SYNTHESIS AND CHARACTERIZATION OF HETEROCYCLIC MOTIFS FOR THE MANAGEMENT OF ALZHEIMER'S DISEASE

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ABSTRACT

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by cognitive decline, memory loss, and neuronal dysfunction. Despite extensive research, there is no definitive Scure for AD, making the development of novel therapeutic agents imperative. Heterocyclic compounds have emerged as promising candidates due to their diverse biological activities, including neuroprotection, cholinesterase inhibition, and antioxidant properties. This review focuses on the synthesis and characterization of various heterocyclic motifs and their potential applications in AD management. Key synthetic approaches, structure-activity relationships (SAR), and pharmacological evaluations are discussed.

INTRODUCTION

Alzheimer's disease (AD) is a major global health concern, affecting millions worldwide. The accumulation of amyloid-beta plaques, tau protein hyperphosphorylation, oxidative stress, and cholinergic dysfunction contribute to the pathogenesis of AD. Heterocyclic compounds, including pyrimidines, quinolines, and benzothiazoles, have shown promise in modulating these pathological mechanisms. This review provides an overview of the recent advances in heterocyclic chemistry relevant to AD treatment. Heterocyclic compounds have gained significant attention in the field of medicinal chemistry due to their versatile biological activities. These compounds have demonstrated potential in addressing multiple pathological mechanisms associated with AD. By modulating cholinergic function, reducing oxidative stress, and inhibiting amyloid aggregation, heterocyclic motifs offer promising therapeutic strategies. This review aims to explore the latest advances in the synthesis, characterization, and pharmacological evaluation of heterocyclic compounds in AD treatment.

HETEROCYCLIC MOTIFS AND THEIR SIGNIFICANCE IN AD TREATMENT

Heterocyclic compounds are widely used in medicinal chemistry due to their structural versatility and ability to interact with biological targets. The following classes of heterocycles have demonstrated therapeutic potential against AD:

- **Pyridines and Pyrimidines:** These heterocycles are known for their ability to inhibit cholinesterase enzymes, thereby enhancing cholinergic transmission and reducing oxidative stress. Their neuroprotective properties make them potential candidates for AD drug development.
- **Quinoline Derivatives:** These compounds have shown efficacy in modulating amyloid-beta aggregation and acting as metal chelators, which help in reducing amyloid plaque formation and neurotoxicity associated with AD.
- **Thiazoles and Benzothiazoles:** These structures inhibit tau protein phosphorylation, thereby preventing neurofibrillary tangle formation, which is a hallmark of AD pathology. Additionally, they provide neuroprotection by modulating cellular pathways involved in neuronal survival.
- **Indoles and Carbazoles:** Due to their strong antioxidant and anti-inflammatory properties, these heterocycles play a crucial role in mitigating neuroinflammation and oxidative damage, two key contributors to AD progression.

SYNTHESIS STRATEGIES OF HETEROCYCLIC COMPOUNDS FOR AD

Several synthetic methodologies have been employed for the development of heterocyclic motifs with potential AD therapeutic effects. Some of the common strategies include:

- **Cyclization Reactions:** The formation of fused heterocycles through well-established cyclization techniques such as Pictet-Spengler and Biginelli reactions. These methods allow for the construction of complex heterocyclic frameworks with potential bioactivity against AD.
- **Metal-Catalyzed Reactions:** The use of palladium-catalyzed cross-coupling reactions enables the functionalization of heterocyclic cores, facilitating the incorporation of pharmacophores relevant to AD treatment.
- **Green Chemistry Approaches:** Sustainable and eco-friendly synthesis techniques, such as microwave-assisted synthesis and solvent-free methodologies, are being increasingly employed to reduce environmental impact and improve reaction efficiency.

CHARACTERIZATION TECHNIQUES

The structural elucidation and confirmation of synthesized heterocyclic motifs are achieved through various analytical techniques, including:

- **Fourier-Transform Infrared Spectroscopy (FTIR):** Used for identifying functional groups and molecular interactions that contribute to biological activity.
- **Nuclear Magnetic Resonance (NMR) Spectroscopy:** Essential for structural determination, purity assessment, and understanding molecular conformation.
- **Mass Spectrometry (MS):** Facilitates molecular weight confirmation and fragmentation pattern analysis, aiding in compound identification.
- **X-ray Crystallography:** Provides 3D structural insights, allowing for a detailed understanding of molecular interactions and binding mechanisms relevant to AD targets.

DRUG PROFILE: DONEPEZIL (ARICEPT®)

1. Drug Name:

- **Generic Name:** Donepezil
- **Brand Names:** Aricept®, Adlarity®

2. Chemical Structure:

- **Class:** Piperidine-based heterocyclic compound
- **Molecular Formula:** $C_{24}H_{29}NO_3$
- **Molecular Weight:** 379.50 g/mol
- **IUPAC Name:** (±)-2-[(1-Benzylpiperidin-4-yl)methyl]-5,6-dimethoxy-2,3-dihydroinden-1- one
- **Structure:** Contains a **piperidine** ring that interacts with cholinesterase enzymes to enhance cognitive function.

3. Mechanism of Action:

- Donepezil is a **reversible acetylcholinesterase inhibitor (AChEI)**.
- It prevents the breakdown of **acetylcholine (ACh)** in the synaptic cleft, enhancing cholinergic neurotransmission in the brain.
- This results in improved **cognitive function, memory, and learning ability** in AD patients.

4. Pharmacokinetics:

- **Absorption:** Rapid oral absorption, peak plasma concentration in ~3–4 hours.
- **Bioavailability:** ~100% (not affected by food).
- **Distribution:** o **Crosses the blood-brain barrier (BBB)** efficiently. o **Plasma Protein Binding:** ~95%.

5. Pharmacological Evaluation and Biological Activities The efficacy of heterocyclic compounds in AD treatment is evaluated through in vitro and in vivo studies:

- **Cholinesterase Inhibition Assays:** Assess the ability of compounds to inhibit acetylcholinesterase (AChE) and butyrylcholinesterase (BChE), key enzymes in cholinergic signaling.
- **Amyloid-Beta Aggregation Studies:** Determine the anti-amyloidogenic potential of heterocycles, which can reduce plaque formation and toxicity.
- **Neuroprotective Assays:** Evaluate cell viability and neuroprotection using neuronal cell models to assess oxidative stress resistance and apoptosis inhibition.
- **In Vivo AD Models:** Utilize transgenic AD mouse models to assess behavioral and cognitive improvements following treatment with heterocyclic derivatives.

REVIEW OF LITERATURE

- **Sugimoto et al. (1995)** synthesized Donepezil, a selective acetylcholinesterase inhibitor (AChEI) that increases acetylcholine levels in the synaptic cleft, thereby improving cognitive function. Donepezil remains a first-line treatment for mild to moderate AD due to its long half-life and fewer side effects compared to earlier drugs like tacrine.
- **Narahashi et al. (2004)** explored quinoline-based dual AChE and butyrylcholinesterase (BChE) inhibitors, revealing that targeting both enzymes could provide a broader neuroprotective effect, especially in the later stages of AD when BChE activity increases.
- **Hardy & Selkoe (2002)** proposed the amyloid cascade hypothesis, which posits that the accumulation of amyloid-beta (Aβ) plaques is the primary driver of AD pathogenesis. This theory has influenced many drug discovery efforts, particularly in the development of amyloid- targeting therapies.
- **Gella & Durany (2009)** reviewed benzothiazole derivatives, including flortaucipir (AV-1451), which selectively binds to **tau protein aggregates**. This has led to improved imaging techniques for tau pathology in AD patients.
- **Zhang et al. (2018)** synthesized quinoline-based metal chelators, which prevent Aβ aggregation by reducing oxidative stress and metal-induced neurotoxicity. Their findings suggest that metal chelation therapy could serve as a neuroprotective approach in AD.
- **Biginelli (1893)** developed the Biginelli reaction, a three-component cyclization process for synthesizing dihydropyrimidines, which later proved useful in designing AChE inhibitors. This reaction remains a cornerstone in medicinal chemistry for heterocyclic drug development.
- **Kumar et al. (2016)** optimized the Pictet–Spengler reaction, enabling the synthesis of indole- based neuroprotective **agents** with improved blood-brain barrier (BBB) permeability. This modification enhanced drug delivery to the central nervous system (CNS).
- **Tiwari et al. (2020)** applied a palladium-catalyzed Suzuki-Miyaura reaction to synthesize thiazole derivatives, showing potent AChE inhibition and antioxidant activity, making them promising candidates for AD treatment.
- **Singh et al. (2021)** developed microwave-assisted synthesis of carbazole derivatives, reducing reaction time and enhancing biological activity while adhering to green chemistry principles.
- **Silverman et al. (2005)** utilized Fourier-Transform Infrared Spectroscopy (FTIR) to confirm the functional groups in newly synthesized pyridine analogs, ensuring their structural integrity for drug efficacy.
- **Wishart et al. (2012)** employed **Nuclear** Magnetic Resonance (NMR) spectroscopy to assess the purity and stereochemistry of heterocyclic drug candidates, which is critical for pharmacokinetic optimization.

- **Shen et al. (2019)** performed **X-ray crystallography** to analyze quinoline-metal complexes, demonstrating their ability to **bind amyloid-beta fibrils**, supporting their role in Aβ-targeting therapies.
- **Ellman et al. (1961)** developed the Ellman's **assay**, a widely used enzyme activity test for measuring AChE and BChE inhibition, which remains a gold standard in AD drug screening.
- **Chebib et al. (2015)** examined benzothiazole derivatives, identifying potent dual cholinesterase inhibitors with neuroprotective effects, highlighting the potential of multi-target drug development in AD.
- **Oddo et al. (2003)** introduced the triple-transgenic AD (3xTg-AD) mouse model, which develops both amyloid plaques and tau tangles, providing a reliable in vivo model for AD drug testing.
- **Zhao et al. (2022)** tested indole derivatives in transgenic AD mice, reporting significant improvements in memory and cognitive function, validating their potential as disease-modifying agents.
- **Pardridge (2012)** identified **poor** BBB permeability as a major limiting factor in CNS drug delivery, urging the development of lipophilic and transporter-mediated drug designs.
- **Mehta et al. (2017)** emphasized the multi-target-directed ligands (MTDLs) approach, which combines AChE inhibition, tau aggregation prevention, and oxidative stress reduction in a single therapeutic agent.
- **Chakraborty et al. (2023)** proposed nanoparticle-based drug delivery to enhance the bioavailability of heterocyclic AD drugs, paving the way for nanomedicine applications in neurodegenerative disorders.

CHALLENGES AND FUTURE PERSPECTIVES

Despite the promising potential of heterocyclic compounds in AD therapy, several challenges remain:

- **Poor Blood-Brain Barrier (BBB) Penetration:** The ability of therapeutic compounds to cross the BBB is a major limitation in AD treatment. Future research should explore nanoparticle-based delivery systems and prodrug strategies to enhance CNS bioavailability. **Toxicity and Side Effects:** Many heterocyclic compounds exhibit cytotoxicity and off- target effects, necessitating rigorous safety evaluations and pharmacokinetic optimizations to improve therapeutic index.
- **Clinical Translation:** While preclinical studies show promise, the translation of heterocyclic compounds into clinically viable AD therapeutics remains a challenge. Future efforts should focus on multi-target-directed ligands (MTDLs) that integrate multiple therapeutic actions within a single molecule for enhanced efficacy and reduced side effects.
- **Combination Therapies:** The integration of heterocyclic compounds with existing AD treatments, such as cholinesterase inhibitors and neuroprotective agents, may provide synergistic effects and improved patient outcomes.

- **Computational Drug Design:** Advances in molecular docking, QSAR studies, and artificial intelligence-driven drug discovery can accelerate the identification of novel heterocyclic compounds with high specificity and potency for AD targets.

Alzheimer's Disease Hypotheses

In the 1970s, neocortical and presynaptic cholinergic deficits were reported to be related to the enzyme choline acetyltransferase (ChAT), which is responsible for the synthesis of acetylcholine (ACh). Due to the essential role of ACh in cognitive function, a cholinergic hypothesis of AD was proposed. ACh is synthesized in the cytoplasm of cholinergic neurons from choline and acetyl-coenzyme A by the ChAT enzyme and transported to the synaptic vesicles by vesicular acetylcholine transporter (VAChT) (**Figure 1**). In the brain, ACh is involved in several physiological processes such as memory, attention, sensory information, learning, and other critical functions. Degeneration of the cholinergic neurons was found to take place in AD and to cause alternation in cognitive function and memory loss. *B*-amyloid is believed to affect cholinergic neurotransmission and to cause a reduction in the choline uptake and a release of ACh. Studies demonstrated that cholinergic synaptic loss and amyloid fibril formation are related to Aβ oligomers' neurotoxicity and to interactions between AChE and Aβ peptide. Additional factors also contribute to the progression of AD, such as a reduction in nicotinic and muscarinic (M2) Ach receptors, located on presynaptic cholinergic terminals, and the deficit in excitatory amino acid (EAA) neurotransmission, where glutamate concentration and D-aspartate uptake are significantly reduced in many cortical areas in AD brains. This is in addition to the use of cholinergic receptor antagonists such as scopolamine, which was found to induce amnesia. This effect can be reversed by using compounds that activate acetylcholine formation.

Figure 1. The pathway for the synthesis and transportation of acetylcholine between presynaptic and postsynaptic nerve terminals.

As a result, the cholinergic hypothesis is based on three concepts: reduced presynaptic cholinergic markers in the cerebral cortex, severe neurodegeneration of nucleus basalis of Meynert (NBM) in the basal forebrain, which is the source of cortical cholinergic innervation, and the role of cholinergic antagonists in memory decline compared to the agonists, which have the opposite effect .

Amyloid

For decades, it was recognized that abnormal deposition of β-sheets in the central nervous system has a strong correlation with dementia, which led to the concept of the amyloid hypothesis. However, it was found that the amyloid plaques (AP) also deposit in normal healthy brains with aging, which raised the question of whether AP deposition is responsible for AD onset or not? Therefore, in the recent years, alternative hypotheses were proposed for the non-inherited form of AD (NIAD), but at present, the amyloid hypothesis remains the most accepted

pathological mechanism for inherited AD (IAD). The amyloid hypothesis suggests that the degradation of Aβ, derived from APP by β- and γ-secretase, is decreased by age or pathological conditions, which leads to the accumulation of Aβ peptides (Aβ40 and Aβ42). Increasing the ratio of Aβ42/Aβ40 induces Aβ amyloid fibril formation, resulting in neurotoxicity and tau pathology induction, and consequently, leading to neuronal cell death and neurodegeneration. AD risk factors and mutations of several genes like APP, PSEN1, and PSEN2 were found to affect Aβ catabolism and anabolism, which rapidly cause an accumulation of Aβ and fast progression of neurodegeneration.

Alzheimer's Disease Risk Factors

Aging

The most important risk factor in AD is aging. Younger individuals rarely have this disease, and most AD cases have a late onset that starts after 65 years of age. Aging is a complex and irreversible process that occurs through multiple organs and cell systems with a reduction in the brain volume and weight, a loss of synapses, and ventricles' enlargement in specific areas accompanied by SP deposition and NFT. Moreover, several conditions might emerge during aging such as glucose hypometabolism, cholesterol dyshomeostasis, mitochondria dysfunction, depression, and cognitive decline. These changes also appear in normal aging, which makes it difficult to distinguish the cases in early AD. AD can be divided based on age of onset into early- onset AD (EOAD), the rare form with around 1–6% of cases, in which most of them are familial AD characterized by having more than one member in more than one generation with AD, and ranges from 30–60 or 65 years. The second type is the late-onset AD (LOAD), which is more common with age of onset above 65 years. Both types may occur in people who have a family with a positive history of AD and families with a late-onset disease.

Genetics

Genetic factors were discovered over the years and were found to play a major role in the development of AD. 70% of the AD cases were related to genetic factors: most cases of EOAD are inherited in an autosomal dominant pattern and mutations in the dominant genes such as *Amyloid precursor protein (APP),* Presenilin-1 (PSEN-1), *Presenilin-2 (PSEN-2),* and apolipoprotein E (ApoE) are associated with AD.

Herein, we discuss the strong genetic risk factors in AD.

- Amyloid Precursor Protein (APP)

APP is a type I transmembrane protein cleaved by α-, β-, and γ-secretase to release Aβ and other proteins and is encoded by the APP gene on chromosome 21. Thirty mutations have been found in the APP gene in which twenty-five of them are related to AD and cause an accumulation of Aβ with elevated amounts. Meanwhile, there is one protective mutation, A673T, which protects against AD by decreasing Aβ, Aβ40, and Aβ42 secretion. All mutations

surround the secretase cleavage site, for example, the KM670/671NL mutation in mouse models has shown an increasing level of amyloid plaques in the hippocampus and cortex with no NFTs. A673V, D678H, D678N, E682K, and K687N mutations have shown cortical atrophy, whereas E682K has shown hippocampal atrophy. Neuropathological reports for the A673V mutation demonstrated a presence of NFTs and Aβ, activation of microglia and astrocytes, and neuronal loss, compared to the rest of the mentioned mutations, which show no change in the intracellular Aβ according to neuropathological reports. Other mutations such as T714I, V715A, V715M, V717I, V717L, L723P, K724N, and I716V affect the γ-secretase cleavage site and cause an increase in the Aβ42/Aβ40 ratio, while E693G, E693K, D694N, and A692G mutations affect the α-secretase cleavage site and cause polymorphic aggregates with the ability to disrupt bilayer integrity. Also, the E693delta is a deletion mutation that enhances the formation of synaptotoxic Aβ.

- **Presenilin-1 (PSEN-1) and Presenilin-2 (PSEN-2)**

PSEN1 and *PSEN2* genes are also the autosomal dominant form of EOAD located on chromosomes 14 and 1, respectively. PSEN-2 and PSEN-1 are homologous, with 67% similarity, with a difference in the *N*-terminus and the hydrophilic region. Mutation in *PSEN1* gene is more common, with more than 200 mutations, while a rare form with less than 40 mutations was identified in the *PSEN2* gene.

PSEN1 is a core protein that activates the γ-secretase complex and plays an important role in the production of Aβ from APP. Knockout studies of PSEN1 showed synaptic dysfunction and memory impairment in mice, which indicate its essential role in maintaining memory and neurons. *PSEN1* mutations are simple ones which include single amino acid substitution, and severe mutation can result from the substitutions of two amino acids. Mutations in the *PSEN1* gene increase the ratio of Aβ42/Aβ40 by decreasing Aβ40 levels. The results obtained by Sun et al. study demonstrated that C410Y or L435F mutations in *PSEN1* knock-in mice increased the Aβ42/Aβ40 ratio due to a greater reduction in Aβ40.

In contrast, PSEN-2 mutations are rare and play a minor role in Aβ production. Any mutation in *PSEN-2* might have a severe effect on the Aβ 42/40 ratio, causing familial AD in the presence of normal *PSEN-1* alleles. Some of the *PSEN-2* mutations cause a significant increase in γ-secretase activity with an elevation in the Aβ-42 and Aβ 42/40 ratio level, such as N141I, T122P, M239V, and M239I, while others are rare polymorphisms and have no effect on Aβ-42, - 40, and Aβ 42/40 ratio levels and are not considered as pathogenic mutations.

- **Apolipoprotein E (ApoE)**

ApoE protein is a glycoprotein expressed highly in the liver and brain astrocytes and some microglia and serves as a receptor-mediated endocytosis ligand for lipoprotein particles like cholesterol, which is essential for myelin production and normal brain function. The ApoE gene located on chromosome 19 has three isoforms, ApoE2, ApoE3, and ApoE4, due to single-nucleotide polymorphisms (SNPs) which cause changes in the coding sequence. The ApoEε4

allele is a strong risk factor for both EOAD and LOAD compared to ApoEε2 and ApoEε3 alleles that are associated with a lower risk and protective effect, respectively. ApoEε4 plays an important role in Aβ deposition as a senile plaque and causes cerebral amyloid angiopathy (CAA), which is known as a marker for AD. ApoEε4 was also shown to be associated with vascular damage in the brain, which leads to AD pathogenesis.

- **ATP Binding Cassette Transporter A1 (ABCA1)**

Adenosine triphosphate (ATP)-binding cassette transporter A1 (ABCA1) is part of a large ABC transporters family that regulate cholesterol efflux in the circulation, like apolipoproteins-AI (ApoAI), and into the brain, like ApoE. In addition, ABCA1 maintains the stability of ApoE lipidation and serves as a mediator for high-density lipoprotein (HDL) generation, which reflects its role in atherosclerosis and cardiovascular diseases. Studies on the AD mice model showed that ABCA1 deficiency increases amyloid plaques and eliminates the lipidation of ApoE. In humans, a mutation in ABCA1 results in Tangier disease, which is characterized by low levels of high-density lipoprotein (HDL) and ApoAI in plasma, accumulation of cholesterol in tissues, and AD pathogenesis.

- **Clusterin Gene (CLU) and Bridging Integrator 1 (*BIN1*)**

In contrast to *PSEN1*, *PSEN2*, and *APP* mutations, which result in familial or EOAD, clusterin (*CLU)* and Bridging Integrator 1 (*BIN1*) genes are novel risk factors for LOAD. In 2009, Genome-Wide Association Studies (GWAS) identified the CLU gene located on chromosome 8, which is upregulated in the cortex and hippocampus of AD brains, in addition to AD cerebrospinal fluid (CSF) and plasma, which make the CLU a promising biomarker for AD. The CLU may play a protective role by interacting with Aβ and promoting its clearance, or a neurotoxic role by reducing Aβ clearance. The Aβ ratio values determine whether

Symptomatic Treatment of AD

Cholinesterase Inhibitors

According to the cholinergic hypothesis, AD is due to the reduction in acetylcholine (ACh) biosynthesis. Increasing cholinergic levels by inhibiting acetylcholinesterase (AChE) is considered one of the therapeutic strategies that increases cognitive and neural cell function. AChEIs are used to inhibit acetylcholine degradation in the synapses, which results in continuous accumulation of ACh and activation of cholinergic receptors. Tacrine (tetrahydroaminoacridine) was the first FDA (Food and Drug Administration)-approved cholinesterase inhibitor drug for the treatment of AD, which acts by increasing ACh in muscarinic neurons, but it exited the market immediately after its introduction due to a high incidence of side effects like hepatotoxicity and a lack of benefits, which was observed in several trials. Later on, several AChEIs were introduced, such as donepezil, rivastigmine, and galantamine, and are currently in use for the symptomatic treatment of AD. Another strategy that may help in the treatment of AD is increasing choline reuptake and as a result, increasing

acetylcholine synthesis at the presynaptic terminals. This can be achieved by targeting choline transporter (CHT1) which is responsible for supplying choline for the synthesis of ACh. Developing drugs that are capable of increasing CHT1 at the plasma membrane may become the future therapy of AD.

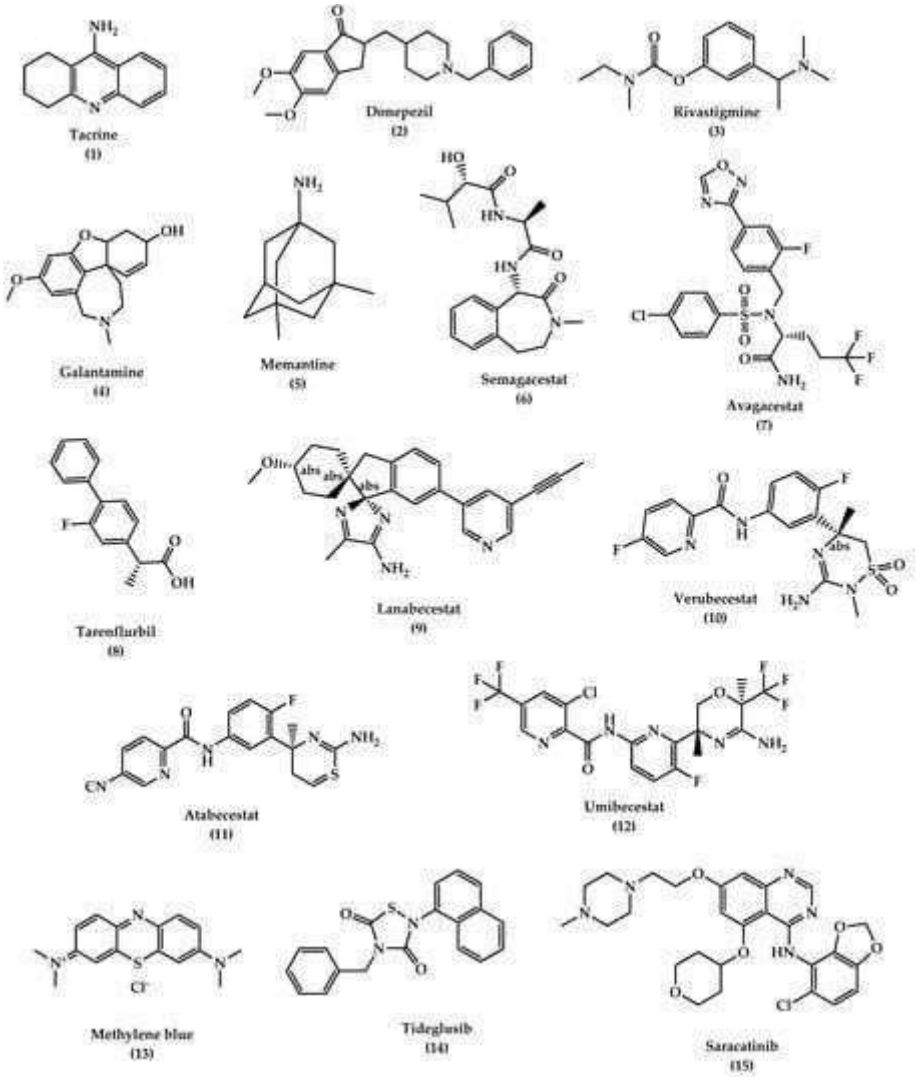

Figure 2. The chemical structures of approved drugs for symptomatic treatment of AD

Disease-Modifying Therapeutics (DMT)

Disease-modifying treatment or therapy (DMT) alter the progression of AD by working on several pathophysiological mechanisms. This is in contrast to symptomatic therapy which works on improving the cognitive functions and decreasing symptoms such as depression or delusions without affecting or modifying the disease. DMTs, either immunotherapies or small molecules, are administrated orally and are being developed to prevent AD or decrease its progression. Several DMTs have been developed and entered the clinical trials, such as AN-1792, a synthetic Aβ peptide (human $A\beta_{1–42}$ peptide of 42-amino acids with the immune adjuvant QS-21) and the first active immunotherapy for AD which entered phase II clinical trials and discontinued due to a meningoencephalitis side effect in 6% of the patients.. DMTs

failures are due to several factors, such as starting therapy too late, giving treatment for the wrong main target, use of inappropriate drug doses, and misunderstanding of the pathophysiology of AD. Several immunotherapies described in **Table 1** have been developed over decades, including: CAD106, an active Aβ immunotherapy that induces Aβ antibodies in animal models and consists of multiple copies of Aβ1–6 peptide coupled to Qβ coat protein, a virus-like particle, and is still in clinical trials, and CNP520 (umibecestat, **12**) a small molecule that inhibits beta-scretase-1 (BACE-1) and therefore inhibits Aβ production. CNP520 was found to reduce Aβ plaque deposition and Aβ levels in the brain and CSF in rats, dogs, and healthy adults ≥ 60 years old, and is still under clinical trials. Furthermore, aducanumab, gantenerumab, and crenezumab are all human Aβ monoclonal antibody that bind with high affinity to aggregated Aβ, and they are still under study in the clinical phases with other DMTs described in **Table 1**

Table 1. Disease modifying agents for the treatment of Alzheimer's disease in clinical trials.

Disease Modifying Agents	Mechanism of Action
Aducanumab	Monoclonal antibody—targets β-amyloid and removes it.
Gantenerumab	Monoclonal antibody—binds and removes β-amyloid.
CAD106b	Amyloid vaccine—stimulates production of antibodies against β-amyloid.
BAN2401	Monoclonal antibody—reduces protofibrillar β-amyloid.
TRx0237 (LMTX)	Tau protein aggregation inhibitor.
AGB101	Low-dose levetiracetam—improves synaptic function and reduces amyloid-induced neuronal hyperactivity
ALZT-OP1 (cromolyn + ibuprofen)	Mast cell stabilizer and anti-inflammatory—promotes microglial clearance of amyloid
Azeliragon	RAGE (Receptor for Advanced Glycation End-products) antagonist—reduces inflammation and amyloid transport into the brain
Disease Modifying Agents	**Mechanism of Action**
BHV4157 (troriluzole)	Glutamate modulator—reduces synaptic levels of glutamate and improves synaptic functioning

Crenezumab	Monoclonal antibody—targets soluble oligomers and removes β-amyloid
ABBV-8E12	Monoclonal antibody—prevents tau propagation
Riluzole	Glutamate receptor antagonist—reduces glutamate-mediated excitotoxicity
Thiethylperazine (TEP)	Activates ABCC1 (ATP binding cassette subfamily C member 1 transport protein)—removes amyloid
BIIB076	Monoclonal antibody—removes tau and reduces tau propagation
Lu AF87908	Monoclonal antibody—removes tau
anle138b	Aggregation inhibitor—reduces tau aggregation
RO7126209	Monoclonal antibody—removes amyloid
TPI-287	Stabilizes tubulin-binding, microtubule, and reduces cellular damage mediated by tau

Natural Extract

For a long time, natural compounds have been used as therapeutic agents for several pathological diseases, and recent studies showed that they possess a neuroprotective effect. In vitro and in vivo studies have proven that natural compounds possess a therapeutic potential for AD, which allowed some of them to enter the clinical trials stages. Nicotine was the first natural compound entered in the clinical trials for AD, then other compounds like vitamins C, E, and D gained more attention and interest due to their protective role against neuroinflammation and oxidative damage. Recently, bryostatin, a macrolide lactone extract from *bryozoan Bugula neritina*, has been evaluated and showed the ability to induce α-secretase activity, reduce Aβ production, and enhance the learning and memory in an AD mice model. Other natural compounds used in folk medicine (traditional Chinese medicine (TCM)) demonstrated a great potential in treating AD by acting on several mechanisms, as shown in **Table 2** below.

Table 2. Natural compounds used in folk medicine and their mechanism of actions.

Natural Compounds	Mechanism of Action
Schisantherin A, Ginsenoside Rh2, and Angelica sinensis extracts	Aβ formation inhibitors

Shengmai (SM) formula, Uncarinic acid C, andTanshinone IIA (TIIA) extract	Reduction of Aβ accumulation
Onjisaponin B, Notoginsenoside R1, and delta-9-Tetrahydrocannabinol (THC)/cannabidiol (CBD)	Promotion of Aβ degradation
Rhynchophylline (RIN), INM-176 (ethanolic extract of *Angelica gigas*), *Houttuyniacordata* Thunb. (Saururaceae) water extracts, Huperzine A, and ethyl acetate extract from *Diospyros kaki* L.f	Inhibition of Aβ Neurotoxicity and reduce over-activation of microglial cells, neuroinflammation, oxidative stress, and disruption of calcium homeostasis, which lead to neuron loss
Tongmai Yizhi Decoction (TYD) (which includes six raw materials: safflower yellow (SY) from *Carthamustinctorius* L., geniposide from the fruit of *G. jasminoides* J. Ellis, ginsenoside Rd from *Panax ginseng* C. A. Mey, crocin from *Crocus sativus* L., and quinones)	Inhibition of hyperphosphorylated tau protein and its aggregation

CONCLUSION

Heterocyclic compounds hold significant promise in the management of Alzheimer's disease due to their diverse pharmacological activities. Advances in synthetic strategies, coupled with rigorous characterization and biological evaluation, are crucial for the development of effective AD therapeutics. Further interdisciplinary research integrating medicinal chemistry, computational drug design, and pharmacological testing will pave the way for novel AD treatments. Despite that, the treatment of AD remains symptomatic, without alteration in the disease's prognosis. Inhibitors to cholinesterase enzyme such as galantamine, donepezil, and rivastigmine, and NMDA antagonists such as memantine, improve memory and alertness but do not prevent progression. Several studies have shown that modification in lifestyle habits like diet and exercise can improve brain health and reduce AD without medical intervention and is considered as a first-line intervention for all AD patients. Recently, the research is focusing on targeting the pathological features of AD such as Aβ and p-tau. Future therapies such as disease- modifying treatment can alter the progression of AD by targeting the Aβ pathway, and many drugs have entered the clinical trials, like AN-1792, solanezumab, bapineuzumab, semagacestat, avagacestat, and tarenflurbil, but failed in demonstrating efficacy in the final clinical stages.

Other DMTs are still under investigation, such as those targeting Aβ and tau pathologies, such as aducanumab, gantenerumab, crenezumab, tideglusib, lithium, and others.

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