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Small-Molecule Amyloid Beta-Aggregation Inhibitors in Alzheimer's Disease Drug Development

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Abstract

Alzheimer's disease (AD) is still an incurable neurodegenerative disease that causes dementia. AD changes the brain function that, over time, impairs memory and diminishes judgment and reasoning ability. Pathophysiology of AD is complex. Till now the cause of AD remains unknown, but risk factors include family history and genetic predisposition. The drugs previously approved for AD treatment do not modify the disease process and only provide symptomatic improvement. Over the past few decades, research has led to significant progress in the understanding of the disease, leading to several novel strategies that may modify the disease process. One of the major developments in this direction is the amyloid β (Aβ) aggregation. Small molecules could block the initial stages of Aβ aggregation, which could be the starting point for the design and development of new AD drugs in the near future. In this review we summarize the most promising small-molecule Aβ-aggregation inhibitors including natural compounds, novel small molecules, and also those are in clinical trials. Moreover, we briefly summarized some reported docking studies of small-molecule Aβ aggregation inhibitors. These will give us an idea about the chemical features required to design novel small molecules with anti-Aβ aggregation properties.

Keywords

- Alzheimer's disease
- small molecule amyloid β-aggregation inhibitors
- drug design

Introduction

Alzheimer's disease (AD) is the most common form of dementia and is still an incurable, progressive neurodegenerative disorder.[1] AD is a multifactorial disease in which a complex of proteins, enzymes, or receptors is involved. The pathogenesis of AD is not completely clear. However, the typical pathological hallmarks are amyloid β (Aβ) deposits, tau (τ) protein aggregation, oxidative stress, and decreased levels of acetylcholine (ACh) in the brain.[2] The etiological mechanisms underlying the neuropathological changes in AD remain unclear but are probably affected by both environmental and genetic factors.[3] AD is characterized by relatively slow, chronic but progressive neurodegeneration and impairment in cognition accompanied by abnormal behavior and personality changes, ultimately leading to full dementia. Incidence increases with age, affecting an estimated 35 million patients worldwide.[4] However, since dementia primarily affects those aged over 60, increased longevity has led to increased rates of AD.[5]

Currently there are no effective treatments or interventions to mitigate AD progression, and the incidence rates for AD doubled every 5 years from age 65. The global burden of AD patients is therefore expected to be 106.8 million by 2050.[6] Current treatment of the disease, essentially symptomatic, is based on three cholinesterase inhibitors (donepezil, galantamine, and rivastigmine) and memantine, affecting the glutamatergic system (►**Table 1**). Unfortunately, none of these drugs stop the progressive loss of neurons and there is no treatment that can halt the progressive deterioration of cognitive faculties in AD patients.[7] Despite enormous information gained, the prevailing hypotheses regarding AD pathogenesis have failed to deliver strategies for mitigation of symptoms.[8]

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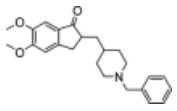
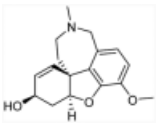
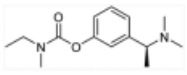
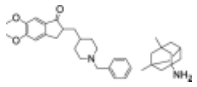
Table 1 Medication for Alzheimer's disease

Drug name	Brand name	Structure	FDA approved in
Donepezil	Aricept		1996
Galantamine	Razadyne		2001
Memantine	Namenda		2003
Rivastigmine	Exelon		2000
Donepezil + Memantine	Namzaric		2014

Abbreviation: FDA, U.S. Food and Drug Administration.

Amyloid Cascade Hypothesis of Alzheimer's Disease

The amyloid hypothesis proposes Aβ as the main cause of the disease. It suggests that misfolding of the extracellular Aβ protein accumulated in senile plaques (SPs) and the intracellular deposition of misfolded tau protein in neurofibrillary tangles (NFTs) cause memory loss and confusion (also cause personality and cognitive decline over time). Accumulated Aβ peptide is the main component of SPs and is derived from the proteolytic cleavage of a larger glycoprotein named amyloid precursor protein (APP). APP is a transmembrane protein that plays an important role in a range of biological activities, including neuronal development, signaling, intracellular transport, and other aspects of neuronal homeostasis. APP is the precursor molecule cut by β- and γ-secretases to produce a 37 to 49 amino acid residue peptide. Aβ lies at the heart of the amyloid cascade hypothesis and its amyloid fibrillar form is the primary component of amyloid plaques found in the brains of AD patients.[9–15] Aβ peptides are mainly observed in the region of the hippocampus and the neocortex as well as in the cerebrovasculature.[9–13] Human APP can be processed via two alternative pathways: amyloidogenic and nonamyloidogenic. APP is first cleaved by α-secretase (nonamyloidogenic pathway) or β-secretase (amyloidogenic pathway), generating membrane-tethered α- or β-C terminal fragments.[9]

Since the first description of presenile dementia by Alois Alzheimer in 1907, SPs and NFTs are considered as the key pathological hallmarks of AD. The identification of Aβ in SPs and genetic studies that identified mutations in the APP, presenilin 1 (PSEN1), and presenilin 2 (PSEN2) genes leading to the accumulation of Aβ and early-onset familial dementia resulted in the formulation of the "amyloid cascade hypothesis."[15,16]

The enzymatic processes responsible for the metabolism of APP to Aβ are now reasonably well understood. APP is sequentially cleaved by β- and γ-secretases. β-Secretase first cleaves APP to release a large secreted derivative, sAPPβ. A fragment of 99 amino acids remains membrane bound, and is rapidly cleaved by γ-secretase to generate Aβ. Hence, numerous different Aβ species exist, but those ending at position 40 (Aβ40) are the most abundant ones (~80–90%), followed by Aβ42 (~5–10%). The longer forms of Aβ, particularly Aβ42, are more hydrophobic, fibrillogenic, and are the principal species deposited in the brain.[9]

The primary amino acid sequence of Aβ (►**Fig. 1**) was first discovered from extracellular deposits and amyloid plaques in 1984. Aβ monomers aggregate into various types of assemblies, including oligomers, protofibrils, and amyloid fibrils (►**Fig. 2**). Amyloid fibrils are larger and insoluble, and they can further assemble into amyloid plaques. While amyloid oligomers are soluble and may spread throughout the brain. Amyloid plaques with Aβ as the main component are most commonly found in the neocortex in the brain of AD patients.[9] Amyloid cascade hypothesis (►**Fig. 3**) proposes that the deposition of Aβ is the initial pathological event in AD leading to the formation of SPs and then to NFTs, neuronal cell death, and ultimately dementia. While there is substantial evidence supporting the hypothesis, there are also limitations, such as SPs and NFTs may develop independently, and SPs and NFTs may be the products rather than the causes of neurodegeneration in AD.[15] On the other hand, tau (τ) proteins are also found in several less common neurodegenerative diseases, notably in the absence of neurotic plaques. The NFTs in the different diseases have some distinctive morphological features and may exhibit a distinct composition of tau isoforms that differ from AD.[17,18]

In contrast, the amount of oligomeric Aβ is increased in AD brain extracts. Aβ oligomers trigger synapse failure and memory impairment, resulting in impaired brain function in the final stages of the disease. Further studies reported that cognitive deficits appeared before plaque deposition or the detection of insoluble amyloid fibrils. These all evidence proved that Aβ oligomers trigger neuronal death rather than insoluble fibrils or plaques.[9]

Current Trend of AD Research

AD has been studied over a century, but acetylcholinesterase inhibitors and memantine are the only drugs currently approved for its management (►**Table 1**). These drugs

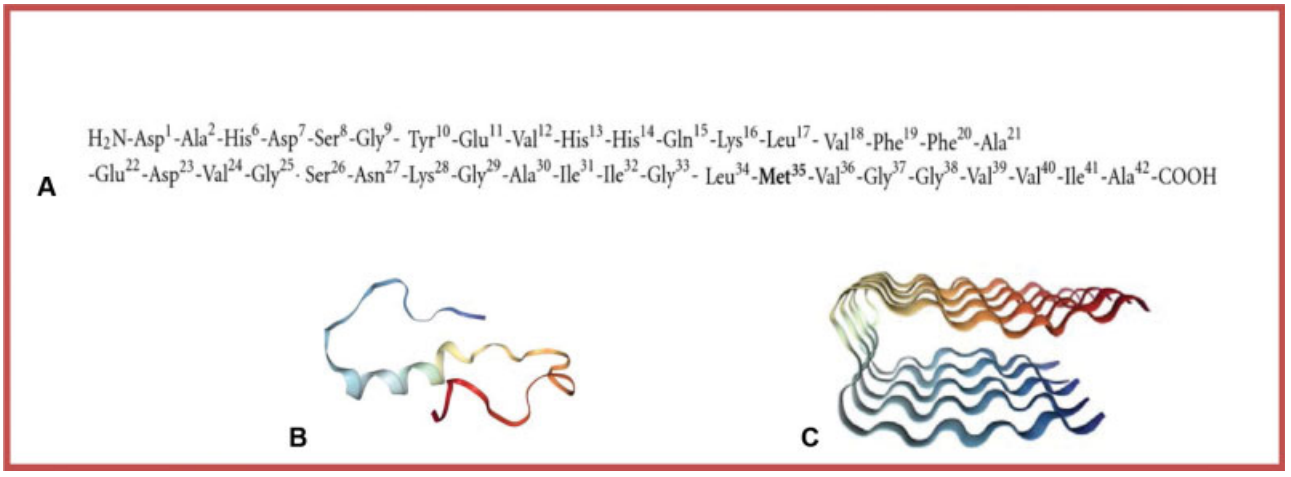


Fig. 1 Structure of Aβ monomer and fibrils. (**A**) The primary amino acid sequence of the 42-amino acid Aβ, (**B**) 3D structure of Aβ 1–40 monomer (PDB code: 2LFM), and (**C**) Aβ 1–42 fibrils, homopentamer structure (PDB code: 2BEG).

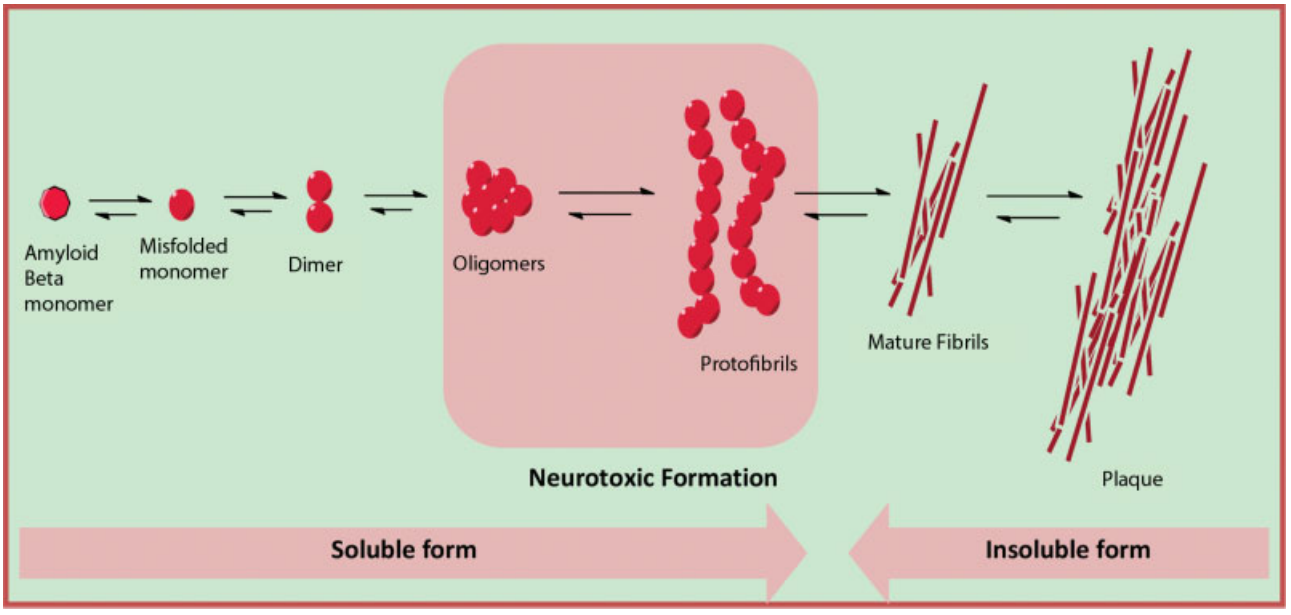


Fig. 2 Conversion of amyloid β (Aβ) monomers to oligomers, protofibrils and fibrils.

provide symptomatic improvement alone but do less to modify the disease process. The extensive insight into the molecular and cellular pathomechanism in AD over the past few decades has provided us significant progress in the understanding of the disease. Several novel strategies that seek to modify the disease process have been developed.[1]

Current directions in the search for novel, potentially effective agents for the treatment of AD include agents acting upon Aβ (early-stage intervention), such as vaccines, antibodies, and small-molecule inhibitors or modulators of β- and γ-secretases; agents directed against the tau protein as well as compounds acting as antagonists of neurotransmitter (mild-stage intervention), and agents targeting microglia or some anti-inflammation (late-stage intervention) (►**Fig. 4**). The major developments in the amyloid and tau-based therapeutics could hold the key to treatment of AD in the near future.[1] Development of new effective drugs acting upon the central nervous system is usually a difficult and time-consuming process, and in the case of AD to date clinical trials have had a very high failure rate. Most of phase II clinical trials end with a positive outcome, but do not succeed in phase III, often due to serious adverse effects or lack of therapeutic efficacy. Now it becomes one of the greatest challenges in modern medicine to develop novel drugs with strong disease-modifying properties.[19,20]

Several large clinical trials are actively studying individuals to discover potential therapies by 2025.[21] Preclinical studies performed in academic as well as industrial settings focus on many potential molecular targets involved in the pathogenesis of AD. Because of a huge attrition rate, only selected candidates are accepted into clinical trials as potential anti-AD agents. Due to the importance of these studies, several comprehensive reviews on anti-AD drug development prospects have been published in recent years.[1,22–27] In

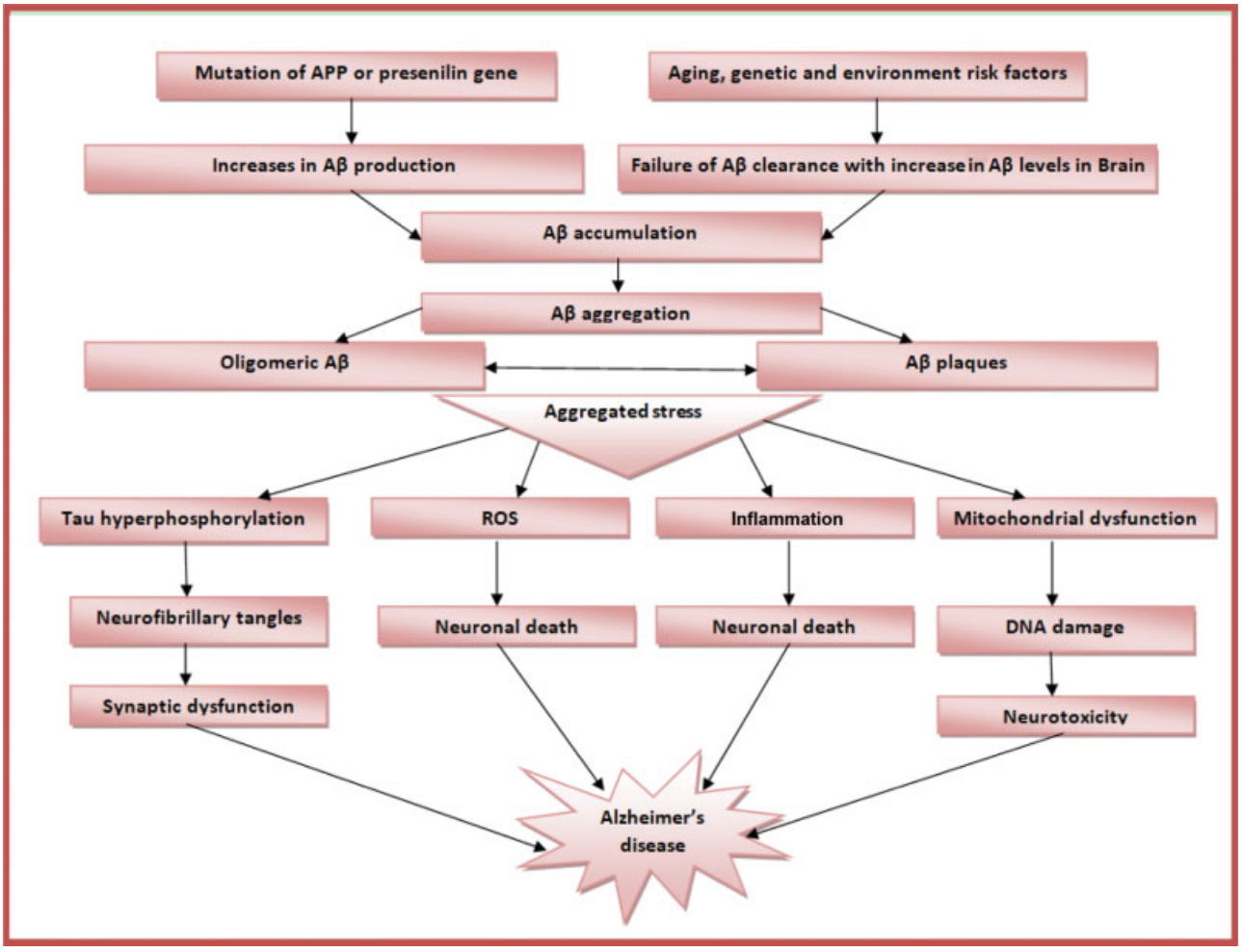


Fig. 3 Proposed amyloid cascade hypothesis.

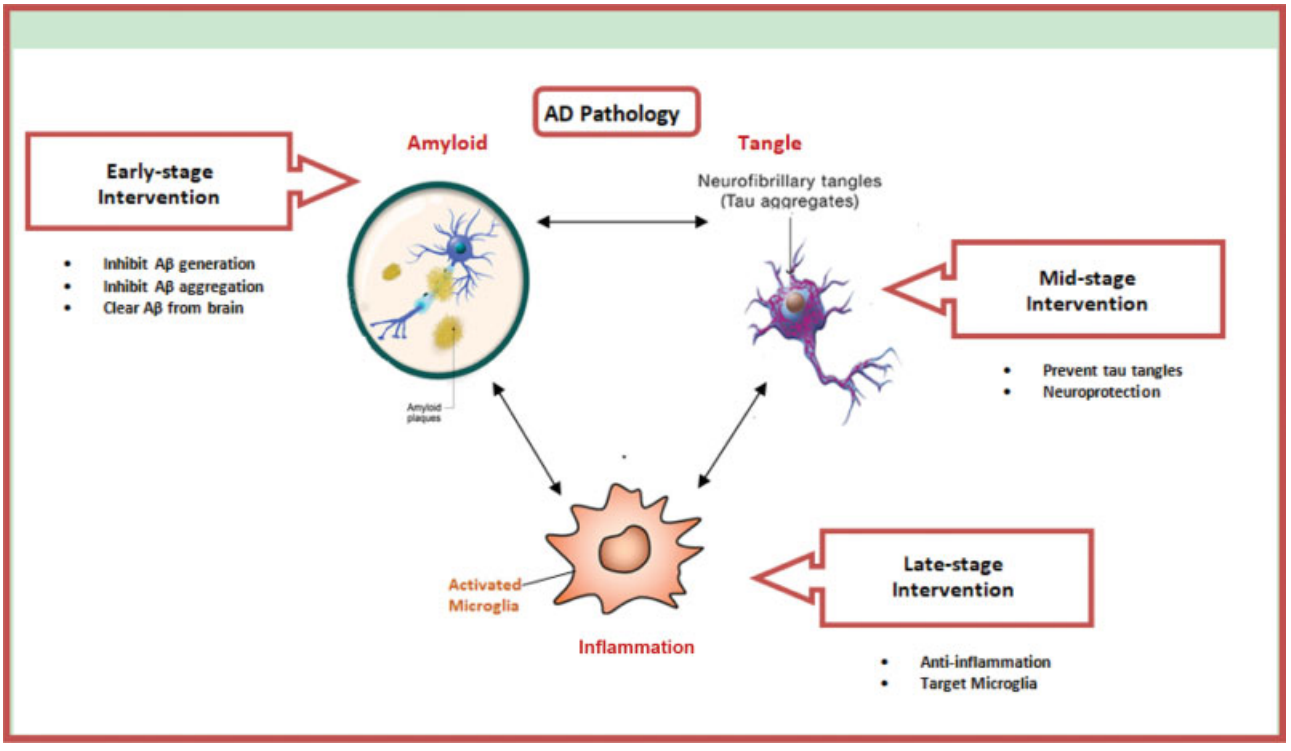


Fig. 4 Current trend of Alzheimer's disease research.

this review we present the latest advances in the scope of the most promising small-molecule Aβ-aggregation inhibitors that are currently undergoing AD drug development and clinical trials.

Small-Molecule Amyloid β-Aggregation Inhibitors

The progressive production and subsequent accumulation of Aβ play a central role in AD. Aβ is released in a soluble form that may be responsible for cognitive dysfunction in the early stages of the disease, then progressively forms oligomeric, multimeric, and fibrillar aggregates, triggering neurodegeneration. Eventually, the aggregation and accumulation of Aβ culminates with the formation of extracellular plaques, one of the morphological hallmarks of AD. Based on the conformation/oligomerization hypothesis, molecules able to stabilize the soluble Aβ conformation destabilize the altered amyloidogenic conformer or prevent the required conformational transition, which could be effective inhibitors of amyloid plaque formation. These could be very potent drug candidates for AD treatment.[28] Indeed, recent and ongoing clinical trials in AD continue to experiment with very early drug interventions in attempts to develop a disease-modifying agent but unfortunately, so far, no such approved agents are currently available.[29] Some small molecules are able to inhibit the formation and extension of Aβ fibrils, and also destabilize Aβ fibrils in vitro. These include natural compounds or commercially available bioactive compounds, drugs, surfactants, Cu/Zn chelators, phenothiazines, and sulfonated dyes such as Congo red (CR) and thioflavin T (ThT).[30–32] As the strategy of inhibiting Aβ aggregation has increasingly gained acceptance, greater numbers of inhibitors have been developed and the structure–activity relationships of potent inhibitors have been systematically explored.[28,33,34] CR was the first small molecule reported to bind to amyloid in tissue sections.[35] Later ThT and thioflavin S were also shown to stain amyloid deposits. CR and ThT, the two dyes (►**Fig. 5**), are the classical reagents to detect characteristic Aβ sheet-mediated fibrillization. CR and ThT have also been shown to inhibit Aβ fibril formation at higher concentrations.[36,37]

Anti-Aβ Natural Compounds

Several plant-derived natural compounds are known to exhibit antiamyloid aggregation activity which makes them attractive as potential therapies to treat AD. These natural compounds are known to exhibit direct binding to various amyloid species including oligomers and fibrils, which in turn can lead to conformational change in the β-sheet assembly to form nontoxic aggregates.[40] Several polyphenols (►**Fig. 6**), including curcumin, resveratrol, and epigallocatechin-3-gallate (EGCG), have progressed to clinical trials for AD treatment. Moreover, based on their multiple functions, including antioxidant, anti-inflammatory, and metal chelating capacities, polyphenols are a rich source for a variety of different structural backbones that can be utilized in rational drug design efforts to find multifunctional antiamyloid agents.[38–41] Several recent reviews summarized the progress in natural product-based amyloid inhibitors and also analyzed their mechanisms of inhibition in vitro.[38,39]

Small Molecules in Clinical Trials

Compounds such as small molecules that target specific Aβ subregions represent the first generation of amyloid-based therapeutics with the potential to demonstrate disease-modifying activity. Although the results of ongoing clinical trials are inconclusive, these compounds hold the promise of a new day in the development of disease-modifying therapies for AD.[42]

Phase III clinical trials are currently underway for agent **ALZT-OP1** developed by AZ Therapeutics[43] for the prevention and treatment of early AD. It is a combination drug therapy consisting of the administration of two previously approved drugs, which have been shown to inhibit Aβ aggregation and neuroinflammation. **GV-971** (Shanghai Green Valley) is a sodium oligo-mannurarate developed for the oral treatment of mild-to-moderate AD and its phase III clinical trials also finished on October 25, 2018 as a safe, well-tolerated oral drug. It showed the ability to reduce the toxicity of Aβ peptide in vitro.[44,45] **KHK6640** (Kyowa Hakko Kirin Pharma), also an Aβ aggregation inhibitor, is in phase III clinical trial.[46]

Phase II clinical trials include several low-molecular-weight compounds that could be attributed to the general group of "antiamyloidogenic" drugs.[47] **Scyllo-Inositol (ELND005)**[48] is a small-molecule inhibitor of Aβ aggregation in phase II/III clinical development at Transition Therapeutics for the oral treatment of AD. **Posiphen**,[49] discovered by the U.S. National Institute on Aging, is a small, orally active antiamyloidogenic agent which is in phase II clinical trials for the treatment of AD and Parkinson's disease. **Bexarotene** (Cleveland Clinic) is a U.S. Food and Drug Administration approved anticancer agent but is not approved for the use of AD. It reduced Aβ in the brain in experimental models of AD, currently in phase II clinical study.

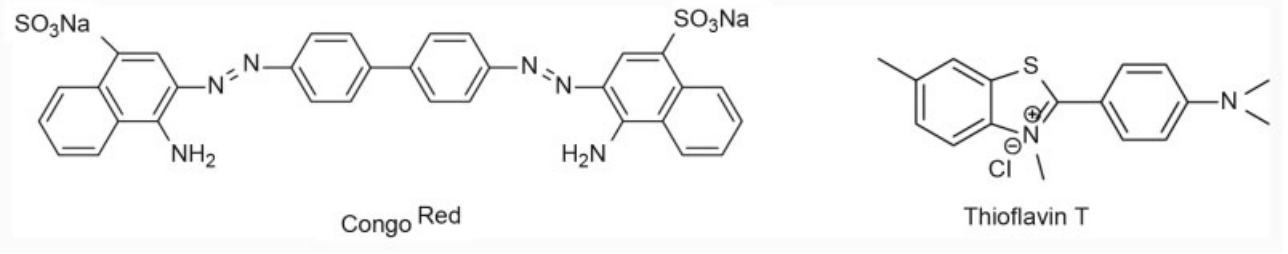


Fig. 5 Chemical structures of Congo red and thioflavin T.

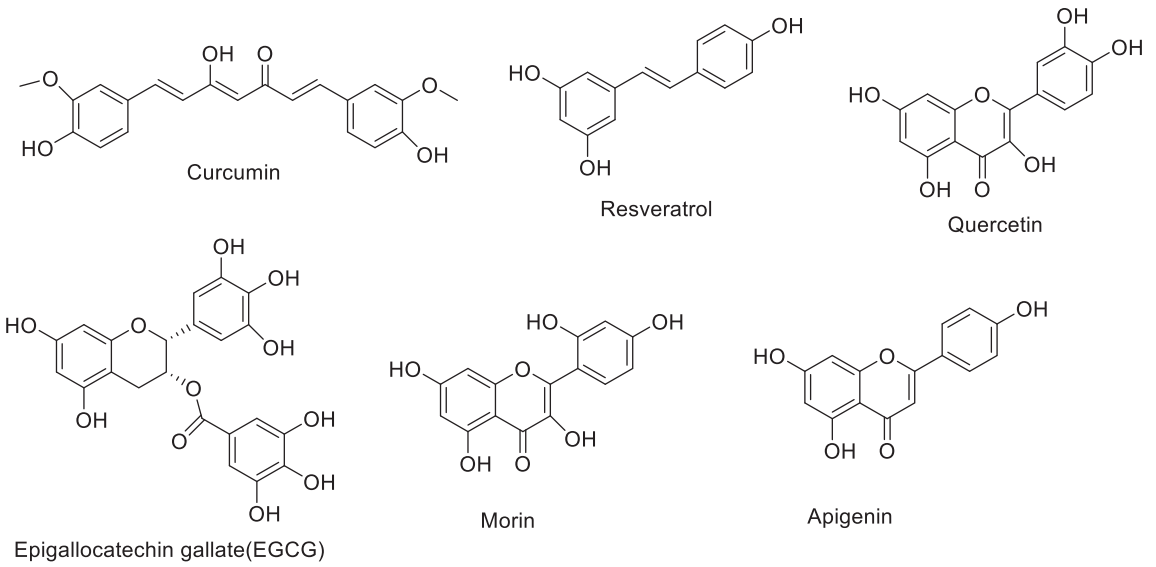


Fig. 6 Chemical structures of natural products identified as inhibitors of amyloid β aggregation.

AZD-3293 (AstraZeneca) is in phase I clinical study. Successfully it finished single and multiple ascending dose studies on Japanese volunteers. **PPI1019** (PRAECIS Pharmaceuticals Inc.) is in phase I trial, completed single-dose escalation safety study of PPI-1019 in patients with mild–moderate AD. **AD-04** (German Center for Neurodegenerative Diseases) is in phase I clinical trial (www.clinicaltrials.gov). **ALZ-801** (Alzheon)[50] and **Ro-63–8695** (GlaxoSmithKline)[51] target amyloid aggregation and are currently in phase I trials. Phase I clinical trials are initiated for **SAN-61** (Diamedica company) and **Exebryl-1** (Proteo Tech) also as a potential dual-action small molecule. Both simultaneously work as an inhibitor on amyloid plaques and neurofibrillary aggregates.[52,53] Available structures of some small-molecule Aβ-aggregation inhibitors are summarized in ►**Fig. 7**.[42,47]

Molecular Docking Studies of Small-Molecule Amyloid β-aggregation Inhibitors

Studies suggest that monomeric Aβ is nontoxic and prevents neuronal cell death caused by oxidative stress.[54] The toxic

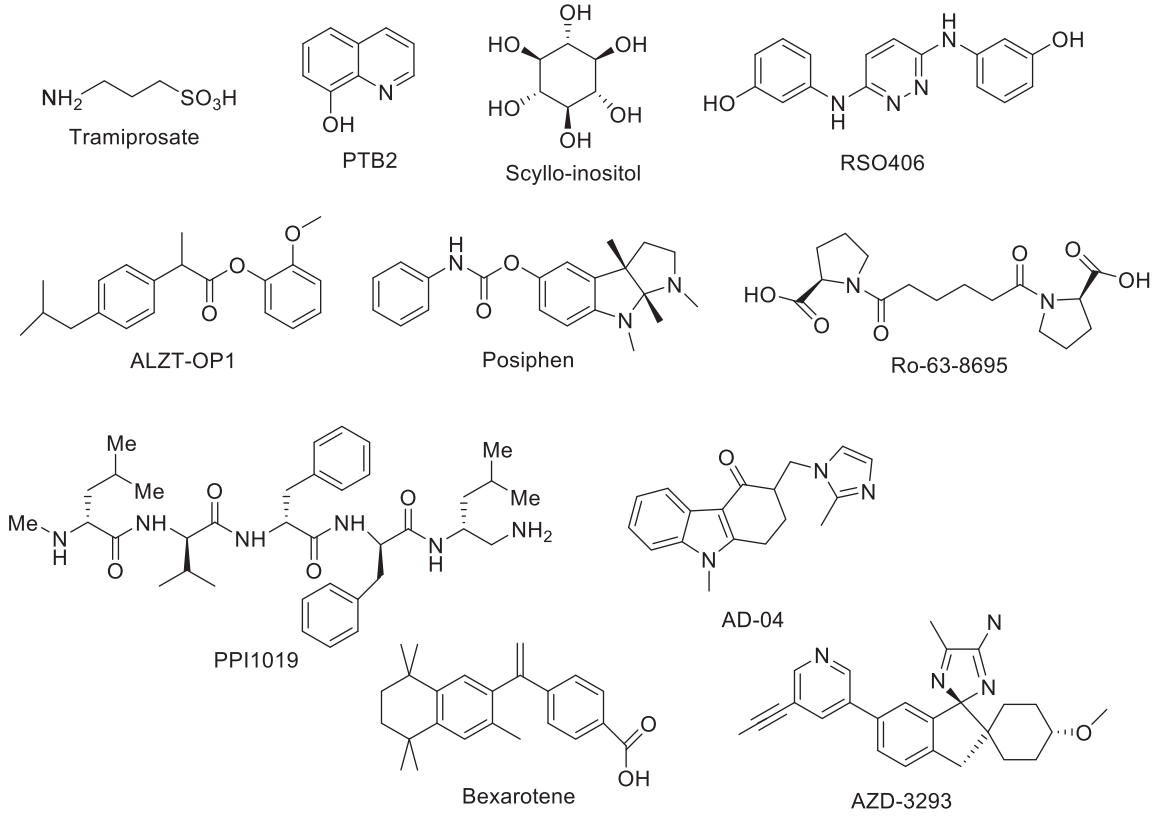


Fig. 7 Available structures of some small-molecule amyloid β-aggregation inhibitors.

effects of aggregation-prone Aβ result from conformational transition of Aβ monomers from predominantly α-helical to β-sheet structures that result in monomeric Aβ aggregation and fibrillization. Therefore, preventing the conformational transition of the Aβ monomer from an initial random coil or α- helix into a β-sheet is the primary goal of blocking Aβ toxicity by small-molecule inhibitors.[38]

The amino acid sequence of human Aβ42 is: NH2-^{1}Asp-^{2}Ala-^{3}Glu-^{4}Phe-^{5}Arg-^{6}His-^{7}Asp-^{8}Ser-^{9}Gly-^{10}Tyr-^{11}Glu-^{12}Val-^{13}His-^{14}His-^{15}Gln-^{16}Lys-^{17}Leu-^{18}Val-^{19}Phe-^{20}Phe-^{21}Ala-^{22}Glu-^{23}Asp-^{24}Val-^{25}Gly-^{26}Ser-^{27}Asn-^{28}Lys-^{29}Gly-^{30}Ala-^{31}Ile-^{32}Ile-^{33}Gly-^{34}Leu-^{35}Met-^{36}Val-^{37}Gly-^{38}Gly-^{39}Val-^{40}Val-^{41}Ile-^{42}Ala-COOH. Residues ^{1}Asp-^{28}Lys and ^{29}Gly-^{42}Ala respectively represent a hydrophilic domain and a hydrophobic domain. Unfolded and soluble monomeric Aβ primarily have a random-coil structure when they are released into extracellular matrix.[55] Conformational transition of Aβ from an unfolded monomeric native state to a β-sheet happens rapidly and initiates the aggregation process to form toxic Aβ oligomers.[56] Aβ42 oligomers are the most toxic form and play important causal roles in AD.[9] Numerous studies indicate that some of the amino acid residues are responsible for the aggregation, these are (1) the fibril-forming Aβ fragment: amino acid residues ^{12}Va-^{24}Val and ^{30}Ala-^{40}Val, responsible for their native states, self-assembling into a β-sheet structure;[57] (2) amino acid residues ^{24}Val-^{28}Lys in a β-sheet conformation promote Aβ oligomerization;[58] (3) the nucleation site of aggregation: hexapeptide sequence ^{16}KLVFFA^{19} (^{16}Lys-^{21}Ala) acting as a steric zipper, which leads to dimer formation and eventually larger aggregates;[38,59–61] (4) aromatic residues in the Aβ monomer, phenylalanine (Phe^{4}, Phe,^{18} and Phe^{1}), and tryptophan (Tyr^{10}) play a significant role in the Aβ self-assembly process by enhanced fibril assembly kinetics;[62,63] (5) the three specific sites, Arg-to-Gly, Tyr-to-Phe, and His-to-Arg, are believed to be important in Aβ aggregation or Aβ-induced neurotoxicity;[64,65] and (6) the amino acid residues His^{13} and Met^{33} also promote toxic conformations in Aβ oligomers.[66–68]

A wide range of natural and synthetic molecules (both large and small molecules) has been investigated for their ability to counteract Aβ aggregation and toxicity.[38,69] In this review, we will summarize the molecular modeling studies of some important natural and synthetic inhibitors of Aβ aggregation.

Curcumin

The antiaggregating activity of curcumin (►**Fig. 6**) against Aβ has been extensively investigated including its structural features that contribute to the antioligomerization activity. Curcumin can interact with Aβ oligomers and Aβ fibrils. Modeling studies have shown that curcumin interacts with the ^{12}V and ^{16}KLVFFA^{19} residues of the Aβ.[70–72] Also, it interacts with ^{37}Gly in Aβ42 in the C-terminus of the Aβ fibrils[73] and the aromatic residues (Tyr, Phe, and His) in the Aβ dimer.[74] Another computational investigation suggested that amino acids ^{16}K, ^{17}L, ^{18}V, and ^{20}F in ^{16}KLVFFA^{19} residues were involved in stabilizing the curcumin-Aβ octamer assembly. These investigations show that curcumin binding to Aβ-aggregates leads to significant conformational change and shifts the equilibrium toward the formation of nontoxic Aβ aggregates including dimers, oligomers, protofibrils, and fibrils in the Aβ-aggregation pathways which prevent neurotoxicity associated with various forms of Aβ-aggregates.[75]

Resveratrol

Several studies indicate that resveratrol (►**Fig. 6**) directly interacts with Aβ monomers and fibrils. It inhibits Aβ fibrillization and converts toxic oligomers into nontoxic species. Interaction between resveratrol and aromatic side residues (^{4}Phe, ^{10}Tyr, ^{19}Phe, and ^{20}Phe) of Aβ selectively remodeled Aβ conformers that possess β-sheet structures into nontoxic species. Researchers found that its polyphenol aglycones and glycosides were responsible for remodeling toxic Aβ oligomers into nontoxic species.[76–79]

Epigallocatechin Gallate

EGCG (►**Fig. 6**) inhibits conformational change from a random-coil to a β-sheet structure and Aβ oligomers formed in the presence of EGCG.[80] There are 12 important residues (^{4}Phe, ^{5}Arg, ^{19}Phe, ^{20}Phe, ^{22}Glu, ^{28}Lys, ^{29}Gly, ^{34}Leu to ^{37}Gly, and ^{41}Ile of Aβ) that strongly interact with EGCG. Simultaneously, the side chains of some hydrophobic residues (Phe, Met, and Ile) and the main chains of ^{28}Lys and ^{29}Gly provide nonpolar interactions with Aβ. These causes remodeling of mature Aβ fibrils and toxic oligomers into smaller nontoxic aggregates with the loss of β-sheet content.[38,81] Modeling studies reveal that EGCG displays an antiaggregation effect from mainly two pathways: first, EGCG binds to the native form of Aβ through interactions with the side chains of specific residues, and second, EGCG binds to the misfolded Aβ species with noncovalent interactions involving the Aβ backbone and subsequently remodels toxic aggregates into small nontoxic, off-pathway oligomers.[38]

Tramiprosate

3-Aminopropanesulfonic acid (►**Fig. 7**) targets the ^{13}HHQK^{16} subregion (^{13}His-^{16}Lys) at the N-terminus of Aβ. ^{13}His-^{16}Lys amino acids are important for oligomerization, fibril propagation, and neurotoxicity.[42] Due to its structural simplicity, tramiprosate is highly specific to Aβ. But unfortunately, it failed in the late stages of a phase III clinical trial.[28] Despite its clinical failure, the data obtained from the studies will assist us in the design and development of novel small molecules with antiamyloid aggregation properties.[82]

Scyllo-Inositol

Scyllo-Inositol (►**Fig. 7**), a potential therapeutic compound for AD, has been shown to inhibit Aβ (1–42) fibrillogenesis in vitro. It stabilizes cell-derived small molecular weight oligomers and reduces amyloid plaque load. Also, it has shown promise in current phase II/III clinical trials.[48,83,84] Modeling studies revealed that *scyllo*-Inositol interacts with the C-terminus of Aβ.[42]

RS-0406

N,*N*′-Bis(3-hydroxyphenyl)pyridazine-3,6-diamine (►**Fig. 7**) is a small molecule which inhibits Aβ1–42 fibrillogenesis and

a novel β-sheet breaker.[85] RS-0406 interacts with the **^{16}KLVFFA**^{19} residues and inhibits Aβ fibrillation.[85,86]

New Small Molecules

The last few years have seen a surge in the discovery of small molecules as disease-modifying therapies for AD.[87] Here, we will highlight some recent developments in the design of the small-molecule Aβ-aggregation inhibitors as potential disease-modifying agents and briefly summarized some previously reported docking studies of these recently developed small molecules.

In a recent study, Sancho and coworkers identified compounds **I–III** (►**Fig. 8**) as Aβ aggregation inhibitors based on a high-throughput study by screening a chemically diverse compound library.[88] Molecular modeling study of compound **I** (2-methyl-5,6,7,8-tetrahydro-4*H*-[1]bbenzothieno[2,3-*d*][1,3]oxazin-4-one) with an Aβ dimer assembly showed that the tetrahydrobenzenethieno ring was in van der Waal's contact with ^{16}KLVFFA^{19} residues, whereas benzenethieno and oxazinone rings were in contact with side chains of isoleucine and leucine at the C-terminal via nonpolar contact. Modeling compound **II** (2,5-dichloro-*N*-(4-piperidinophenyl)-3-thiophenesulfonamide) in the Aβ-dimer showed that the phenylpiperidine substituent was oriented toward the *N*-terminal in the LVFF region. The phenyl ring underwent T-shaped π–π interaction with ^{16}KLVFFA^{19} residues. The 2,5-dichlorothiophenesulfonamide was oriented toward the C-terminal, where it was in van der Waal's contact with amino acid side chains of isoleucine, glycine, and leucine. In contrast, the modeling study of compound **III** (*N*-(4-chloro-2-nitrophenyl)-*N*′-phenylurea) in the Aβ-dimer model showed that this compound only interacted at the *N*-terminal region. The two phenyl rings linked to the urea moiety were in close proximity to the ^{16}KLVFFA^{19} region. Compound **IV** (6-(4-chlorophenyl)sulfonyl)-2-phenylpyrazolo[1,5-*a*]pyrimidin-7-amine) exhibits a V-shaped conformation in the Aβ dimer assembly. The bicyclic pyrazolopyrimidine underwent π–alkyl interactions with amino acid side chains of isoleucine and leucine at the C-terminal, whereas the chlorophenyl ring interacts with the phenylalanine ring at the *N*-terminal. Compared with compounds I–IV, compound IV is a larger molecule, longer along its axis, which helps in making additional contacts in the steric-zipper assembly and provides better interaction.[87,88]

Luo and coworkers reported the design of novel tacrine-alkoxybenzene hybrids, compound **V** (►**Fig. 8**), as dual inhibitors of cholinesterases and Aβ aggregation. They reported that these compounds were able to prevent self-induced Aβ-aggregation.[89] The tetrahydroacridine ring was oriented toward the LVFF region, where it underwent π–alkyl interactions with leucine and valine side chains of ^{16}KLVFFA^{19} residues and the NH of tetrahydroacridine ring formed a hydrogen bond with the backbone C = O of valine.[87,89]

Kanai and coworkers reported compound VI (4-benzyl-*N*-isoneopentyl-6-phenoxypicolinamide, ►**Fig. 8**), which exhibited dose-dependent inhibition of Aβ aggregation.[90]

Modeling study of compound **VI** in the steric-zipper model showed that it exhibited a Y-shaped conformation. Benzyl, phenoxy, and pyridine aromatic rings undergo π–π stacked interactions with phenylalanine rings on either side of steric-zipper interface. Significantly, the isopentyl side chain undergoes several nonpolar contacts with side chains of

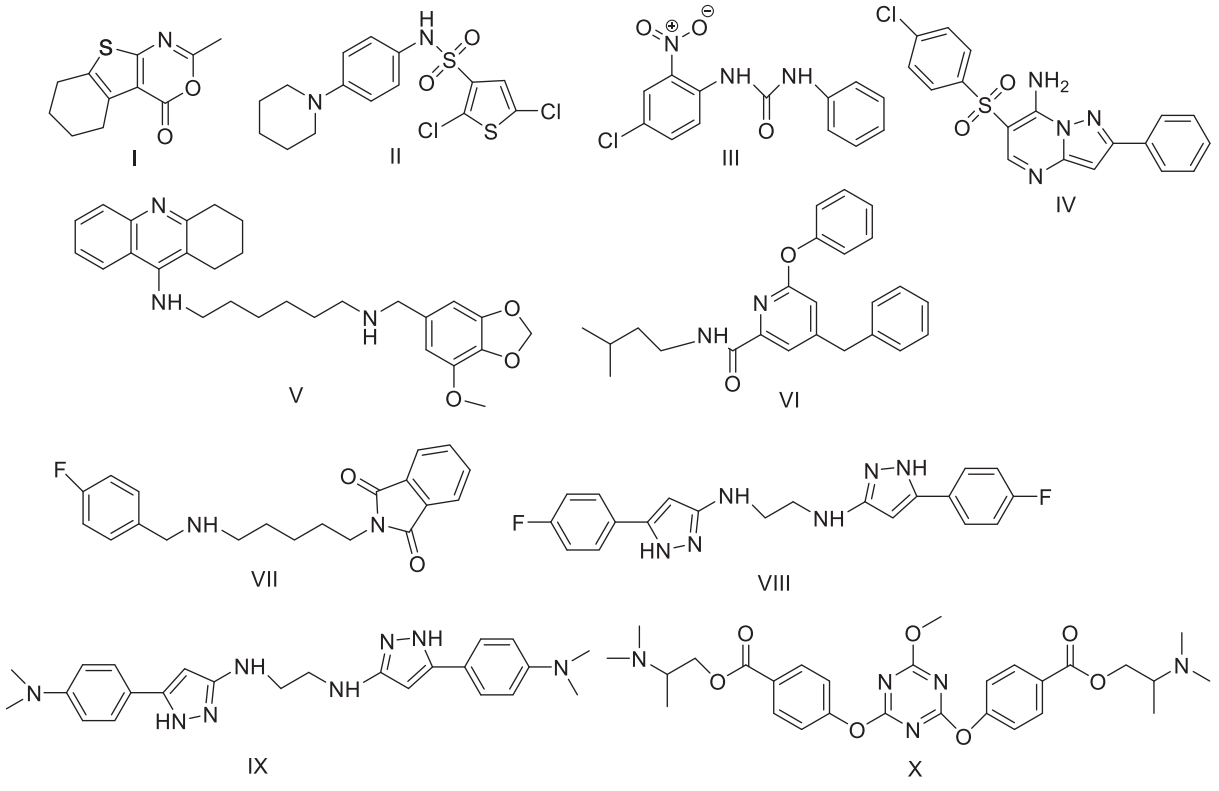


Fig. 8 Recently developed some small-molecule amyloid β-aggregation inhibitors.

phenylalanine and valine, respectively, and the pyridine nitrogen forms hydrogen bonds with lysine side chains.[87,90]

Inspired by the chemical structure of the cholinesterase inhibitor donepezil (►**Table 1**), Malawska and coworkers developed heterodimeric isoindoline-1,3-dione derivatives of AChE inhibitors with anti-Aβ aggregation activity.[91] Molecular modeling of the most potent isoindoline-1,3-dione derivative VII (2-(5-(4-fluorobenzylamino)pentyl)isodindoline-1,3-dione) (►**Fig. 8**) showed that it exhibited a linear binding mode with the steric-zipper assembly. The isoindole ring undergoes multiple π–alkyl and π–π interactions with side chains of valine and phenylalanine, respectively, with <5Å distance. The fluorobenzene substituent undergoes π–alkyl interactions with valine side chains on either side and more interestingly, the fluorine atom forms hydrogen bonds with lysine side chains. These multiple polar and nonpolar contacts are able to stabilize the steric-zipper assembly, which can lead to conformational changes and reduce the cytotoxicity of Aβ aggregates.[87,91]

In a recent study, Muhs and coworkers used a rational design approach to develop small molecules based on a 3-aminopyrazole scaffold.[92] The idea was to design small molecules that can undergo complimentary interactions with the donor–acceptor–donor hydrogen bonding pattern seen in the β-sheet assembly of Aβ. This approach led to the identification of dimeric 3-aminopyrazole derivatives **VIII** and **IX** (►**Fig. 8**) that were able to prevent Aβ oligomerization, fibril formation, and reduce cytotoxicity.[87,92] The most potent compound IX formed a more stable complex in the steric-zipper octamer assembly, exhibited a linear conformation, and is able to fit nicely at the steric-zipper interface. The phenylpyrazole moieties underwent π–π, π–alkyl, and π–cation interactions with phenylalanine, valine, and lysine amino acid residues respectively on either side of the steric-zipper interface. These results support anti-Aβ aggregation properties of compound **IX**.[87,93]

A novel small library of triazine-based small molecules was reported as multitargeting agents with dual cholinesterase and amyloid inhibition.[93] The most potent triazine compound **X** (►**Fig. 8**) undergoes favorable interactions with several amino acids located at both the C- and N-terminals the Aβ-dimer model due to its larger size of the compound. The central triazine ring with two dimethylaminopropyl benzoate units was oriented closer to the ^{16}KLVFFAED^{21} region with the triazine and benzoate aromatic rings undergoing π–π stacking contacts with phenylalanine and alanine side chains. However, the presence of three ionizable groups (tertiary amines) will diminish its blood–brain barrier permeability.[87,93]

Future Perspectives

Currently there were 132 agents in 156 trials of anti-AD therapies.[94] According to the Cummings et al's review, in 2018 a total of 26 agents were in phase III trial. Among them 54% are anti-amyloid (three are antiaggregation).[95] Recent reviews show that lessons are learned from all trials; even negative and futile outcomes are highly informative and provide guidance for future trials.[94] Although the results of ongoing clinical trials are inconclusive, these compounds hold the promise of a new day in the development of disease-modifying therapies for AD. As our knowledge of their molecular structures and the molecular interactions responsible for activity of small molecules advances, more new generation of small-molecule Aβ-aggregation inhibitors will be developed in the near future. Effective drugs will have a dramatic impact on the number of persons affected in the future and also the quality of life of the AD patients. Advanced research in the field of AD will lead us to a better future for aging populations.

Conclusion

AD is still an incurable neurodegenerative disorder that has proved challenging to manage and treat with current therapies. Disease modification is the ultimate goal for AD drug development but has, so far, remained elusive. In this circumstance, small-molecule Aβ-aggregation inhibitors could be the key to treat AD.

Conflict of Interest

The authors declare no conflict of interest.

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