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A Comprehensive Review of Integrated Approaches to Alzheimer's Drug Design: Heterocyclic Scaffolds for Multi-Target Modulation

Riswana R[1], Dr. S M Sandhya[2], Dr. Shaiju S Dharan[3]
[1]*M Pharm student, Department of Pharmaceutical Chemistry, Ezhuthachan College of Pharmaceutical Sciences.*
[2]*Professor, HOD, Department of Pharmaceutical Chemistry, Ezhuthachan College of Pharmaceutical Sciences.*
[3]*Principal, Ezhuthachan College of Pharmaceutical Sciences.*

ABSTRACT:
Alzheimer's disease (AD) is a chronic and advancing neurological disease involving neuronal deterioration and a critical challenge to population well-being, with cases in the United States projected to reach 13.8 million by 2050. Despite its growing prevalence, a definitive ante mortem diagnosis remains unavailable, and current treatments provide only symptomatic relief without modifying the underlying disease progression. This review highlights key therapeutic targets in AD and the most effective heterocyclic scaffolds employed in the design of anti-Alzheimer's agents. Critical targets include amyloid-beta, tau protein, tau-associated kinases like glycogen synthase kinase-3β (GSK-3β) and cyclin-dependent kinase 5 (CDK5), heat shock proteins, oxidative stress pathways, and neuroinflammatory processes. The heterocyclic scaffolds commonly used in drug design include coumarin, pyridine, carbazole, piperidine, piperazine and pyrrolidine. The multi target direct ligand (MTDL) strategy has emerged as a promising approach by incorporating multiple pharmacological actions within a single molecule to address AD's multifaceted pathology. MTDLs have demonstrated potential in modulating amyloid and tau aggregation, reducing oxidative stress, and suppressing neuroinflammation offering new hope for disease-modifying therapies. Advances in computational drug design, structure-based optimization, and hybrid pharmacophore modeling continue to accelerate the development of these novel therapeutic agents.

KEYWORDS: ***Alzheimer's disease, MTDL, Drug targets, AChE, Heterocycle based scaffolds***

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I. INTRODUCTION :

Alzheimer's disease (AD) is a intensifying disease marked by the decline of neuronal integrity, predominantly affecting the elderly, with a largely elusive and multifactorial pathophysiology. It is marked by cognitive impairments, memory loss, behavioural disturbances, and personality changes that significantly impact patients' daily lives[1]. According to the World Health Organization (WHO) the number of individuals living with dementia will rise to 152 million by 2050, up from 82 million by 2030. Although the underlying causes of AD remain unclear, several hypotheses have been put forward to explain its development, including the cholinergic deficit theory, the β-amyloid (Aβ) cascade hypothesis, and the tau protein dysfunction theory[2].

Alzheimer's disease (AD) is a slowly worsening brain condition first reported in 1906 by the German doctor Alois Alzheimer. It predominantly affects older individuals, as aging is considered the most significant contributing factor. The origin of the condition is attributed to a combination of hereditary and environmental elements, but it remains a complex and multifaceted issue. AD leads to a steady deterioration in thinking, memory, and overall mental functioning, creating major emotional, societal, and financial burdens for families and healthcare systems. On a biological level, the disease is marked by two key abnormalities: the accumulation of amyloid-beta proteins outside brain cells, forming sticky plaques, and the buildup of altered tau protein within nerve cells, resulting in twisted fibers called neurofibrillary tangles. These changes disturb normal brain activity, trigger harmful inflammation, and contribute to the breakdown of nerve cell networks ultimately driving the decline in cognitive abilities[3].

Alzheimer's disease (AD) is broadly classified as twain types: sporadic and familial. Sporadic AD, typically occurs in individuals over 65 years and is mainly influenced by environmental factors, though certain

genetic factors like the Apolipoprotein E4 (ApoE4) epsilon 4 allele increase risk. Familial AD, or early-onset AD (EOAD), appears between 30–65 . The most AD cases are sporadic, both types share common pathological features. Current approved treatments include anticholinesterase, NMDA receptor antagonists, and some combination therapies, provide symptomatic relief. However, multiple pathways like neuroinflammation, oxidative stress, vascular dysfunction, metal imbalance, and impaired protein clearance contribute to disease progression and represent promising therapeutic targets. Newer strategies aim not only at extracellular amyloid plaques and intracellular tau tangles but also at these additional mechanisms[4].

The currently approved FDA drugs for Alzheimer's disease (AD) primarily provide symptomatic relief rather than altering disease progression. These include three selective acetylcholinesterase (AChE) inhibitors tacrine (approved in 1993 but later withdrawn due to significant hepatotoxicity), galantamine (approved in 1995), and donepezil (1997) as well as AChE/butyrylcholinesterase inhibitor, rivastigmine (1997), and the NMDA receptor inhibitor memantine (2003). Cholinesterase inhibitors are indicated for managing mild to moderate stages of AD by enhancing acetylcholine levels, while memantine is used for moderate to severe cases to regulate glutamatergic activity. Although these therapies can offer temporary cognitive benefits, they do not prevent neurodegeneration or halt the progression of dementia. Moreover, their long-term use is often limited by adverse effects, including gastrointestinal disturbances, central nervous system complications, cardiac arrhythmias, and, in the case of tacrine, hepatotoxicity[5].

Alzheimer's disease (AD) involves multiple overlapping and interacting biological disturbances, making it difficult for therapies that act on only one target to deliver lasting benefits. Treatments aimed solely at a single pathway such as blocking amyloid-beta production or inhibiting cholinesterase have not been able to stop or slow the progression of the disease in a meaningful way. To overcome this, researchers are now focusing on multi-target strategies that can influence several disease processes at once. These include efforts to design single compounds, called multi target direct ligands (MTDLs), that can mark problems like amyloid buildup, tau abnormalities, inflammation, oxidative damage, and synaptic failure. For complex conditions like AD, where many pathways contribute to disease progression, multi-target strategies represent a more promising path than single-target treatments that often fall short in clinical trials[6,7].

Multi-target-directed ligand (MTDL) strategy

The MTDL strategy represents an ingenious direction in the search for effectual AD therapies. MTDLs are single chemical entities specifically designed to act on two or more key molecular targets involved in AD pathology at the same time. By addressing multiple pathways simultaneously, this approach has the potential to offer broader protection, limit the chance of treatment failure due to the brain's compensatory mechanisms, and simplify therapy by reducing the need for multiple drugs. In addition, MTDLs may help lower the risk of harmful drug interactions and improve patient adherence to treatment. For complex conditions like AD, where many pathways contribute to disease progression, multi-target strategies represent a more promising path than single-target treatments that often fall short in clinical trials Many MTDLs are engineered to merge cholinesterase inhibition with additional properties such as antioxidant effects, anti-amyloid or anti-tau activity, and neuroprotection. Early research and clinical studies on these compounds have produced promising outcomes, highlighting their potential to go beyond symptom management and slow or alter disease progression[8].

Table 1. Currently identified biomarkers and therapeutic options for Alzheimer's disease [9]

Target	Mechanism of Action	Current Drugs / Approaches	Development Stage / Remarks
Acetylcholinesterase (AChE)	Inhibits breakdown of acetylcholine (ACh), enhancing cholinergic transmission	Donepezil, Rivastigmine, Galantamine	Clinically approved; symptomatic relief
Amyloid-β (Aβ) Peptides	Inhibits Aβ aggregation and promotes its clearance	Passive immunotherapies (e.g., monoclonal antibodies)	In clinical trials; aim to reduce plaque burden
β-Secretase (BACE1)	Blocks Aβ formation by inhibiting cleavage of APP	Atabecestat, Rosiglitazone,	In clinical trials; aim to reduce plaque formation
γ-Secretase	Prevents Aβ peptide formation by inhibiting γ-secretase enzyme	Semagacestat (Phase III), MK-0752 (Phase I)	Trials ongoing; mixed efficacy and safety concerns
Tau Protein Aggregation	Inhibits abnormal tau aggregation leading to neurofibrillary tangles	Anti tau agents	Under research; limited clinical success so far
Tau Kinases	Inhibits tau phosphorylation by targeting kinases	Antibodies like Bapineuzumab, Solanezumab	Experimental; clinical studies ongoing
GSK-3β (Glycogen Synthase Kinase-3β)	Prevents activation or tau phosphorylation	Direct and indirect GSK-3β inhibitors	Preclinical/clinical studies in progress

Cyclin-dependent kinase 5 (CDK5)	Inhibits tau hyperphosphorylation	CDK5 inhibitors	Shown promise in animal models; not yet confirmed in humans
Heat Shock Proteins (HSPs)	Enhances HSP expression to stabilize misfolded proteins	CHIP (C-terminus of Hsc70-Interacting Protein); other inducers	Experimental; aims to promote protein homeostasis
Oxidative Stress (ROS/RNS)	Neutralizes free radicals to protect neurons	Antioxidants: Estrogen, Melatonin, Vitamins C & E, Ginkgo biloba, Curcumin, Flavonoids	Shown efficacy in animal studies; not yet validated in humans
Neuroinflammation	Reduces inflammation mediated by microglia and cytokines	NSAIDs, PPARγ agonists	Evidence suggests possible benefit; further validation needed

Drug target networks in AD

Acetylcholinesterase (AChE)

Acetylcholine (Ach) is a major neurotransmitter produced and secreted by cholinergic nerve cells and has a pivotal role in the nervous system. The cholinergic system is a major contributor to the memory and learning process. Impairment of cholinergic neurotransmission, responsible for producing acetylcholine, is believed to contribute to memory loss observed in Alzheimer's disease[10]. Acetylcholine plays a crucial role in certain types of learning and cortical plasticity. During cholinergic signaling, ACh is released from presynaptic terminals and binds to receptors on postsynaptic cholinergic neurons, facilitating communication between nerve cells. The levels of ACh in the synaptic cleft are controlled by cholinesterase enzymes mainly acetylcholinesterase (AChE) which degrade ACh through hydrolysis. Cholinesterase inhibitors prevent this breakdown by interacting with these enzymes, thereby increasing ACh concentration at synapses. This elevated ACh enhances parasympathetic activity, leading to effects such as vasodilation, pupil constriction, slower heart rate, greater production of saliva, sweat, and tears, increased mucus secretion in the airways, and bronchial narrowing. The development of AChE inhibitors is driven by findings that disruption of cholinergic circuits in the brain which contributes to cognitive decline in AD. At present, four AChE inhibitors donepezil, galantamine, rivastigmine, and tacrine are approved for alleviating symptoms in AD patients[11,12].

Computational biology techniques, particularly drug design and computational studies, have provided strategies for identifying and evolving more effective therapeutic targets for various diseases. Recently developed flavonoid derivatives have been designed to target both sites, exhibiting stronger inhibitory effects than conventional drugs such as rivastigmine and donepezil[13]. In one study, chemically and computationally tested derivatives of quercetin, rutin, kaempferol, and macluraxanthone showed that macluraxanthone and quercetin derivatives exhibited significant cholinesterase inhibition[14]. Several newly synthesized carbamate derivatives have also shown potent AChE inhibitory activity in both *in silico* and *in vitro* evaluations[15]. Additionally, compounds such as pyridopyrimidines have demonstrated greater inhibitory potency against AChE than galantamine, as indicated by molecular docking and experimental studies[16,17]. These hybrids act as dual-site inhibitors, binding both the catalytic site and PAS. Furthermore, several piperazine derivatives have been identified as AChE inhibitors, with some capable of dual-site binding[18,19].

N-methyl D-aspartate (NMDA) receptor

Excessive activation of NMDA glutamate receptors in Alzheimer's disease (AD) leads to an abnormal influx of calcium ions (Ca^{2+}) through their associated ion channels. The primary excitatory neurotransmitter in the brain, plays a crucial role in maintaining normal synaptic transmission and neural function. However, when NMDA receptors are overstimulated by glutamate, it triggers the formation of free radicals and harmful enzymes, ultimately resulting in neuronal cell death. In neurodegenerative disorders both acute and chronic the normal clearance of glutamate is impaired, and its inappropriate release further exacerbates excitotoxic damage. Energy-deficient neurons lose their ability to maintain ionic balance, leading to depolarization and the removal of the magnesium (Mg^{2+}) block from NMDA receptor channels. This facilitates excessive receptor activation during conditions like ischemia and neurodegeneration[20].

Structurally, NMDA receptors are hetertetrameric complexes formed by various combinations of subunits, primarily NR1 and NR2A-D, with occasional inclusion of NR3A or NR3B. The specific arrangement of these subunits influences the receptor's pharmacological and functional properties. Additionally, alternative splicing of the NR1 subunit further modulates receptor behavior. Memantine, the only approved NMDA receptor antagonist, is known for its fast receptor binding and unbinding kinetics, which contribute to its clinical efficacy. Due to the

limited availability of approved NMDA antagonists, ongoing molecular docking studies aim to identify new ligands with potential therapeutic value in AD[21].

Tau protein

Tau is a microtubule protein which present in neurons, where it helps stabilize microtubules key components of the cytoskeleton that support cell shape and enable the transport of nutrients and organelles along axons. Under normal conditions, tau is present in a soluble, phosphorylated form within axons. In AD, tau protein becomes abnormally hyperphosphorylated, reducing its ability for binding. This leads to microtubule disassembly, disrupting intracellular transport and weakening the structural integrity of neurons. The separated tau proteins then aggregate into paired helical filaments, which accumulate into neurofibrillary tangles a hallmark of AD pathology. These tangles interfere with normal neuronal function and correlate with the progression of cognitive decline, first appearing in memory related regions like the hippocampus and spreading to other parts of the brain. Moreover, abnormal tau can propagate between neurons, inducing misfolding of normal tau and contributing to disease progression. Beyond structural damage, tau aggregates impair synaptic communication, hinder processes critical for learning and memory, and trigger oxidative stress, inflammation, and mitochondrial dysfunction. Collectively, these effects accelerate neurodegeneration in Alzheimer's disease[22,23].

Beta-secretase enzyme

Beta-secretase (BACE1) is a key enzyme which has the capacity of initiating the production of amyloid-beta (Aβ) peptides, central to the pathology of Alzheimer's disease (AD). Because of its pivotal role in Aβ generation, BACE1 has emerged as an important therapeutic target for lowering amyloid burden in the brain. Amyloid precursor protein (APP) can be processed through twain major pathways: the non amyloidogenic and amyloidogenic pathways. In the non amyloidogenic route, APP first cleaved by alpha-secretase, followed by gamma-secretase, leading to soluble, non-toxic fragments that do not contribute to plaque formation. In contrast, when APP is cleaved by beta-secretase (BACE1) and subsequently by gamma-secretase, it produces amyloid-beta peptides. These peptides, especially Aβ42, are prone to aggregation and form the insoluble fibrils characteristic of AD plaques. Additionally, the amyloidogenic cleavage also generates the APP intracellular domain (AICD), which can influence various cellular processes[24].

APP is produced in neuronal cell bodies and transported along axons within vesicles. The release of Aβ occurs predominantly at presynaptic terminals, contributing to extracellular amyloid deposits seen in AD. Certain mutations linked to familial AD (FAD) enhance beta-secretase cleavage or alter gamma-secretase function, leading to an increased ratio of $A\beta_{42}$ to $A\beta_{40}$ the former being more aggregation-prone. Structurally, BACE1 is a type I transmembrane aspartyl protease mainly localized in acidic intracellular body compartments, with the highest expression levels found in neurons. Two water molecules are crucial for stabilizing the enzyme's catalytic function. Experimental studies have shown that increasing BACE1 expression boosts Aβ production, while its suppression reduces Aβ levels, underscoring its therapeutic relevance[25]. Early BACE1 inhibitor design focused on mimicking natural substrates, leading to the development of OM99-2 and OM00-3 through molecular docking studies. Further exploration yielded various classes of BACE1 inhibitors, including derivatives of hydroxyethylene (HE), hydroxyethyleneamine (HEA), carbinamine, macrocyclic compounds, acylguanidines, aminoimidazoles, and aminoquinazolines. Statine-based peptidomimetic inhibitors have also shown potent binding and low IC50 values, making them promising candidates[26].

Tau kinases

In AD, tau protein, which normally helps stabilize microtubules within neurons, undergoes harmful changes that contribute to neurodegeneration. A key factor driving this process is the abnormal activity of tau kinases enzymes responsible for adding phosphate groups to tau. Under healthy conditions, tau phosphorylation is carefully regulated and necessary for normal neuronal function. However, in AD, several kinases become overactive or dysregulated, leading to hyperphosphorylation of tau protein. Excessive phosphorylation diminishes tau's property to bind microtubules, leading to the microtubule network break down. As a result, the transport of essential nutrients and cellular components along the axon is impaired, weakening the neuron's structural integrity[27].

The hyperphosphorylated tau detaches from microtubules and begins to aggregate, forming paired helical filaments that accumulate as neurofibrillary tangles (NFTs). These tangles disrupt neuronal communication, contribute to synaptic loss, and are strongly linked to the gravity of memory decline. Among the kinases implicated in tau pathology, glycogen synthase kinase-3 beta (GSK-3β), cyclin-dependent kinase 5 (CDK5), microtubule affinity-regulating kinase (MARK), and casein kinase 1 (CK1) are prominent. GSK-3β and CDK5, in particular, have been vastily studied for their impact in driving tau hyperphosphorylation. The combined actions of these kinases result in a pattern of abnormal tau modifications that favor aggregation and spread[25]. Importantly, hyperactive tau kinases not only promote tangle formation but may also contribute to other damaging processes,

such as oxidative stress, inflammation, and mitochondrial dysfunction. Given their central role in tau pathology, tau kinases is best target in efforts for slow or halt AD progression. Inhibiting these kinases or modulating their activity could help restore tau's normal function, reduce tangle formation, and protect neurons from degeneration[28].

Monoamine oxidase (MAO)

Monoamine oxidase is a crucial enzyme in the outer mitochondrial membrane, responsible for the oxidative deamination of monoamine neurotransmitters and other amines, resulting in the production of hydrogen peroxide (H_2O_2), which can contribute to cellular oxidative stress generation. MAO exists as twain forms, MAO-A and MAO-B, each encoded by separate genes and differing in their tissue distribution parameter, substrate specificity, and physiological roles. In the brain, MAO-B is the predominant form, especially involved in the dopamine metabolism and trace amines such as 2-phenylethylamine (PEA) metabolism. In Alzheimer's disease (AD), research has consistently shown that MAO-B levels are significantly elevated in regions of brain critical for memory and cognition, such as the hippocampus and cerebral cortex, compared to healthy controls. Notably, reactive astrocytes surrounding amyloid plaques display more than a threefold increase in MAO-B activity. This heightened MAO-B activity leads to excessive breakdown of monoamines and increased generation of reactive oxygen species, including hydrogen peroxide and free radicals, which can damage neurons and accelerate neurodegenerative processes. This upregulation of MAO-B is observed early in AD and persists as the disease progresses[29,30].

Given its role in oxidative stress and neurodegeneration, inhibiting MAO-B is best option for the designing of an anti-Alzheimer's agent. Selegiline, an MAO-B irreversible inhibitor, has shows some cognitive improvement in AD patients. Lazabemide, another potent MAO-B inhibitor, showed promising results in early trials, reducing cognitive decline by 20–40% compared to controls; however, its development was halted due to safety concerns. These findings underscore the therapeutic potential of targeting the monoaminergic system in neurodegenerative diseases like AD, while also highlighting the need for further research to clarify the clinical benefits and safety of MAO-B inhibitors in this context[31].

Heat shock proteins and Ubiquitin Proteasome System

The Heat Shock Proteins (HSPs) function as molecular chaperones that helps in the actual folding of freshly tuned proteins and help refold misfolded parts of protein to prevent their aggregation. Under conditions of cellular stress, including oxidative stress and the presence of misfolded proteins, HSP expression is upregulated as a protective response. Specific HSPs, such as HSP70 and HSP90, have been shown to interact directly with tau and amyloid-beta, limiting their aggregation and toxicity. HSPs not only assist in folding but also help shuttle irreparably damaged proteins toward degradation pathways. However, in the AD brain, the overwhelming production of misfolded proteins exceeds the capacity of HSPs to manage these aggregates, resulting in their accumulation and contributing to disease progression[32].

In parallel, the ubiquitin-proteasome system (UPS) serves as the primary pathway for degrading damaged or misfolded proteins in cells. The system works by attaching a small protein, ubiquitin, to defective or unneeded proteins, marking them for degradation. The tagged proteins are then transported to the proteasome, a complex that breaks them down into small peptides. This process is essential for maintaining protein balance within neurons and preventing the formation of toxic protein inclusions. In Alzheimer's disease, UPS activity is impaired. Proteasome function is often reduced, leading to inefficient degradation of ubiquitin-tagged proteins. As a result, proteins that should be cleared continue to accumulate within neurons, contributing to synaptic dysfunction and neuronal death. Indeed, ubiquitin-positive inclusions are frequently seen in the regions of brains of individuals with AD, highlighting failure of this critical system[33].

These protective systems, although initially effective, become overwhelmed as the disease advances. Enhancing the activity of HSPs or restoring proteasome function represents a promising therapeutic strategy in the fight against AD. Several experimental approaches are currently exploring how these systems can be modulated to promote the clearance of toxic proteins and potentially slow or halt the neurodegenerative process[34,35].

Oxidative stress role in AD

The brain is naturally more vulnerable to oxidative damage compared to other organs. This is because, despite its small size relative to total body mass, it consumes a substantial portion of the body's oxygen about one-fifth. The brain's high oxygen use, its richness in lipids that are easily oxidized, and the presence of metals like iron and copper, all make it susceptible to harmful oxidative reactions. Furthermore, its antioxidant systems are relatively modest, increasing its risk. In Alzheimer's disease, this inherent vulnerability is further worsened by disease-related changes that increase the production of ROS[36,37].

A key factor in the oxidative stress seen in AD is the development of amyloid beta (Aβ) peptides. These peptides tend to clump together and form plaques. When they bind with metals such as copper or iron, they can

produce ROS like hydrogen peroxide. These ROS damage essential components of neurons, including cell membranes, proteins, and DNA, contributing to cell dysfunction and death. As AD progresses, evidence of oxidative damage such as oxidised lipids and DNA modifications becomes more pronounced in affected areas of the brain. Another contributor is the brain's immune response[33]. Microglia, the brain's defense cells, become activated around amyloid plaques. In doing so, they release ROS and reactive nitrogen species as part of their effort to clear harmful substances. However, instead of helping, this prolonged activation increases oxidative stress and speeds up neuronal damage. Additionally, when mitochondria the energy producers of cells become dysfunctional in AD, they generate more ROS, which further harms brain cells and reduces energy supply, creating a damaging cycle[38,39].

Inflammations in AD

As we age, the normal functioning of our immune and metabolic systems becomes disrupted, leading to a persistent, mild form of inflammation known as inflammaging. This long-term inflammatory state stems from several age-related processes, including the buildup of aged or senescent cells, a weakening of the immune system's protective capabilities (immunosenescence), and malfunctioning mitochondria[40]. In addition, the body's ability to clear out damaged components through autophagy, mitophagy, and the ubiquitin–proteasome system declines over time. Lifestyle factors, such as excessive calorie intake, obesity (also called metaflammation), and imbalances in gut bacteria, further fuel this harmful inflammation. These changes are reflected in increased levels of markers like C Reactive Protein (CRP), Interleukin-6, Tumor Necrosis Factor-alpha (TNF-α). Together, they contribute to a higher risk of diseases linked to aging, including AD. As the number of older adults worldwide is expected to more than double by 2050, the number of people vulnerable to inflammaging and AD is likely to rise sharply[41].

While rare inherited forms of AD appear earlier in life due to mutations in genes like PSEN1, PSEN2, and APP, most cases occur later in life (late-onset AD) and are influenced by aging and genetic risk factors such as the APOE gene. More recently, scientists have identified other genes that increase AD risk, many of which are involved in the brain's immune defense and microglial function examples include TREM2, CLU, BIN1, and PICALM. For instance, TREM2 plays a role in helping microglia remove amyloid plaques and manage inflammation, but certain variants of this gene reduce its effectiveness and raise the risk of disease[42].

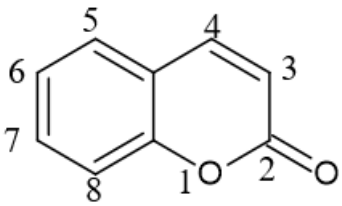
Promising heterocycle based scaffolds in designing of an anti-Alzheimer's agents in drug discovery

1. Coumarin/chromone-based molecules

Coumarin derivatives have emerged as promising multi-target agents in AD research because of their capability to inhibit both AChE and MAOs, with several studies reporting that structural modifications such as the introduction of benzyloxy, piperidine, or N-benzylpiperidine groups at specific positions on the coumarin scaffold can yield potent and selective inhibitors, particularly against MAO-B, with some compounds achieving nanomolar inhibitory concentrations and displaying additional, though generally moderate, cholinesterase inhibition; these findings underscore the potential of coumarin-based hybrids as structural templates for the development of dual or multifunctional inhibitors, capable of targeting key enzymes implicated in neurodegenerative processes, and highlight the importance of further structure-activity relationship exploration to optimize selectivity and potency for therapeutic applications in Alzheimer's disease[43].

Structure Activity Relationship (SAR) of Coumarin/Chromone-Based Molecules in Alzheimer's Disease Drug Design[44,45,46]

Coumarin and chromone derivatives have emerged as promising scaffolds in Alzheimer's disease (AD) drug development. Their effectiveness is often attributed to structure activity relationship (SAR) analyses, which elucidate how specific molecular modifications impact biological activity against AD targets.



1. Core Scaffolds and Modification Sites

- Coumarin: The benzopyrone structure allows diverse substitutions at the 3, 4, 6, 7, and 8 positions, modulating interaction with multiple AD-relevant enzymes.
- Chromone: This benzopyran-4-one ring is structurally similar but generally requires different substitution strategies for activity optimization

2. Key SAR Features Relevant to AD

A. Cholinesterase Inhibition (AChE, BChE)

❖ Substitutions at C6, C7, C8 (Coumarin):

- Introducing alkyl, aryl, or heterocyclic groups at these positions enhances binding with cholinesterase active sites.
- Long-chain alkyl or aryl groups (especially at C6/C8) increase both AChE and BuChE inhibition.
- Methoxy, hydroxy, or amino substituents at these sites can further boost potency and selectivity.

❖ Hybrid Molecules:

- Coumarin hybrids (e.g., coumarin–triazole, coumarin–chromone) combine multiple pharmacophores, resulting in higher multitarget activity (inhibiting both AChE and BACE1, or AChE and MAO-B).

B. β-Amyloid Aggregation and Neuroprotection

- Bulky substitutions (often at the C8 position for coumarins) hinder amyloid fibril formation by sterically blocking the aggregation process.
- Electron-donating groups (hydroxy, methoxy) can stabilize interactions with amyloid peptides, enhancing anti-aggregation activity.

C. Metal Chelation and Redox Properties

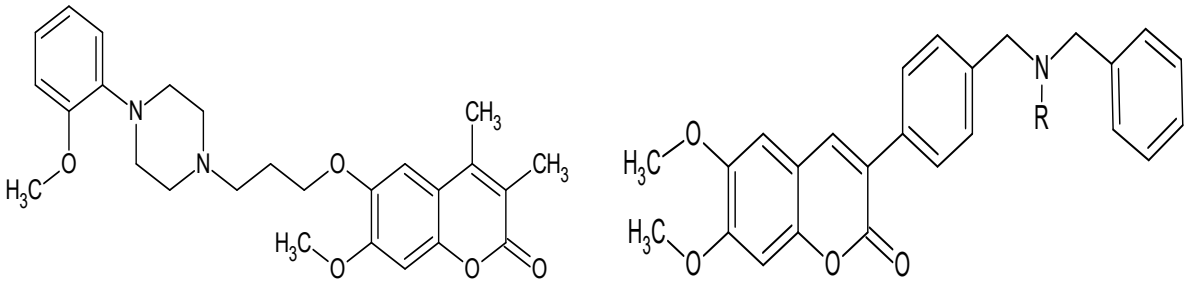
- The presence of carbonyl, hydroxy, or amino groups—especially adjacent on the aromatic ring enables chelation of metal ions (e.g., Cu^{2+}, Fe^{2+}), a property significant in countering metal-induced amyloid toxicity.

3. Chromone-Based SAR Distinctions

- Chromone derivatives generally show weaker base potency than coumarins for cholinesterase inhibition but can be optimized by introducing electron-withdrawing or donating substituents at the C6 and C8 positions.
- Hybridization with coumarins or triazoles markedly improves their activity profile and selectivity for neuro targets like MAO-B and AChE.

4. Multitarget Approaches and CNS Optimization

- Lipophilicity: Structural modifications that increase lipophilicity without compromising solubility are beneficial for blood–brain barrier (BBB) permeability.
- Dual/Multitarget Activity: Combining features that address both cholinesterase inhibition and amyloid aggregation enhances overall neuroprotective efficacy.



1(i) Ensaculin **1(ii) AP2238: R= CH_3** **1(iii) AP2243: R=C_2H_5**

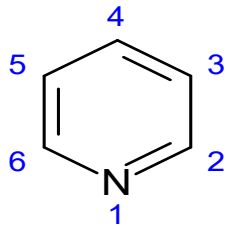
Fig 1i-iii. Examples of AChE inhibitors: Ensaculin, AP2238 and AP2243

2. Pyridine analogues

Pyridine analogs have attracted considerable attention in development of anti-Alzheimer's agents due to structural versatility to interact with multiple targets involved in the pathophysiology of AD. The nitrogen atom in pyridine ring forms hydrogen bonding and coordination with enzyme active sites, making these compounds suitable for inhibiting enzymes like acetylcholinesterase (AChE) and monoamine oxidase (MAO), which are central to AD pathology. In particular, pyridine-containing compounds have shown the ability to enhance cholinergic transmission by inhibiting AChE, while others can block beta-amyloid (Aβ) aggregation or reduce oxidative stress through MAO-B inhibition. Structural modifications, such as the addition of hydroxyl, methoxy, or bulky amine groups to the pyridine ring, can further improve binding affinity and selectivity. Additionally, hybrid molecules that combine pyridine with other pharmacophores such as coumarin or pyrazole have demonstrated enhanced neuroprotective, antioxidant, and anti-inflammatory properties. These compounds often show good blood-brain barrier permeability and metabolic stability, which are essential features for central nervous system drug candidates. Overall, pyridine derivatives offer a promising scaffold for designing multifunctional therapeutics aimed at slowing the development of Alzheimer's disease[47,48].

Structure Activity Relationship (SAR) of Pyridine Molecules in AD Drug Design[49,50,51]

Pyridine derivatives are pivotal in pursuit of effective AD therapeutics. Their unique structural versatility enables targeted interaction with multiple AD-relevant biological pathways. The following sections summarize key SAR insights elucidating how modifications to pyridine scaffolds improve activity and selectivity against AD's multifaceted pathology.



1. Role of Pyridine Core in AD Drug Design

- Pharmacophoric Scaffold: The pyridine ring serves as a privileged structure for constructing ligands that bind cholinesterases (AChE/BuChE), modulate amyloid-beta (Aβ) aggregation, and target other AD-associated enzymes and receptors.
- Versatile Substitution: Different positions on the pyridine ring (mainly 2-, 4-, and 6-) can be substituted with a variety of groups, tuning lipophilicity, binding affinity, and central nervous system (CNS) penetration.

2. Key SAR Findings for Pyridine-Based AD Agents

A. Cholinesterase Inhibition (AChE/BuChE)

- Ring Substitutions: Alkyl, aryl, or amino substituents, particularly at the 2- or 4-positions, significantly enhance binding and inhibitory activity towards cholinesterases.
- Electron-Donating Groups: Introduction at key sites often increases inhibitory potency and selectivity, balancing activity and toxicity profiles.
- Hybrid Designs: Fusing pyridine with other scaffolds (such as sultone, coumarin, or pyrazole) can yield potent, multitarget inhibitors enhancing both AChE inhibition and other neuroprotective mechanisms.

B. Amyloid Aggregation Inhibition

- 2,6-Disubstituted Pyridine Derivatives: These can interact via hydrogen bonding with β-sheet structures of Aβ peptides, disrupting aggregation and potentially limiting plaque formation a hallmark AD pathology.
- Hydrophilic/Hydrophobic Balance: Modifying substituents alters affinity for Aβ and blood-brain barrier permeability.

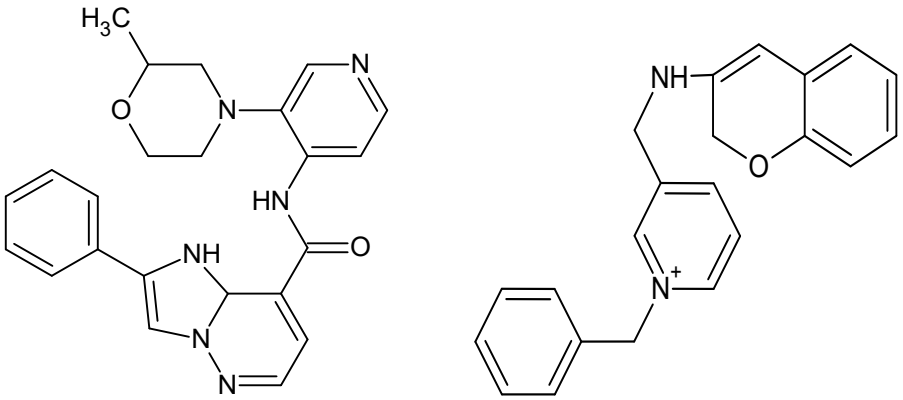
C. Multi-Target Activities & CNS Drug Properties

- Optimized Substituents: Balance between electron-withdrawing and electron-donating groups affects overall drug-likeness, metabolism, and brain penetration.
- Receptor Modulation: Imidazo[1,5-a]pyridine derivatives demonstrate agonistic activity at 5-HT4R, which is linked to cognitive benefit and disease modification in AD.
- Linker Chemistry: In hybrids, linker length and flexibility tune target selectivity and binding efficacy.

3. Design Example: Balanced Multifunctional Pyridine Analogs

- 2-Aminoalkyl-6-(2-hydroxyphenyl)pyridazin-3 (2H)-one Derivatives:

❖ The 2-aminoalkyl group promotes strong AChE interaction.
❖ The pyridazinone core is associated with antioxidant and anti-inflammatory effects.
❖ The appended 2-hydroxyphenyl moiety increases solubility and stabilizes protein interactions, resulting in both effective cholinesterase inhibition and moderate β-amyloid aggregation blockage.
❖ Such multifunctional agents combine improved ADMET profiles (absorption, distribution, metabolism, excretion, toxicity) with high target affinity.

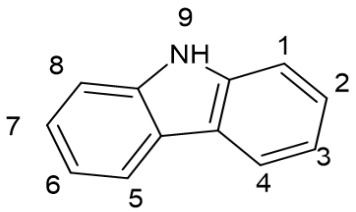


2(i) **2(ii)**

Fig 2i-ii. Examples of strong AChE and MAO-B inhibitors of Pyridine derivatives.

3. Carbazole scaffolds

Carbazole scaffolds have gained significant attention in recent years as versatile chemical frameworks for the design of agents targeting AD. Their rigid, tricyclic aromatic structure contributes to favorable physicochemical properties such as planarity, lipophilicity, and the capability to cross the blood brain barrier, making them ideal candidates for central nervous system (CNS) drug design. These scaffolds have been widely explored for their multifunctional capabilities, which are particularly beneficial in addressing the multifactorial nature of AD pathology. Carbazole-based derivatives have shown promising inhibitory activity against acetylcholinesterase (AChE), thereby enhancing cholinergic neurotransmission a mechanism that helps alleviate cognitive symptoms in AD patients. Additionally, carbazole-containing molecules have been reported to inhibit monoamine oxidase (MAO), contributing further to neuroprotection by regulating neurotransmitter levels and reducing oxidative byproducts. Recent research has focused on modifying the carbazole core or incorporating it into hybrid structures with other pharmacophores to enhance multi-target activity. This approach has led to the development of novel compounds that act on several AD-related targets simultaneously, reflecting a shift towards multi target directed ligands (MTDLs) in modern drug discovery. Overall, the structural flexibility and pharmacological versatility of carbazole scaffolds make them a promising foundation for designing effective and comprehensive anti-Alzheimer's therapeutics[52,53,54].



Key SAR Features of Carbazole Analogs in AD Drug Design[55,56,57]

1. Core Carbazole Scaffold as a Multi-Target Platform

- The rigid, planar carbazole ring provides a privileged structure for binding to multiple AD-relevant targets due to its aromaticity and ability to accommodate various substituents at multiple positions.

2. Substitution Patterns and Multitarget Effects

- N-Alkylation or N-Substitution increases lipophilicity and can enhance BBB penetration and binding affinity for cholinesterases and amyloid peptides.
- Adding moieties via flexible linkers enables simultaneous binding with the catalytic active sites and peripheral anionic sites of acetylcholinesterase or butyrylcholinesterase (BuChE), leading to mixed-type inhibition and improved efficacy.
- Some derivatives effectively inhibit both AChE and BuChE at low micromolar or sub-micromolar concentrations, with selectivity and potency intimately related to length of the linker and the electronics of the attached group.

3. Anti-Amyloid Aggregation

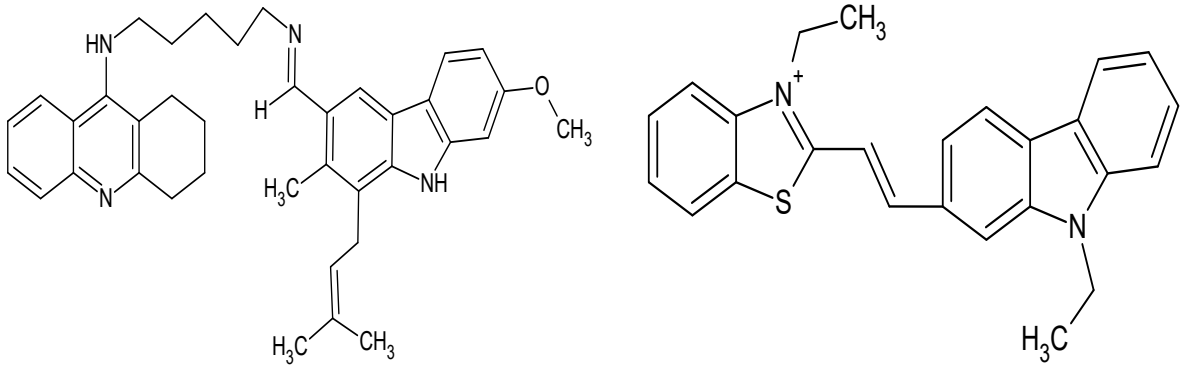
- Substituents at the 3-position or other positions that increase planarity or provide hydrogen-bonding capability can disrupt Aβ self-assembly and aggregation, stabilizing soluble forms and reducing toxicity.
- Molecular docking indicates that bulky carbazole derivatives can engage key binding residues involved in Aβ fibrillization and effectively inhibit aggregation in cell models.

4. Antioxidant and Neuroprotective Activity

- Electron-donating groups (e.g., methoxy, hydroxy) on the carbazole ring enhance radical scavenging, providing additional neuroprotection against oxidative stress.

5. Metal Chelation

- Hybrid compounds with appropriate chelating groups (e.g., thiourea) demonstrated specific Cu(II) chelation, potentially mitigating metal-induced Aβ aggregation and oxidative pathways.



3(i) Carbazole- tacrine hybrid **3(ii) Carbazole – thiazole derivative**

Fig 3i-ii. Examples of MTDL of Carbazole derivatives.

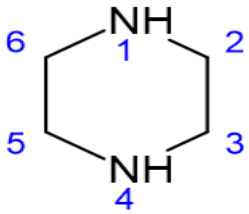
4. Piperidine and piperazine derivatives

Piperidine and piperazine derivatives have emerged as crucial scaffolds in the design of novel therapeutic agents for AD, primarily because of their flexibility, pharmacokinetic properties, and capability to modulate key targets involved in neurodegeneration. The piperidine ring forms the core of many cholinesterase inhibitors, most notably donepezil, a drug for symptomatic treatment of AD. This six-membered nitrogen-containing ring can interact effectively with the sites of the acetylcholinesterase enzyme, thereby enhancing cholinergic transmission and improving cognitive function. Similarly, piperazine-containing compounds have shown promise in multi-target-directed ligand (MTDL) strategies by combining AChE or butyrylcholinesterase (BuChE) inhibition with other therapeutic activities such as inhibition of β-amyloid aggregation, antioxidant properties, and metal-chelating capabilities. The presence of nitrogen atoms in these heterocycles not only enhances water solubility but also improves brain penetration, a critical factor for central nervous system drug development. Recent research has focused on hybrid molecules integrating piperidine or piperazine moieties with other bioactive pharmacophores like coumarins, carbazoles, or benzothiazoles to achieve synergistic effects on multiple AD-related targets. These hybrid derivatives have demonstrated significant in vitro and in vivo efficacy[58,59].

Key SAR Features of Piperidine and piperazine Analogs in AD Drug Design[60,61,62]

The structure–activity relationship (SAR) of piperidine and piperazine derivatives plays a central role in their development as candidate drugs for Alzheimer's disease (AD). Specific structural alterations to these nitrogen-containing heterocycles significantly affect their potency, selectivity, and multitarget profile against cholinesterases, amyloid aggregation, and other AD-related pathological factors.

Piperazine Derivatives



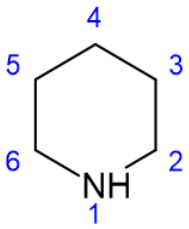
1. Benzyl Substitution and Core Modulation
- N,N'-Bis(benzyl) substitution on the 1,4-positions of the piperazine ring, particularly with electron-withdrawing (e.g., chloro) groups on the benzyl moiety, enhances both the potency and selectivity for cholinesterase inhibition.

2. Functional Group Effects
- Carboxylic acids on the piperazine core favored AChE selectivity, while conversion to hydroxamic acids or carboxamides enhanced BChE selectivity and potency.
- SAR rationale: Different polar groups interact differentially at the active sites of AChE and BChE, altering both binding affinity and selectivity.

3. Peripheral Anionic Site Binding and Brain Permeability
- Conjugation with aromatic systems (like oxadiazole or pyridyl moieties) and terminal substitutions can create molecules that bind to the peripheral anionic site (PAS) of AChE, block Aβ aggregation, and retain or improve BBB permeability.

4. Mixed-type Enzyme Inhibition and Polypharmacology
- Some piperazine hybrids act as mixed-type AChE inhibitors and show multitarget activity (AChE, BChE, BACE1, anti-aggregation, antioxidant effects).
- SAR studies reveal that substituent size, electronic character, and position all profoundly influence whether a molecule acts as a single- or multi-target agent.

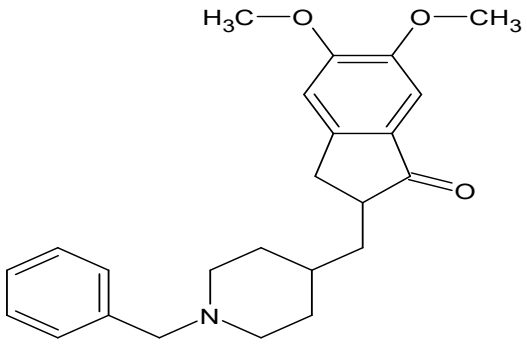
Piperidine Derivatives



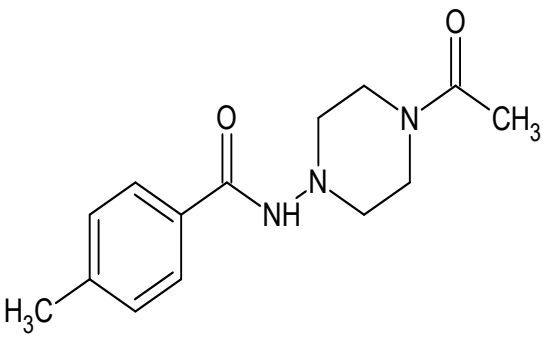
1. Scaffold as a Cholinesterase Inhibitor
- The piperidine ring is the core pharmacophore in several anti-AD drugs (e.g., donepezil).
- Substitution at nitrogen or on the ring (e.g., N-benzyl, N-methyl, aryl at C-4) tunes both AChE/BChE affinity and CNS activity.
- Aromatic substitutions at or near the piperidine nitrogen often lead to enhanced potency and selectivity for AChE, especially when combined with appropriate linker length and branching.

2. Multi-target Profile and CNS Penetration
- Hybrid designs linking piperidine to other bioactive moieties can create MTDLs capable of suppressing AChE, BuChE, and BACE, and interfering with Aβ aggregation.
- Lipophilicity modulation via various substitutions affects BBB penetration, a key factor for CNS-active drugs.

3. Position and Nature of Substituents
- Substitution patterns (electron-donating/withdrawing, positional isomerism) on aromatic rings attached to piperidine or piperazine affect not only potency but also selectivity and off-target profile.



4(i) Donepezil

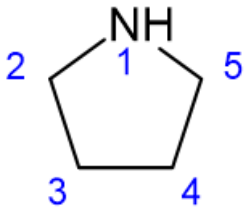


4(ii)FK-960

Fig 4 i-ii. Examples of Piperidine and piperazin derivatives.

5. Pyrrolidine

Pyrrolidine, a five-membered nitrogen-containing heterocycle, has attracted considerable heed in the field of AD drug discovery due to its pharmacologically favorable structure and ability to interact with various neural targets. Its compact, conformationally constrained ring structure allows effective binding within enzymatic active sites, particularly acetylcholinesterase (AChE), where it can modulate cholinergic neurotransmission by inhibiting the breakdown of acetylcholine. Pyrrolidine-based compounds are frequently found in the design of multi-target-directed ligands (MTDLs), especially in hybrid molecules that aim to combine AChE inhibition with additional therapeutic actions such as antioxidant activity, metal ion chelation, and prevention of amyloid-beta (Aβ) aggregation. These derivatives have also demonstrated potential in modulating neuroinflammatory responses and oxidative stress, which are both critical components of AD pathogenesis. By enhancing blood-brain barrier permeability and improving pharmacokinetic profiles, pyrrolidine scaffolds serve as efficient carriers for CNS targeted drug candidates. As research progresses, pyrrolidine continues to offer a promising backbone for the development of multifunctional agents capable of addressing the complex pathology of Alzheimer's disease[63,64].



Key SAR Insights for Pyrrolidine Derivatives in AD Drug Design[65,66,67]

1. N-benzylpyrrolidine Derivatives and Multi-Targeting

- N-benzyl substitution on the pyrrolidine ring is a critical feature for balanced inhibition of AChE, BChE, and BACE-1.
- Hybrid molecules inspired by donepezil (a standard anti-AD drug) replace indanone with N-benzylated pyrrolidin-2-one to maintain strong interactions with cholinesterases, while modifications to the linker region (tail) allow tuning of enzyme binding and selectivity.

2. 3-Hydroxy-Pyrrolidine Analogs and Natural Product-Inspired Design

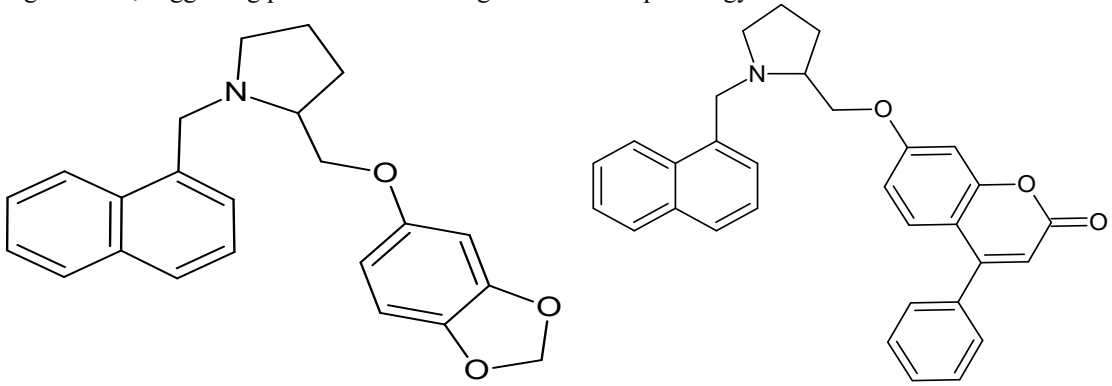
- Semi-synthetic 3-OH pyrrolidine derivatives, inspired by the natural alkaloid vasicine, showed effective dual AChE/BChE inhibition and significant anti-Aβ aggregation.
- A hydroxy group at the 3-position and tailored substitutions enhance interactions at the active site and PAS, supporting both cholinesterase inhibition and anti-aggregation effects.

3. Spatial Arrangement and Stereochemistry

- Enantioselective synthesis of N-substituted aryloxymethyl pyrrolidines demonstrates that spatial orientation and stereochemistry optimize pharmacological activity, influencing multitarget engagement, including AChE, BChE, and other neurodegeneration targets.

4. Pyrrolidine-2,3-Dione Derivatives and Kinase Inhibition

- Computational and molecular studies of pyrrolidine-2,3-dione derivatives as novel inhibitors of the Cdk5/p25 complex, a target in tau hyperphosphorylation and neurodegeneration.
- Core modifications allow the molecules to occupy the kinase ATP-binding pocket and form stable, key hydrogen bonds, suggesting promise for reducing tau-mediated pathology in AD



5(i) **5(ii)**

Fig 5i-ii. Examples of Pyrrolidine derivatives with AChE and BChE inhibition.

II. CONCLUSION:

Alzheimer's disease is a gradually worsening neurological disorder marked by memory impairment, declining cognitive abilities, and difficulties with movement. Existing drugs like Donepezil offer only symptomatic relief, emphasizing the urgent need for more effective therapeutic strategies. Recent research highlights the potential of heterocyclic scaffolds in developing anti-AD agents because of their varying biological activities and structural versatility. Heterocyclic compounds such as coumarin, pyridine, carbazole, piperidine, piperazine, and pyrrolidine, have shown promising inhibitory activities against key AD targets like AChE, MAO-B, BACE1, and GSK-3β. The fused pyridine, coumarin cores stand out as especially promising for future drug development. To address the multifactorial nature of AD, the multi target directed ligand (MTDL) approach has emerged as a superior strategy, aiming to simultaneously modulate several pathophysiological pathways. MTDLs offer the advantage of enhanced efficacy and reduced side effects by incorporating multiple actions into a single molecule. Advances in computational modeling and structure-based design are accelerating the development of such multifunctional compounds. Overall, heterocyclic based MTDLs represent a transformative approach with the capability to yield disease modifying therapies for Alzheimer's disease.

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