyloid-directed AD drug development.

Recent advances in drug discovery technologies, including artificial intelligence, multi-target ligand design, and high-throughput screening, are being explored to accelerate the identification and optimization of novel small molecules for AD, in parallel with more traditional discovery approaches. These developments may facilitate the design of next-generation small molecules that more effectively engage clinically validated targets and better align with aggregate-directed therapeutic strategies.

Taken together, these considerations position small molecule approaches not as replacements for biologics but as valuable complements to them. By broadening the scope of therapeutic strategies, such approaches have the potential to address persistent challenges and provide additional avenues to modify the course of AD. A balanced emphasis on both biologics and small molecule interventions will likely be essential as the field seeks durable, accessible, and effective treatments for AD, underscoring the need for a concerted effort across modalities to overcome this disease.

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