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Multi Target Directed Ligand for Alzheimer's Disease: A Review of Therapeutic Strategies and Advances

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Keywords

Alzheimer's disease, Cognitive decline, Amyloid-β aggregation, Tau hyperphosphorylation, Cholinergic dysfunction, multi-target directed ligands.

Abstract

Alzheimer's disease (AD) is a progressive neurodegenerative disorder marked by cognitive decline and memory loss, resulting from various pathological processes such as amyloid-β aggregation, tau hyperphosphorylation, oxidative stress, cholinergic dysfunction, and metal ion imbalance. Current treatments, like acetylcholinesterase inhibitors and NMDA receptor antagonists, only help with the symptoms and don't change how the disease gets worse. The fact that AD has many causes shows how important it is to come up with new ways to treat it. Multi-target directed ligands (MTDLs) have become a promising approach in the last few years. They are meant to work on several important molecular targets that are thought to play a role in the development of Alzheimer's disease. This review summarises progress in the creation and design of MTDLs. It talks about hybrid molecules (like tacrine–chromene derivatives), peptide-based scaffolds, flavonoid conjugates, dual GSK-3β/tau aggregation inhibitors, and new PDE- and AChE-targeting compounds. Compared to regular polypharmacy, MTDLs have more benefits, such as better effectiveness, less toxicity, better compliance, and better pharmacological profiles. Recent advances in medicinal chemistry and structure-based design bolster the argument for MTDLs as next-generation therapeutic candidates, notwithstanding challenges like bioavailability and blood–brain barrier penetration. Ongoing enhancement of these compounds may eventually yield disease-modifying therapies that can impede or avert the advancement of Alzheimer's disease.

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1. Introduction

Alzheimer's disease (AD) is recognized as the predominant form of dementia among neurodegenerative disorders and is characterized by progressive memory loss, cognitive decline, impaired reasoning, and behavioral changes in the aging population. It is a slowly progressive disorder in which pathological changes begin in the brain years before the onset of clinical symptoms. Although the exact cause of AD remains incompletely understood, the accumulation of amyloid-β (Aβ) plaques and neurofibrillary tangles is considered central to disease pathogenesis. These pathological features disrupt neuronal communication, impair synaptic function, and ultimately lead to neuronal degeneration [1]. In addition, oxidative stress and chronic neuroinflammation are widely recognized as major contributors to neuronal injury and disease progression. According to the cholinergic hypothesis, impaired cholinergic neurotransmission also plays a significant role in the cognitive deficits associated with AD. Amyloid-β oligomers promote neuronal death by disrupting synaptic communication, whereas hyperphosphorylated tau proteins interfere with intracellular transport, resulting in widespread

neuronal loss, synaptic dysfunction, and reactive gliosis in brain regions responsible for learning and memory. Understanding these interconnected pathological mechanisms provides an important foundation for developing therapeutic strategies aimed at preventing neurodegeneration [2].

Alzheimer's disease accounts for approximately half of all age-related dementia cases, with its prevalence increasing markedly with advancing age. Owing to its multifactorial nature, AD involves numerous interconnected pathological pathways rather than a single molecular abnormality. Currently approved pharmacological treatments mainly include cholinesterase inhibitors for mild-to-moderate disease and N-methyl-D-aspartate (NMDA) receptor antagonists for moderate-to-severe disease. Although these therapies provide symptomatic relief, they do not halt or reverse disease progression. Consequently, the traditional "one drug–one target" approach has shown limited success in managing such a complex disorder [3].

The multifactorial pathology of AD has shifted drug discovery toward the development of multi-target-directed ligands (MTDLs), which are designed to simultaneously modulate multiple disease-associated pathways within a single molecular entity. Unlike conventional combination therapy, MTDLs may reduce drug–drug interactions, improve pharmacokinetic properties, simplify treatment regimens, and enhance patient compliance while providing synergistic therapeutic effects [4]. By integrating two or more pharmacologically active scaffolds into a single molecule, MTDLs have emerged as a promising strategy for targeting amyloid aggregation, tau hyperphosphorylation, oxidative stress, neuroinflammation, cholinergic dysfunction, and other interconnected mechanisms involved in AD pathogenesis. Furthermore, disease-modifying therapies are also being actively investigated to intervene in the upstream molecular events responsible for disease initiation and progression. Together, these advances represent a significant shift toward more comprehensive therapeutic approaches that may ultimately slow or prevent the progression of Alzheimer's disease [5].

Figure 1 illustrates the two major forms of Alzheimer's disease: early-onset familial Alzheimer's disease (EOAD) and late-onset sporadic Alzheimer's disease (LOAD). EOAD is primarily associated with mutations in the presenilin-1 and presenilin-2 genes and accounts for approximately 10% of cases, whereas LOAD develops after 65 years and increases markedly with advancing age [6].

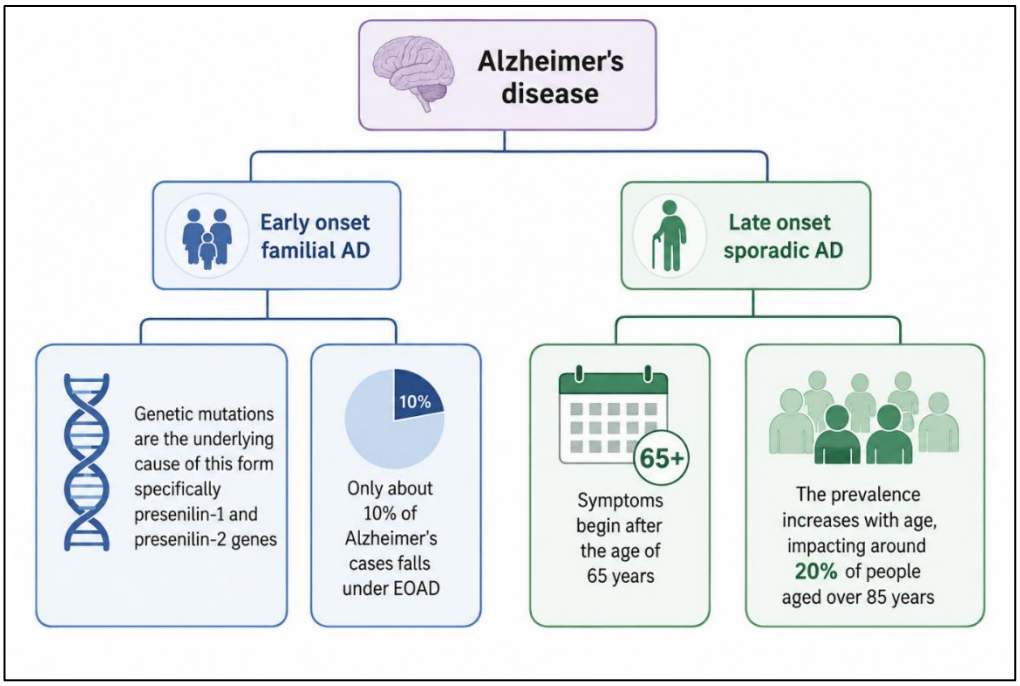


Figure 1. Types of Alzheimer's disease

Figure 2 summarizes the major risk factors associated with Alzheimer's disease, categorized into genetic and acquired factors. Genetic susceptibility includes APOE polymorphisms and inherited mutations, while acquired factors such as cerebrovascular disease, type 2 diabetes, hypertension, smoking, dyslipidaemia, depression, and obesity contribute through oxidative stress, hypoperfusion, and metabolic dysfunction [7].

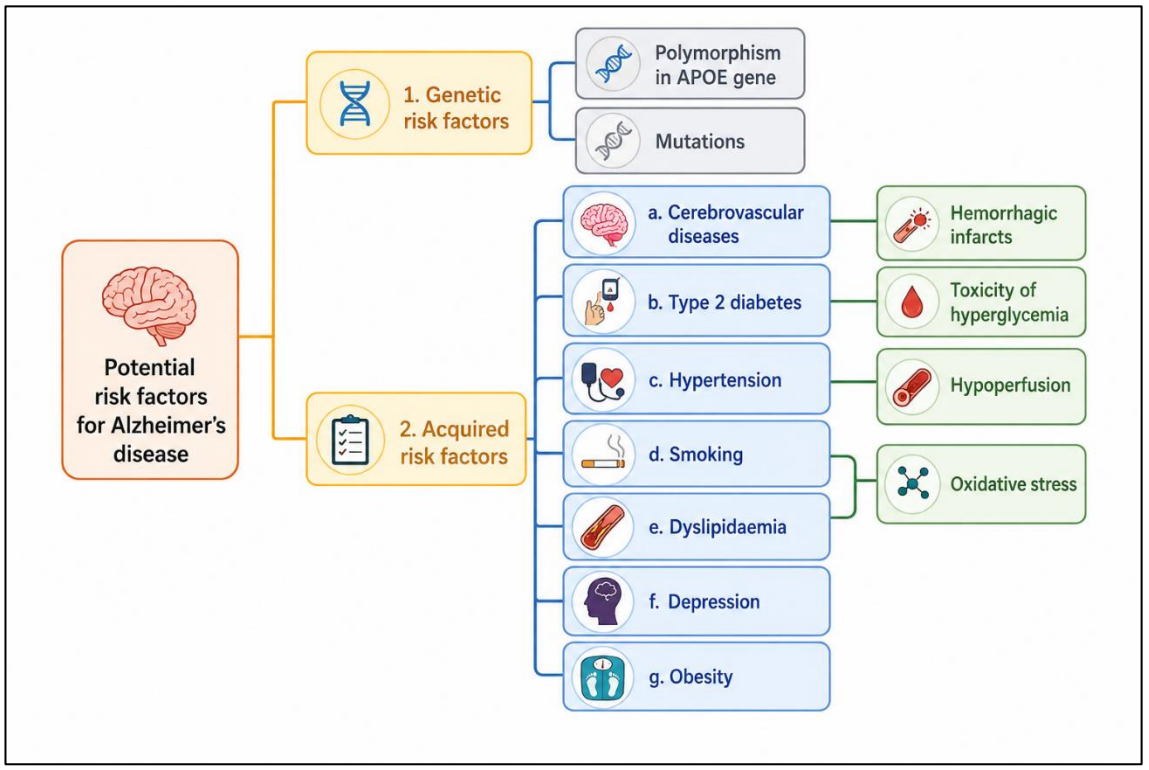


Figure 2. Illustration of different risk factors for Alzheimer's disease

2. Pathogenic Mechanisms in Alzheimer's Disease

2.1 Hyperphosphorylated Tau State

The microtubule-associated protein tau performs several essential physiological functions in the central nervous system, including stabilization of axonal microtubules, regulation of axonal transport, maintenance of synaptic plasticity, neuronal development, and preservation of nucleic acid integrity [8]. Under physiological conditions, tau binds to tubulin and promotes microtubule assembly and stability. However, abnormal interactions between tau and tubulin disrupt microtubule dynamics, while genetic variations can further destabilize the cytoskeletal network, ultimately contributing to neuronal dysfunction and degeneration [9].

Protein phosphatase 2A (PP2A) is the principal phosphatase responsible for maintaining normal tau phosphorylation levels in the brain. Reduced PP2A activity leads to excessive tau phosphorylation and the formation of paired helical filaments (PHFs), which subsequently aggregate into neurofibrillary tangles, one of the pathological hallmarks of Alzheimer's disease [10]. PP2A activity is tightly regulated by endogenous inhibitors and environmental factors, and its inhibition promotes activation of several tau kinases, including cyclin-dependent kinase 5 (CDK5) and glycogen synthase kinase-3β (GSK-3β), thereby accelerating tau hyperphosphorylation. Pathological tau also impairs mitochondrial function by reducing the activity of respiratory chain complexes and antioxidant defense systems, leading to decreased ATP production, impaired synaptic transmission, and progressive neuronal loss [11].

2.2 Oxidative Stress

Oxidative stress is a major contributor to Alzheimer's disease pathogenesis and results from an imbalance between reactive oxygen species (ROS) generation and antioxidant defense mechanisms. Excessive ROS activate microglia, stimulating the release of pro-inflammatory cytokines that sustain chronic neuroinflammation. Activated microglia recognize damaged neurons through purinergic receptors responding to extracellular ATP and adenosine released from injured cells, thereby amplifying inflammatory responses [12].

Neurons are particularly susceptible to oxidative damage because of their high lipid content, elevated oxygen consumption, and abundant transition metals such as iron and copper. Iron accumulated within amyloid-β plaques and neurofibrillary tangles catalyzes the conversion of hydrogen peroxide (H_2O_2) into highly reactive hydroxyl radicals (OH) through the Fenton reaction. These radicals damage proteins, nucleic acids, and membrane lipids, creating a self-perpetuating cycle of oxidative stress that further promotes amyloid aggregation and neuronal degeneration [13]. ROS also initiate lipid peroxidation of polyunsaturated fatty acids, producing highly toxic aldehydes such as 4-hydroxynonenal (4-HNE), 4-oxo-2-nonenal (4-ONE),

acrolein, and 4-oxo-2-hexenal, which impair membrane integrity and synaptic function. Elevated cholesterol levels further exacerbate oxidative injury by enhancing amyloid-β aggregation and increasing cerebral iron accumulation [14]. Oxidative stress additionally induces regulator of calcineurin 1 (RCAN1), suppressing calcineurin-mediated tau dephosphorylation and thereby promoting tau hyperphosphorylation. Mitochondrial dysfunction further amplifies ROS production, particularly within presynaptic terminals where excessive calcium influx disrupts mitochondrial respiration and accelerates synaptic degeneration [15].

Figure 3 illustrates the major oxidative stress pathways involved in Alzheimer's disease. Reactive oxygen species generated through xanthine oxidase, NAD(P)H oxidase, and mitochondrial respiratory chain activity produce superoxide and hydrogen peroxide, which undergo Fenton reactions to generate hydroxyl radicals. These highly reactive species induce DNA damage and lipid peroxidation, producing cytotoxic metabolites such as malondialdehyde and 4-hydroxynonenal that contribute to progressive neuronal injury [16].

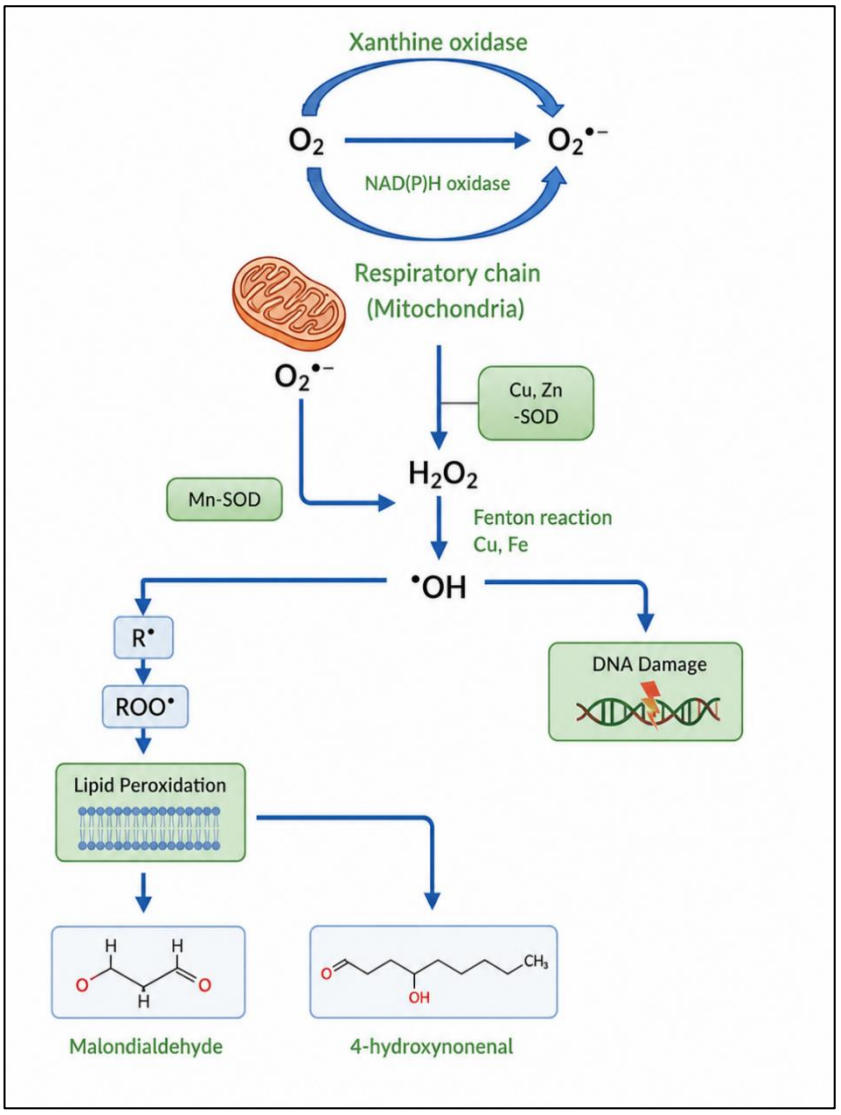


Figure 3. Oxidative stress induced damage leading to AD.

2.3 Amyloid-β Plaque Deposition

2.3.1 Production and Aggregation of Amyloid-β

Amyloid-β (Aβ) is a peptide comprising 36–43 amino acids that is generated through proteolytic cleavage of the amyloid precursor protein (APP), a single-pass transmembrane glycoprotein abundantly expressed in neuronal and non-neuronal tissues of the brain. Under pathological conditions, APP undergoes sequential cleavage by β-secretase (BACE1) and γ-secretase, resulting in the production of Aβ peptides, predominantly Aβ40 and the more aggregation-prone Aβ42 [17]. Among these isoforms, Aβ42 exhibits a greater tendency to self-aggregate because of its increased hydrophobicity and structural instability, making it the principal component of amyloid plaques. Mutations in the APP, presenilin-1 (PSEN1), and presenilin-2 (PSEN2) genes alter γ-secretase

activity and increase the Aβ42/Aβ40 ratio, thereby accelerating amyloid deposition and contributing to the development of early-onset familial Alzheimer's disease [18].

2.3.2 Plaque Formation and Oligomerization

Following their production, soluble Aβ monomers undergo conformational changes that promote self-association into oligomers, protofibrils, fibrils, and ultimately extracellular amyloid plaques, particularly within the hippocampus and cerebral cortex. Although mature plaques are considered pathological hallmarks of Alzheimer's disease, accumulating evidence suggests that soluble Aβ oligomers represent the most neurotoxic species [19]. These oligomers disrupt synaptic transmission, impair long-term potentiation, and induce excitotoxicity by interacting with neuronal receptors, including N-methyl-D-aspartate (NMDA) receptors, especially the NR2A and GluN2B subunits. Their interaction disturbs intracellular calcium homeostasis, resulting in excessive calcium influx, mitochondrial dysfunction, oxidative stress, and activation of apoptotic signaling pathways. Consequently, synaptic plasticity is progressively impaired, leading to deficits in learning, memory formation, and cognitive function [20].

Figure 4 depicts the pathological actions of amyloid-β oligomers generated through sequential β-secretase and γ-secretase cleavage of amyloid precursor protein (APP). Amyloid-β oligomers interact with NMDA, PrP^c, and Frizzled receptors, triggering oxidative stress, synaptic dysfunction, GSK-3β activation, tau aggregation, and ultimately neuronal cell death, thereby accelerating Alzheimer's disease progression [21].

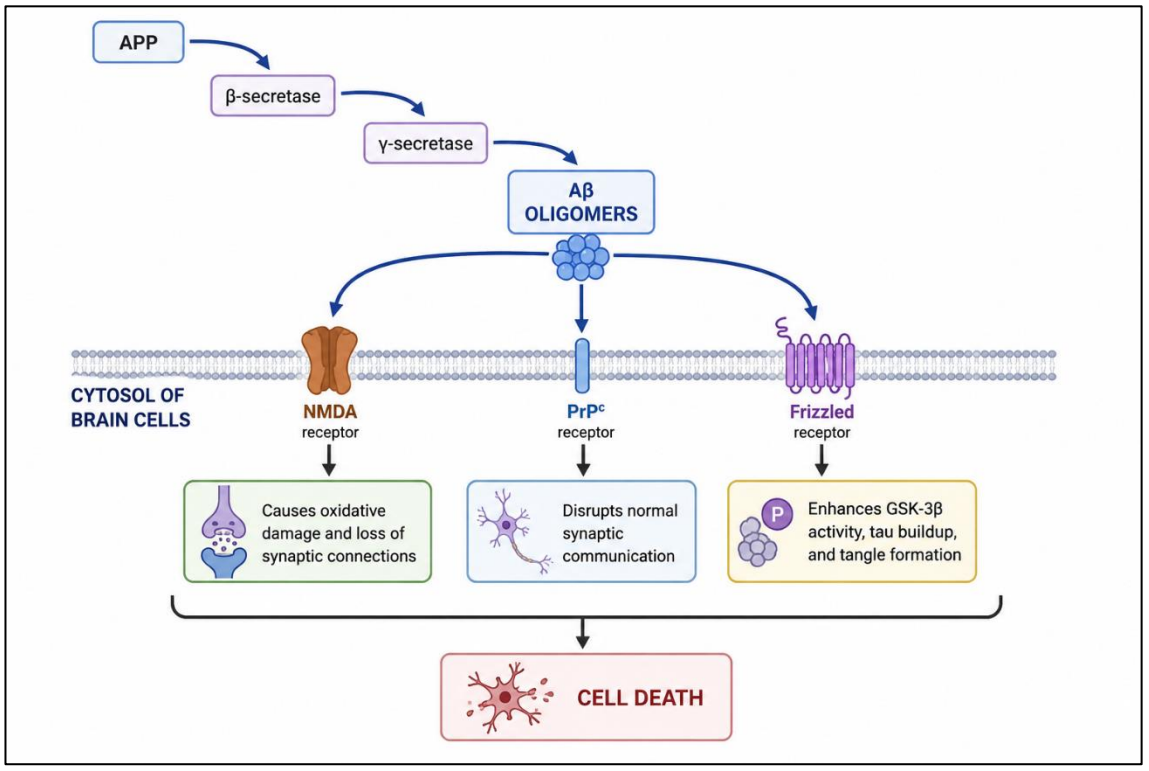


Figure 4. Abnormal effects of amyloid beta oligomers.

2.4 Role of Cholinesterase in Alzheimer's Disease

The cholinergic hypothesis remains one of the most widely accepted explanations for the cognitive impairment observed in Alzheimer's disease (AD). It proposes that progressive degeneration of cholinergic neurons in the basal forebrain leads to a marked reduction in acetylcholine (ACh) levels within the cerebral cortex and hippocampus, resulting in impaired learning, memory, and cognitive function [22]. Acetylcholine acts as a major neurotransmitter involved in attention, memory consolidation, and synaptic plasticity. It exerts its physiological effects through two classes of receptors: muscarinic acetylcholine receptors (mAChRs), which are G protein-coupled receptors mediating slow neuromodulatory responses, and nicotinic acetylcholine receptors (nAChRs), which are ligand-gated ion channels responsible for rapid synaptic transmission. Among the nicotinic receptor subtypes, the α7 nicotinic acetylcholine receptor (α7 nAChR) plays a particularly important role in regulating calcium signaling, neurotransmitter release, and cognitive processing [23].

In Alzheimer's disease, amyloid-β (Aβ) peptides

directly interact with α7 nAChRs, producing concentration-dependent effects on receptor function. At low concentrations, Aβ may transiently activate these receptors; however, prolonged exposure or higher concentrations induce receptor desensitization and internalization of Aβ–α7 nAChR complexes. This process disrupts cholinergic neurotransmission, impairs synaptic plasticity, and contributes to progressive cognitive decline [24]. Furthermore, acetylcholinesterase (AChE), the enzyme responsible for hydrolyzing acetylcholine within the synaptic cleft, exhibits additional pathological roles beyond neurotransmitter degradation. A peptide derived from the C-terminal region of AChE has been identified in increased amounts in the brains of patients with AD and has been shown to promote calcium influx, enhance amyloid precursor protein processing, increase amyloid-β production, and stimulate tau hyperphosphorylation through modulation of α7 nAChRs [25]. These findings indicate that cholinergic dysfunction not only contributes to symptomatic cognitive impairment but also actively participates in the molecular mechanisms driving Alzheimer's disease progression, making cholinesterase and cholinergic receptors attractive therapeutic targets for both symptomatic and disease-modifying interventions [26].

3. Multi-Target Directed Ligand Design Principles

The multifactorial nature of Alzheimer's disease (AD) has prompted a shift from the conventional "one drug–one target" paradigm toward the development of multi-target-directed ligands (MTDLs). Unlike single-target therapies, MTDLs are rationally designed to simultaneously modulate multiple pathological pathways involved in AD, including amyloid-β aggregation, tau hyperphosphorylation, oxidative stress, neuroinflammation, cholinergic dysfunction, and mitochondrial impairment [27]. By integrating multiple pharmacological activities into a single molecular entity, MTDLs have the potential to improve therapeutic efficacy, reduce adverse drug interactions, enhance patient compliance, and overcome the limitations associated with conventional combination therapy. Several complementary design strategies have been proposed for the discovery and optimization of these multifunctional molecules [28].

3.1 Drug Repurposing

Drug repurposing represents one of the most efficient strategies for developing MTDLs. This approach involves identifying existing drugs with established pharmacological and safety profiles and evaluating absorption, distribution, metabolism, excretion, their therapeutic potential against Alzheimer's disease [29]. Since repurposed drugs have already undergone extensive preclinical and clinical evaluation, they generally require shorter development timelines, lower research costs, and reduced regulatory risks. Furthermore, structural modification of these compounds can generate derivatives possessing additional pharmacological activities relevant to AD[1]. Despite these advantages, drug repurposing is often constrained by the limited flexibility of existing molecular scaffolds, which may restrict optimization of potency, selectivity, and multitarget activity [30].

3.2 Target-Based Design

Target-based design involves the rational combination of two or more pharmacologically active scaffolds into a single hybrid molecule capable of interacting with multiple disease-associated targets. This strategy utilizes detailed knowledge of disease biology, target protein structures, and structure–activity relationships to optimize binding affinity and therapeutic efficacy. The resulting chimeric molecules can simultaneously inhibit multiple pathological processes involved in Alzheimer's disease, thereby producing synergistic therapeutic effects [31]. In contrast to administering multiple individual drugs, a single multitarget ligand minimizes drug–drug interactions, simplifies dosing regimens, and reduces the likelihood of therapeutic resistance. Because these compounds interact with several molecular targets simultaneously, the probability of resistance developing through mutations in all target proteins is considerably lower than with single-target agents [32].

3.3 Pathological Network-Oriented Multi-Target Strategies for Alzheimer's Disease Therapy

The pathological network-oriented strategy is based on the concept that Alzheimer's disease results from complex interactions among numerous interconnected molecular pathways rather than a single pathogenic event. Consequently, effective therapy requires simultaneous modulation of several biological mechanisms involved in disease progression. This approach focuses on designing multifunctional ligands capable of targeting amyloid-β accumulation, tau hyperphosphorylation, oxidative stress, neuroinflammation, cholinergic dysfunction, mitochondrial damage, and metal ion dysregulation within a single therapeutic molecule [33]. In addition to enhancing therapeutic efficacy, network-oriented MTDLs are optimized to exhibit favorable pharmacokinetic characteristics, including improved toxicity (ADMET), and blood–brain barrier

permeability[2]. By targeting upstream pathological events before irreversible neuronal damage occurs, these multifunctional compounds hold considerable promise as disease-modifying therapies capable of slowing or preventing the progression of Alzheimer's disease [34].

4. Recent Advances in Multi-Target Directed Ligands for Alzheimer's Disease

4.1 Tacrine-Chromene Derivatives

Tacrine was the first acetylcholinesterase (AChE) inhibitor approved for the symptomatic treatment of Alzheimer's disease. Although its clinical use was discontinued because of hepatotoxicity, the tacrine scaffold remains an attractive pharmacophore for the development of multi-target-directed ligands (MTDLs) [3]. Its potent cholinesterase inhibitory activity provides an excellent foundation for designing multifunctional molecules capable of simultaneously targeting several pathological mechanisms involved in Alzheimer's disease [35].

To overcome the limitations of tacrine while improving its therapeutic profile, researchers have developed a series of tacrine–chromene hybrid molecules by replacing the benzene ring of tacrine with a chromene moiety. This structural modification introduces additional pharmacological properties, enabling simultaneous inhibition of acetylcholinesterase (AChE), β-secretase (BACE-1), monoamine oxidase-B (MAO-B), and amyloid-β (Aβ) aggregation. The chromene fragment also facilitates interaction with the peripheral anionic site (PAS) of AChE, thereby preventing Aβ fibril formation and reducing amyloid plaque deposition [36]. Consequently, tacrine–chromene hybrids combine cholinergic enhancement, anti-amyloid activity, antioxidant potential, and neuroprotective effects within a single molecular framework. These multifunctional properties make tacrine–chromene derivatives promising candidates for disease-modifying therapy, although further optimization is required to improve blood-brain barrier penetration, reduce hepatotoxicity, and establish long-term clinical safety [37].

Figure 5 illustrates the chemical structures of 7-hydroxychromene and tacrine, two pharmacophores combined to develop multi-target-directed ligands for Alzheimer's disease. The tacrine–chromene hybrid is designed to inhibit acetylcholinesterase, β-secretase, and monoamine oxidase-B while reducing amyloid-β aggregation, thereby offering enhanced neuroprotective and disease-modifying therapeutic potential [38].

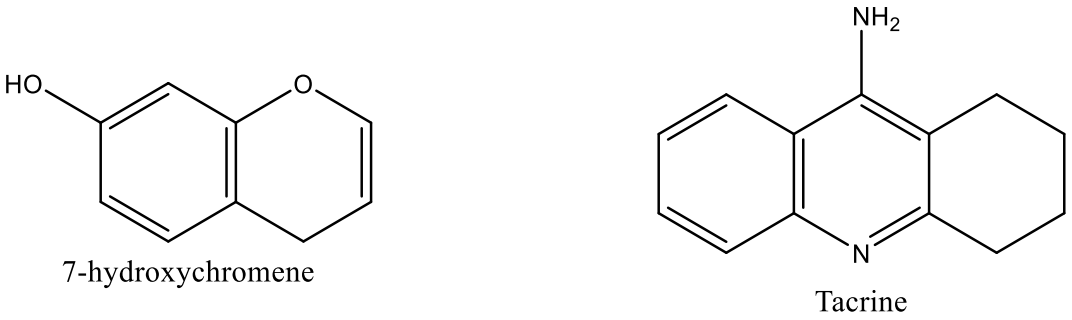


Figure 5: Chemical structures of tacrine and 7-hydroxychromene as pharmacophoric scaffolds for the development of multi-target-directed ligands against Alzheimer's disease.

Designed a series of tacrine–chromene hybrids by combining the potent cholinesterase inhibitory activity of tacrine with the multifunctional pharmacological properties of the chromene scaffold. The chromene moiety was incorporated to confer additional inhibition of β-secretase (BACE-1) and monoamine oxidase-B (MAO-B), thereby targeting multiple pathological pathways involved in Alzheimer's disease [39]. Furthermore, the aromatic chromene ring interacts with the peripheral anionic site (PAS) of acetylcholinesterase (AChE), reducing amyloid-β aggregation while simultaneously enhancing cholinergic neurotransmission. This multifunctional design highlights the therapeutic potential of tacrine-chromene hybrids as promising multi-target-directed ligands for Alzheimer's disease [40].

Figure 6 illustrates the structural design of a tacrine–chromene hybrid as a multi-target-directed ligand for Alzheimer's disease. The tacrine moiety primarily inhibits cholinesterase activity, whereas the chromene fragment interacts with the peripheral anionic site of acetylcholinesterase to suppress amyloid-β aggregation, thereby providing dual neuroprotective therapeutic effects [41].

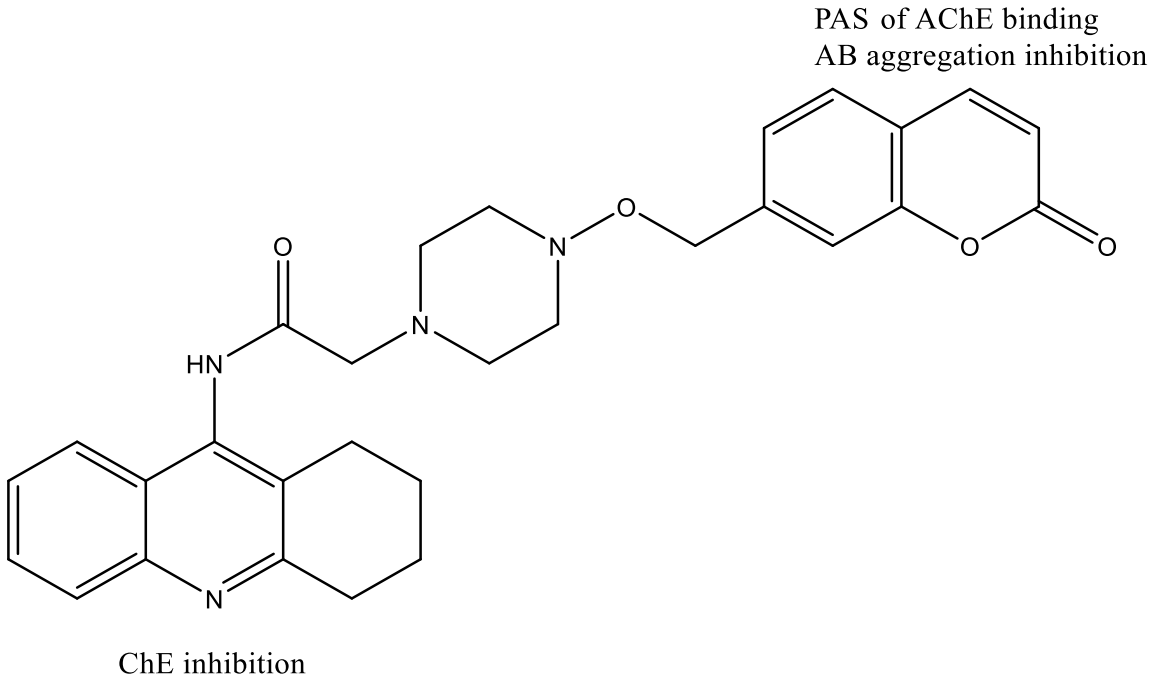


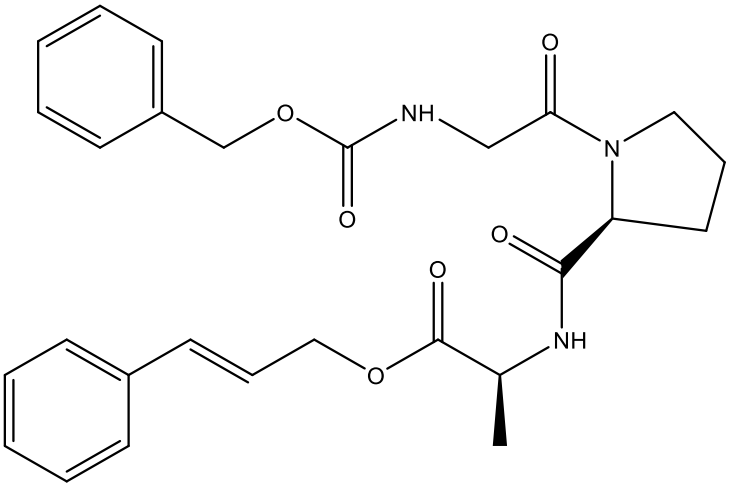
Figure 6: BACE-1, MAO-B and ChE inhibitor

4.2 GPA Tripeptide-Based Multi-Target Ligands

Peptide-based multi-target-directed ligands have emerged as promising therapeutic candidates for Alzheimer's disease because of their high target specificity, biocompatibility, and structural flexibility. However, their intrinsic polarity often limits blood–brain barrier (BBB) permeability. To address this challenge, Singh and co-authors designed a series of peptide derivatives by introducing hydrophobic moieties at both the N- and C-terminal ends to improve BBB penetration and enhance interactions with target enzymes. Proline was selected as the central scaffold because of its ability to regulate molecular flexibility and surface area, while a glycine–proline–alanine (GPA) tripeptide served as the structural backbone. Various terminal modifications were introduced to optimize the hydrophilic–hydrophobic balance and improve pharmacological properties [42].

Among the synthesized compounds, GPA-1 and GPA-2 demonstrated the most promising biological activity. Both peptides exhibited potent β-secretase (BACE1) inhibition with an ID_{50} value of 20 nM, indicating high inhibitory potency. In addition to suppressing BACE1 activity, these compounds effectively reduced amyloid-β_{42} aggregation by inhibiting the formation of β-sheet-rich fibrils. B. Kaur and co-authors reported that GPA-1 and GPA-2 reduced $A\beta_{42}$ aggregation by 54% and 34%, respectively, demonstrating significant neuroprotective potential [43]. These findings suggest that GPA-based peptide ligands represent promising multi-target-directed therapeutic candidates capable of simultaneously reducing amyloid production and aggregation while offering improved pharmacological characteristics for Alzheimer's disease treatment [44].

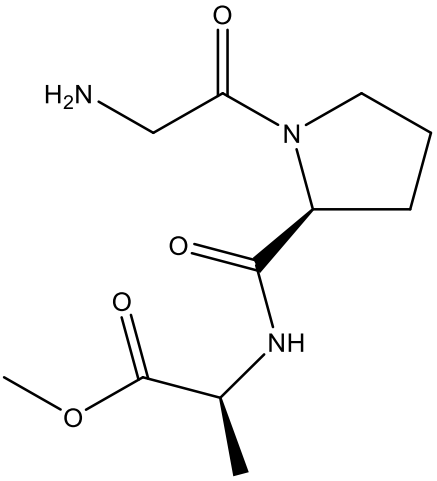
Figure 7 depicts the chemical structure of GPA-2, a peptide-based multi-target-directed ligand developed as a potential therapeutic candidate for Alzheimer's disease. GPA-2 is designed to exert dual inhibitory activity against β-secretase (BACE1) and amyloid-β (Aβ) aggregation, thereby targeting two key pathological processes involved in Alzheimer's disease progression. By inhibiting BACE1, GPA-2 may reduce the generation of neurotoxic Aβ peptides, while its anti-aggregation activity may limit the formation and accumulation of pathogenic Aβ assemblies. The optimized peptide-based scaffold further contributes to target recognition and molecular specificity, potentially enhancing its therapeutic activity. Through these complementary mechanisms, GPA-2 may help reduce amyloid-associated neuronal damage and provide neuroprotective effects. Overall, its multi-target design highlights the potential of peptide-based therapeutic strategies for addressing the complex and multifactorial pathology of Alzheimer's disease [45].



GPA-2

Figure 7: Chemical structure of the GPA-2 peptide-based multi-target-directed ligand for Alzheimer's disease.

Figure 8 illustrates the chemical structure of GPA-1, a peptide-based multi-target-directed ligand developed for Alzheimer's disease therapy. GPA-1 simultaneously inhibits β-secretase (BACE1) activity and amyloid-β aggregation while demonstrating improved blood–brain barrier permeability and neuroprotective potential, making it a promising candidate for disease-modifying therapeutic development [46].



GPA-1

Figure 8: BACE1 and Ab42 aggregation inhibitors

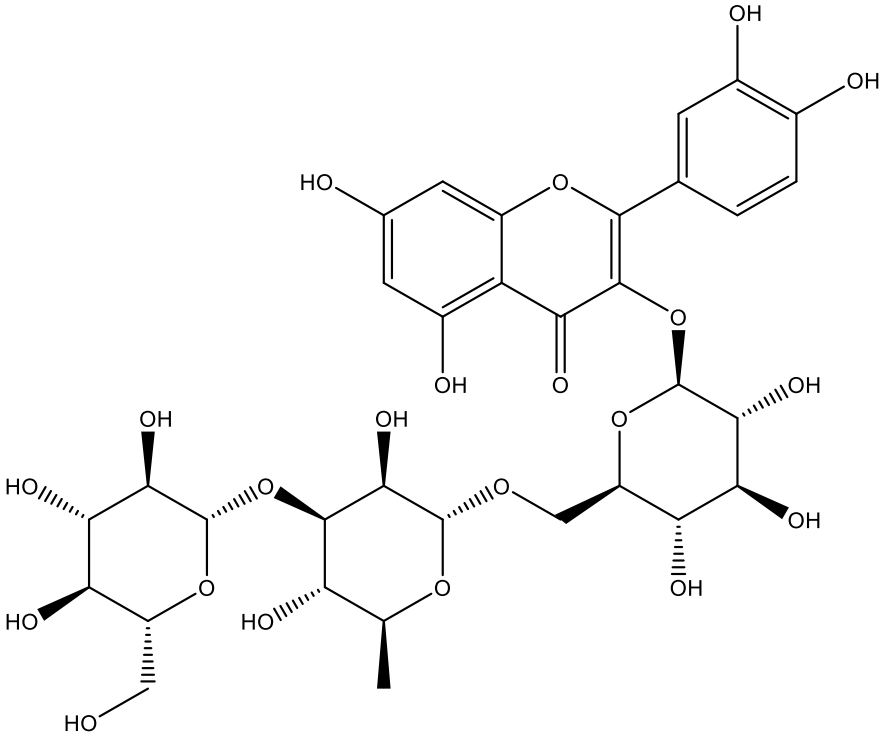
4.3 Quercetin-3-O-glc-1-3-rham-1-6-glucoside as a Multi-Target Directed Ligand

Natural flavonoids have attracted considerable attention as multi-target-directed ligands because of their ability to interact with multiple biological targets through hydrogen bonding, π–π stacking, and hydrophobic interactions. These properties enable flavonoids to modulate several pathological pathways associated with Alzheimer's disease, including amyloid-β production, oxidative stress, and neuroinflammation [47].

A natural flavonoid-carbohydrate conjugate, YCC31 (quercetin-3-O-glc-1-3-rham-1-6-glucoside), as a promising multi-target-directed ligand with potent dual inhibitory activity. YCC31 significantly reduced amyloid-β (Aβ) production in 7PA2 cells by inhibiting β-secretase (BACE1) activity [48]. Molecular interaction studies that the hydroxyl groups and ether oxygen atoms of YCC31 form multiple hydrogen bonds with key BACE1 amino acid residues, including G95, F169, R189, Y259, K285, and D289. Furthermore, the phenyl ring of YCC31 establishes CH–π interactions with T292, thereby limiting substrate accessibility to the catalytic site and reducing Aβ generation. These findings suggest that YCC31 possesses significant therapeutic potential as a multifunctional ligand capable of simultaneously

suppressing amyloid production while providing additional neuroprotective benefits for Alzheimer's disease treatment [49].

Figure 9 presents the chemical structure of YCC31, a flavonoid glycoside developed as a multi-target-directed ligand for Alzheimer's disease. YCC31 inhibits β-secretase-mediated amyloid-β production, suppresses amyloid aggregation, and reduces oxidative stress and neuroinflammation by attenuating reactive oxygen species and inflammatory cytokine production in activated microglia [50].



YCC31

Figure 9: Amyloid beta production and BACE 1 inhibitor

YCC31 also suppressed amyloid-β-induced neuroinflammation by reducing the production of reactive oxygen species (ROS) and nitric oxide (NO) in activated microglia. This dual antioxidant and anti-inflammatory activity helps attenuate oxidative stress, limits microglial activation, and protects neurons from inflammation-mediated damage, further supporting the potential of YCC31 as a promising multi-target-directed therapeutic candidate for Alzheimer's disease [51].

4.4 Multi-Target Ligands Targeting GSK-3β and Tau Aggregation

Glycogen synthase kinase-3β (GSK-3β) is one of the principal kinases responsible for tau hyperphosphorylation and plays a central role in the progression of Alzheimer's disease. Because abnormal tau phosphorylation promotes the formation of neurofibrillary tangles and neuronal degeneration, simultaneous inhibition of GSK-3β and tau aggregation has emerged as an attractive multi-target therapeutic strategy [52].

Synthesis of novel 2,4-thiazolidinedione derivatives containing five-membered heterocyclic fragments to simultaneously target GSK-3β and tau aggregation. Among the synthesized compounds, N-heterocyclic derivatives bearing indole and 5-methoxy-N-methylindole substituents demonstrated potent GSK-3β inhibition, with IC_{50} values of 4.93 μM and 0.89 μM, respectively [53]. These compounds also significantly inhibited tau aggregation, reducing β-sheet formation by 60% and 80% at a concentration of 10 μM, as determined using the Thioflavin T assay with the tau-derived peptide Ac-VQIYK-NH_2 (AcPHF6). Furthermore, both molecules exhibited favorable blood–brain barrier permeability through passive diffusion, highlighting their potential as promising multi-target-directed ligands for Alzheimer's disease therapy [54].

Figure 10 illustrates representative dual GSK-3β and tau aggregation inhibitors developed as multi-target-directed ligands for Alzheimer's disease. These compounds exhibit potent inhibition of glycogen synthase kinase-3β and effectively suppress tau aggregation, demonstrating promising neuroprotective activity and highlighting their

potential as disease-modifying therapeutic candidates for Alzheimer's disease [55].

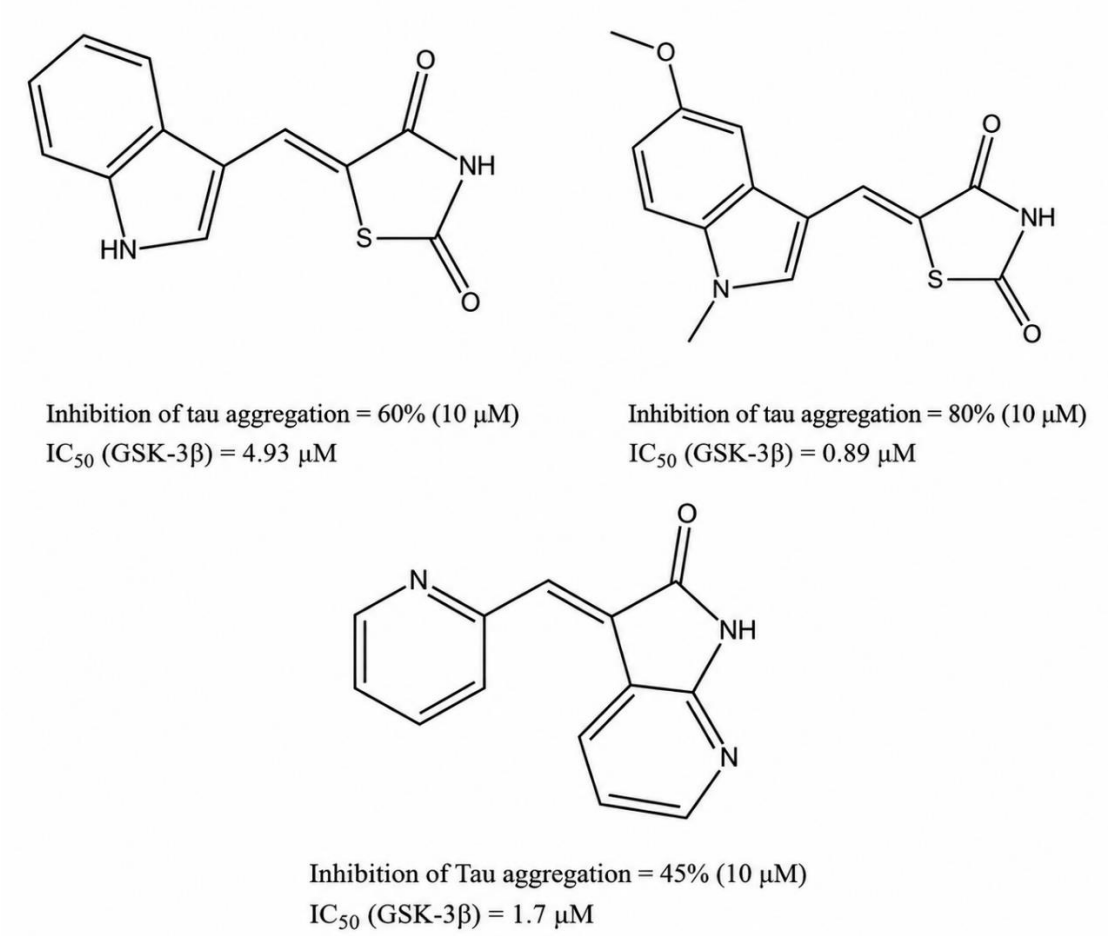


Figure 10: GSK-3β and tau aggregation inhibitor.

A series of dual GSK-3β/tau aggregation inhibitors based on a 3-arylidene-indolin-2-one scaffold has also been developed as potential multi-target-directed ligands for Alzheimer's disease. Among these, compound 7 exhibited potent GSK-3β inhibitory activity with an IC_{50} value of 1.7 μM. Furthermore, it demonstrated a dose-dependent inhibition of tau aggregation in tau^P301L-expressing HeLa cells, reducing tau aggregation by 45% at a concentration of 10 μM. These findings further support the therapeutic potential of dual GSK-3β/tau aggregation inhibitors as promising disease-modifying agents for Alzheimer's disease [56].

Table 1 highlights recent progress in the development of multi-target-directed ligands (MTDLs) for Alzheimer's disease, emphasizing compounds designed to simultaneously modulate multiple pathological mechanisms[4]. These MTDLs target cholinesterases, BACE1, amyloid-β, tau protein, oxidative stress, neuroinflammation, GSK-3β, and phosphodiesterases to achieve broader therapeutic efficacy than conventional single-target drugs [57]. The table includes hybrid molecules, natural product derivatives, peptide-based inhibitors, and synthetic scaffolds with multifunctional pharmacological activities such as cholinesterase inhibition, anti-amyloid effects, antioxidant activity, tau modulation, and cognitive enhancement. Collectively, these advances demonstrate the growing potential of MTDLs as promising disease-modifying therapeutic strategies for Alzheimer's disease [58].

Table 1: Recent advances in multi-target-directed ligands (MTDLs) for Alzheimer's disease.

S. No.	MTDL/Compound	Scaffold/Class	Major Targets	Key Pharmacological Activity	References
1.	Tacrine	Acridine derivative	AChE	Cholinesterase inhibition	[59]
2.	Tacrine-Chromene	Hybrid scaffold	AChE, BACE1, MAO-B	Anti-amyloid and	[60]

	hybrid			cholinergic activity	
3.	Tacrine-Donepezil hybrid	Hybrid scaffold	AChE, BuChE	Improved cholinesterase inhibition	[61]
4.	GPA-1	Tripeptide	BACE1, Aβ	BACE1 inhibition and anti-aggregation	[62]
5.	GPA-2	Tripeptide	BACE1, Aβ	Reduced Aβ42 aggregation	[63]
6.	YCC31	Flavonoid glycoside	BACE1, ROS	Anti-inflammatory and antioxidant	[64]
7.	Quercetin derivatives	Flavonoid	BACE1, ROS	Neuroprotection	[65]
8.	Curcumin hybrids	Polyphenol	Aβ, ROS	Anti-amyloid and antioxidant	[66]
10.	Resveratrol hybrids	Polyphenol	Aβ, Tau	Neuroprotective activity	[67]
11.	Ferulic acid hybrids	Phenolic acid	AChE, Aβ	Antioxidant and anti-amyloid	[68]
12.	Coumarin derivatives	Coumarin	MAO-B, AChE	Multifunctional inhibition	[69]
13.	Cinnamic acid hybrids	Cinnamic acid	AChE, BACE1	Anti-inflammatory and cholinergic	[70]
14.	Benzofuran derivatives	Benzofuran	AChE, ROS	Neuroprotective activity	[71]
15.	Selenium-containing hybrids	Organoselenium	Oxidative stress, AChE	Antioxidant activity	[72]
16.	Deferasirox hybrids	Triazolo-thiadiazine	Neuroinflammation, AChE	Anti-neuroinflammatory activity	[73]
17.	Thiazolidinedione derivatives	Thiazolidinedione	GSK-3β, Tau	Dual inhibition of tau pathology	[74]
18.	Indolin-2-one derivative (Compound 7)	Indolinone	GSK-3β, Tau	Tau aggregation inhibition	[75]
19.	Azaindolin-2-one derivatives	Azaindolinone	GSK-3β, Tau	Neuroprotective activity	[76]
11.	Tadalafil-derived hybrids	PDE5 inhibitor	PDE5, AChE	Improved cognition	[77]
12.	Pyrazolo-pyrimidinone-Donepezil hybrid (Compound 9)	Hybrid scaffold	PDE9A, AChE	Improved memory and BBB penetration	[78]
14.	Donepezil hybrids	Benzylpiperidine	AChE, Aβ	Cholinesterase inhibition with anti-amyloid activity	[79]
15.	Rivastigmine hybrids	Carbamate	AChE, BuChE	Dual cholinesterase inhibition	[80]
17.	Galantamine hybrids	Alkaloid	AChE, nAChR	Cognitive enhancement	[81]
18.	Multi-target flavonoid conjugates	Natural products	Aβ, ROS, Neuroinflammation	Multifunctional neuroprotection	[82]
19.	PDE/AChE dual inhibitors	Hybrid molecules	PDE5/PDE9, AChE	Enhanced synaptic plasticity and cognition	[83]

4.5 Dual Phosphodiesterase and Acetylcholinesterase Inhibitors

Building upon the therapeutic potential of phosphodiesterase (PDE) inhibition, novel multi-

target-directed ligands (MTDLs) have been developed using tadalafil, a clinically approved phosphodiesterase-5A (PDE5A) inhibitor, as the structural scaffold. These hybrid molecules were rationally designed to simultaneously inhibit phosphodiesterase-5 (PDE5) and acetylcholinesterase (AChE), thereby combining enhancement of cholinergic neurotransmission with modulation of cyclic guanosine monophosphate (cGMP)-mediated signaling pathways [84]. This dual-target strategy aims to improve cognitive function, enhance synaptic plasticity, and provide greater therapeutic efficacy than conventional single-target agents, making PDE5/AChE inhibitors promising candidates for Alzheimer's disease therapy [85].

Figure 11 presents representative dual phosphodiesterase (PDE) and cholinesterase inhibitors developed as multi-target-directed ligands for Alzheimer's disease. These compounds exhibit potent inhibition of PDE5A, PDE9A, acetylcholinesterase, and butyrylcholinesterase, thereby enhancing cholinergic neurotransmission, improving cognitive function, and offering promising disease-modifying therapeutic potential in Alzheimer's disease [86].

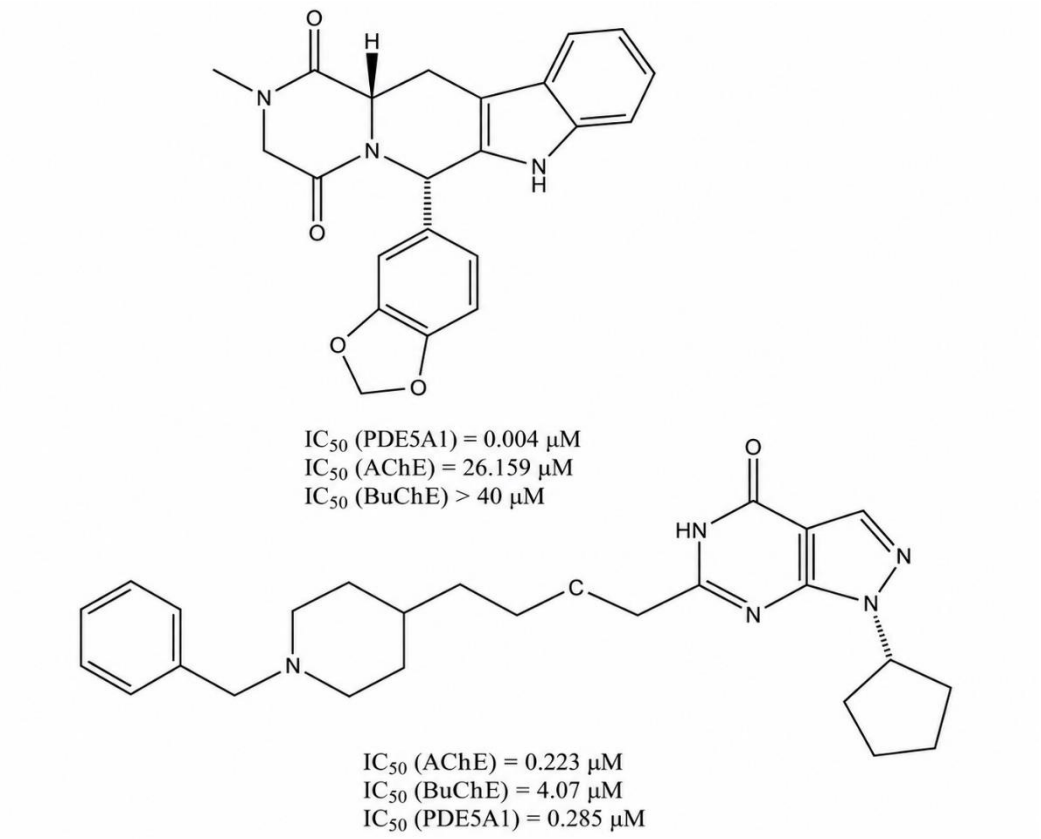


Figure 11: PDEs and AChE inhibitors.

Recent advances in multi-target-directed ligand (MTDL) development have led to the design of novel pyrazolo–pyrimidinone–donepezil hybrids that simultaneously target phosphodiesterases (PDEs) and acetylcholinesterase (AChE). These compounds were developed by integrating the pyrazolo–pyrimidinone pharmacophore of the PDE9A inhibitor C33 with the benzylpiperidine moiety of donepezil through optimized linker groups. Among the synthesized derivatives, compound 9 exhibited significant *in vivo* efficacy by improving scopolamine-induced learning deficits and enhancing cognitive and spatial memory in Aβ25-35-induced Alzheimer's disease mouse models, as demonstrated using the Morris water maze test. Furthermore, compound 9 displayed low neurotoxicity and favorable blood–brain barrier permeability, highlighting its potential as a promising multifunctional therapeutic candidate for Alzheimer's disease [87].

5. Limitations of Current Studies

Despite significant progress in the development of multi-target-directed ligands (MTDLs) for Alzheimer's disease (AD), several limitations continue to hinder their clinical translation. Most published studies remain at the *in vitro* or preclinical stage, with relatively few compounds advancing to human clinical trials. The therapeutic efficacy of many MTDLs has been demonstrated primarily in transgenic mouse models, which do not fully reproduce the complexity and heterogeneity of

human AD pathology [88]. Furthermore, considerable variation exists in experimental models, target selection, and biological evaluation methods, making direct comparison between studies difficult. Many reported compounds also lack comprehensive majority of investigations focus on amyloid-β and tau pathology while comparatively underexploring other important pathological mechanisms, including neuroinflammation, mitochondrial dysfunction, ferroptosis, gut–brain axis interactions, and synaptic repair. These limitations highlight the need for more standardized, translational, and clinically relevant research strategies [89].

6. Current Challenges

The development of effective MTDLs for AD faces several scientific and clinical challenges. Designing a single molecule capable of simultaneously modulating multiple biological targets while maintaining high selectivity remains a major medicinal chemistry challenge. Optimization of blood-brain barrier permeability without compromising systemic safety is another critical hurdle [90]. Achieving favorable pharmacokinetic properties, including adequate oral bioavailability, metabolic stability, and prolonged half-life, is often difficult because increasing molecular complexity can adversely affect drug-like characteristics. In addition, balancing multiple pharmacological activities without introducing off-target toxicity requires extensive structure–activity relationship optimization [91]. The multifactorial and heterogeneous nature of AD further complicates therapeutic development, as disease progression varies considerably among patients. The absence of reliable predictive biomarkers for patient stratification and treatment monitoring also limits clinical success. Finally, the high cost and lengthy duration of clinical trials continue to slow the translation of promising MTDLs from laboratory research to routine clinical practice [92].

7. Future Prospects

Future research should focus on developing next-generation MTDLs capable of simultaneously targeting amyloid pathology, tau hyperphosphorylation, oxidative stress, neuroinflammation, mitochondrial dysfunction, synaptic loss, and metal ion dyshomeostasis. Advances in artificial intelligence, machine learning, and computer-aided drug design are expected to accelerate the identification and optimization of novel multitarget molecules with improved efficacy and safety profiles. Structure-based drug design, molecular dynamics simulations, and multi-omics approaches may further facilitate the discovery of personalized therapeutic candidates tailored to pharmacokinetic, pharmacodynamic, and long-term toxicity evaluations [5]. Limited data are available regarding blood–brain barrier penetration, metabolic stability, and off-target effects. Additionally, the

individual disease mechanisms. Integration of nanotechnology-based drug delivery systems could significantly enhance blood-brain barrier penetration, improve targeted delivery, and reduce systemic toxicity [93]. Furthermore, combination of MTDLs with disease-modifying biologics, gene editing technologies, RNA therapeutics, and precision medicine strategies may provide synergistic therapeutic benefits. Large-scale multicenter clinical trials, standardized preclinical evaluation protocols, and biomarker-guided patient selection will be essential for translating promising MTDLs into effective disease-modifying therapies capable of delaying or preventing Alzheimer's disease progression [94].

Conclusion

Alzheimer’s disease is a multifactorial neurodegenerative disorder marked by amyloid-β aggregation, tau hyperphosphorylation, oxidative stress, cholinergic dysfunction, and metal ion dysregulation, all contributing to progressive neuronal damage and cognitive decline. Current single-target treatments, including acetylcholinesterase inhibitors and NMDA receptor antagonists, provide only symptomatic benefit and fail to stop disease progression. In this context, MTDLs have emerged as a promising therapeutic approach. They involve combining two or more pharmacophoric units within a single molecular framework, MTDLs enable simultaneous modulation of several pathological pathways implicated in AD. This approach offers clear advantages over traditional polypharmacy, including enhanced efficacy, reduced toxicity, improved pharmacokinetics, and greater patient compliance. Recent progress in rational drug design has produced diverse MTDL scaffolds, including peptide-based ligands, hybrid molecules such as tacrine–chromene derivatives, natural product-inspired flavonoid conjugates, and dual inhibitors of GSK-3β and tau aggregation. However, key challenges persist, especially in enhancing bioavailability and BBB permeability-advances in medicinal chemistry, structure-based design, and scaffold optimization are steadily paving the way toward effective next-generation anti-Alzheimer’s agents. Looking ahead, future research should emphasize refining these ligands for safety, selectivity, and clinical efficacy, with the ultimate aim of delivering disease-modifying therapies capable of slowing or halting the progression of Alzheimer’s disease.

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Conflict of Interest
The authors declare no conflict of interest.

AI Declarations
The authors declare that they used AI language tools (ChatGPT and Grammarly Premium) to enhance this manuscript's linguistic clarity and readability. They carefully reviewed and edited all generated text to ensure accuracy and alignment with the research's intended meaning.

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