Medicinal Chemistry Approaches in the Discovery of Therapeutics for Alzheimer's Disease: Progress and Perspectives

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Abstract

Amyloid-β buildup, tau hyperphosphorylation, cholinergic dysfunction, oxidative stress, and neuroinflammation are all hallmarks of Alzheimer's disease (AD), a progressive neurodegenerative illness. Recent anti-amyloid antibodies like aducanumab and lecanemab offer limited disease-modifying benefits with safety concerns, while currently approved FDA medications, such as memantine and cholinesterase inhibitors, only relieve symptoms. Through structure-based design, SAR optimization, and the creation of innovative scaffolds, medicinal chemistry is essential to the advancement of AD therapies. Designing cholinesterase inhibitors, β-/γ-secretase inhibitors, tau aggregation blockers, antioxidants, and metal chelators are important tactics. In order to address the multifactorial nature of AD, multi-target directed ligands, or MTDLs, are becoming more and more popular. Strong synthetic analogs with enhanced brain penetration are inspired by natural leads such as resveratrol, curcumin, and huperzine A. AI, pharmacophore modeling, QSAR, and docking are computational tools that speed up hit identification and optimization. Promising directions for future AD treatments are provided by developments in prodrugs, lipophilic modifications, and nanocarriers, which further improve BBB delivery.

keywords: Amyloid-beta, tau, neuroinflammation, MTDLs, BBB penetration, prodrugs, nanocarriers, docking, QSAR, pharmacophore, neuroprotection, natural products, drug delivery, and Alzheimer's disease

1. Introduction

Over 55 million people worldwide suffer from Alzheimer's disease (AD), a progressive neurodegenerative illness. Amyloid-β plaque buildup, tau protein tangles, cholinergic dysfunction, oxidative stress, and neuroinflammation are its hallmarks. These conditions cause synaptic loss, neuronal death, and severe cognitive decline, mostly in older people [1,2].

1.1. Limitations of current drugs (donepezil, memantine)

Current medications for Alzheimer's, such as memantine and donepezil, only relieve symptoms; they don't stop the disease's progression. Since they are unable to stop neuronal loss, address underlying pathology, or provide long-term efficacy, they only momentarily enhance behaviour or cognition, underscoring the need for innovative, disease-modifying treatments.

1.2. Importance of medicinal chemistry in developing new therapeutics.

The development of novel treatments for Alzheimer's disease (AD) heavily relies on medicinal chemistry [3]. Medicinal chemists can create compounds with enhanced potency, selectivity, and blood–brain barrier permeability by using structural optimization, logical drug design, and an awareness of structure–activity relationships (SAR) [4]. This field makes it possible to develop multifunctional compounds that can affect multiple pathological targets at once, including oxidative stress, tau hyperphosphorylation, amyloid-β aggregation, and cholinergic dysfunction. Medicinal chemistry offers a basis for the development of novel, disease- modifying medications to get around the drawbacks of the existing symptomatic Alzheimer's treatments by combining biological screening, synthetic chemistry, and computational modelling [5].

2. Molecular Targets in AD

Amyloid-β (Aβ) pathology is primarily caused by the aberrant cleavage of amyloid precursor protein (APP) by β- and γ-secretases, which results in the production of neurotoxic Aβ peptides that form plaques. In order to decrease Aβ generation, medicinal chemistry efforts have concentrated on creating β-secretase (BACE1) inhibitors and γ-secretase modulators; however, obtaining selectivity and minimizing side effects are still difficult tasks [6,7]. Abnormal tau protein hyperphosphorylation causes neurofibrillary tangle formation and neuronal dysfunction in tau pathology. To stabilize microtubules and stop tau-mediated toxicity, researchers are investigating tau aggregation inhibitors and kinase modulators (that target GSK-3β and CDK5) [8-10]. Abnormal tau protein hyperphosphorylation causes neurofibrillary tangle formation and neuronal dysfunction in tau pathology. To stabilize microtubules and stop tau-mediated toxicity, researchers are investigating tau aggregation inhibitors and kinase modulators (that target GSK-3β and CDK5) [11-13]. Reduced acetylcholine levels brought on by the degeneration of basal forebrain neurons cause cholinergic dysfunction, a defining feature of cognitive decline in AD. Donepezil and rivastigmine are examples of acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE) inhibitors that increase cholinergic transmission and enhance cognition [14,15]. Neurodegeneration is also made worse by chronic inflammation, metal ion imbalance, and oxidative stress. To counteract reactive oxygen species and restore metal homeostasis, medicinal chemists are creating antioxidants and metal- chelating agents (such as derivatives of 8-hydroxyquinoline). In order to address the multifactorial nature of Alzheimer's disease, anti-inflammatory scaffolds that target microglial activation are also being researched as shown in Figure **1** [16,17].

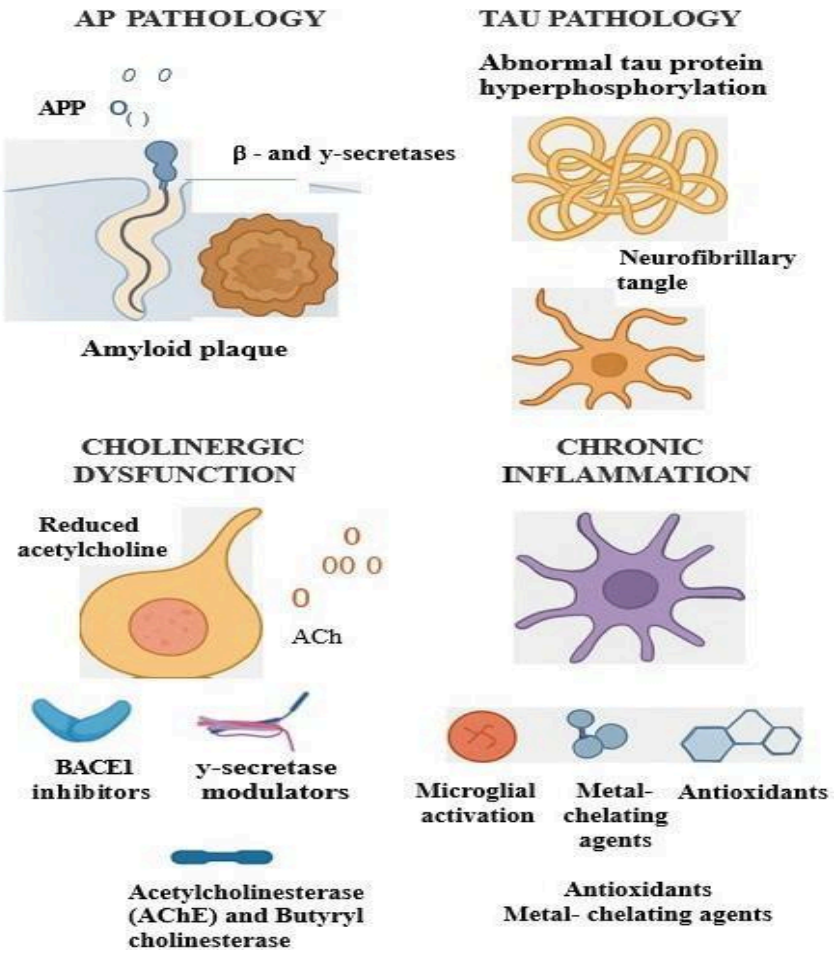

Figure 1. Molecular Targets in Alzheimer's disease.

3. FDA-Approved and Clinical Drugs

There are currently very few FDA-approved medications for Alzheimer's disease (AD), and they mostly treat symptoms rather than altering the disease. The primary classes consist of the NMDA receptor antagonist memantine, which controls glutamate-mediated excitotoxicity, and acetylcholinesterase inhibitors, which improve cholinergic neurotransmission and include donepezil, rivastigmine, and galantamine. These substances do not stop neurodegeneration, but they do provide short-term behavioural and cognitive gains [18].

3.1. Monoclonal Antibodies in Alzheimer's Disease

mAbs have become the most promising disease-modifying strategy among the therapeutic approaches created to combat Aβ pathology. mAbs provide a passive immunization-based mechanism of action that improves Aβ clearance through microglial activation, phagocytosis, and lysosomal degradation of aggregated Aβ deposits, in contrast to secretase inhibitors or anti- aggregation substances, as shown in Figure **2** [19,20].

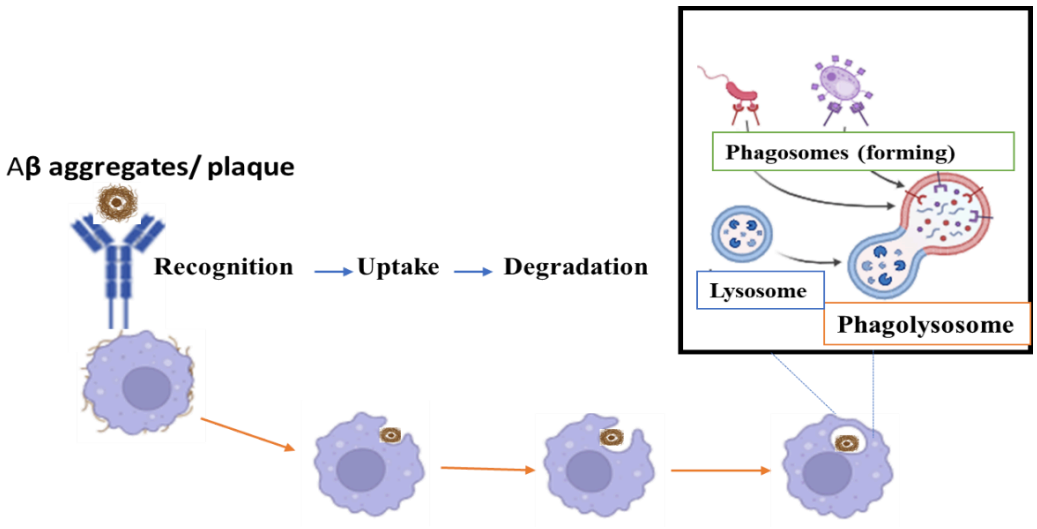

Figure 2. Monoclonal Antibodies in Alzheimer's Disease

3.2. Aducanumab

Aducanumab is a fully human IgG1 monoclonal antibody that was first isolated from elderly people who were showing only mild cognitive decline. For Aβ aggregated forms, such as fibrils and soluble oligomers, this antibody exhibits high selectivity while displaying low affinity for Aβ monomeric species [21]. On June 7, 2021, the U.S. FDA gave it accelerated approval [22].

3.3. Lecanemab

Lecanemab is a monoclonal antibody that targets soluble amyloid-β protofibrils and was approved in 2023. It can somewhat slow cognitive and functional decline in early Alzheimer's disease, according to clinical trials. It represents a significant advancement in disease-modifying therapy and is most beneficial when started in early-stage AD or mild cognitive impairment [23].

3.4. Donanemab

Other antibodies, such as donanemab, are showing encouraging amyloid-clearing and cognitive- slowing effects as they move through late-stage clinical trials. When taken as a whole, these new treatments mark a significant shift from symptomatic care to biomarker-driven, pathology- targeted interventions, underscoring the advancements made in the development of drugs for Alzheimer's disease and the possibility of more potent, disease-modifying approaches.

4. Medicinal Chemistry Approaches

Cholinesterase inhibitors work by increasing cholinergic transmission in the central nervous system; deficiencies in this transmission cause problems with memory and thought processes. Only medications from the N-methyl-D-aspartate (NMDA) antagonist group, like memantine, and the cholinesterase inhibitor group, including rivastigmine, donepezil, and galantamine, are currently approved [23]. Cholinesterase inhibitors have been developed as possible anti-AD medications by our research team. The findings of earlier research served as the foundation for this study. The most intriguing of the various series of compounds we obtained were hybrid structures containing an N-benzyl piperidine moiety, which demonstrated inhibition of both cholinesterase activities in the micromolar range [24]. There are two of them displayed

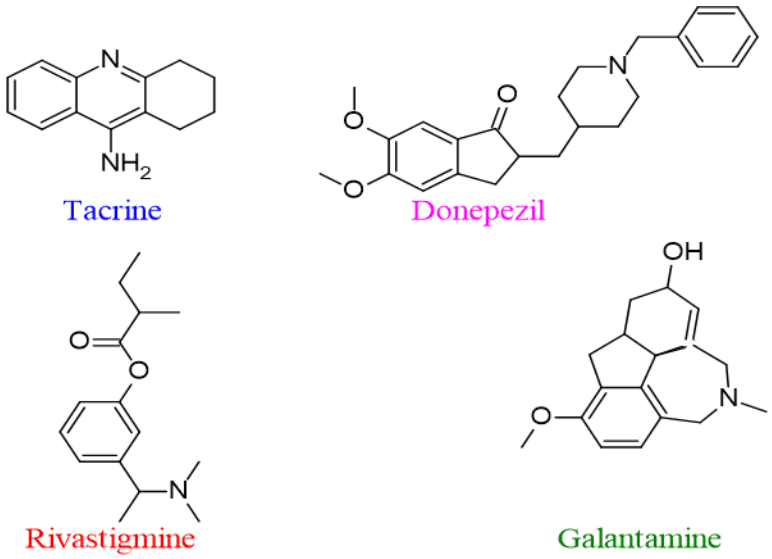

Figure 3. Inhibitors of cholinesterase are used to treat Alzheimer's disease (AD). Despite being withdrawn because of its hepatotoxicity, tacrine is still utilized as a reference inhibitor in experiments

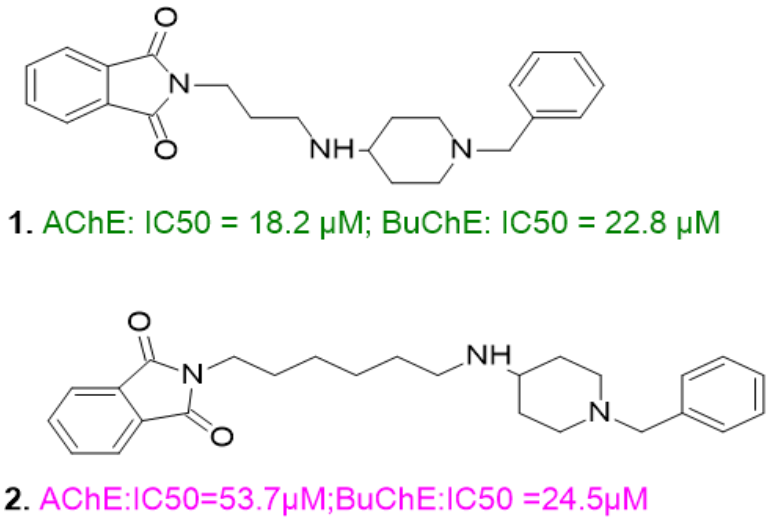

Figure 4. Compounds 1 and 2 are where our investigation began. Both of them have micromolar IC50 values and inhibit acetyl and butyryl cholinesterase.

4.1. Secretase inhibitors

By targeting BACE1 or altering γ-secretase, secretase inhibitors aim to decrease the production of amyloid-β. Transition-state mimics, increasing lipophilicity for BBB penetration, and boosting selectivity to prevent Notch-related toxicity are some strategies. Potency, safety, metabolic stability, and attaining balanced inhibition without interfering with vital physiological pathways are the main goals of optimization.

4.2. Tau aggregation blockers

Heterocycles and aromatic scaffolds are frequently used by tau aggregation blockers to prevent fibril formation by interfering with π–π interactions. Phenyl-based compounds, benzothiazoles, and quinolines all efficiently prevent tau aggregation and maintain microtubule function [26].

4.3. Multi-target directed ligands (MTDLs)

It makes sense to combine pharmacophores that act on several AD pathways to create multi- target directed ligands (MTDLs). Hybrids with enhanced overall efficacy that target cholinesterase, amyloid aggregation, oxidative stress, and metal imbalance are demonstrated in case studies [27].

5. Natural and Synthetic Compounds

By inhibiting cholinesterase, having antioxidant properties, and modifying the amyloid and tau pathways, natural leads like resveratrol, huperzine A, and curcumin have demonstrated strong neuroprotective activity. Nevertheless, a lot of natural substances have limited brain penetration, low bioavailability, and poor stability. Therefore, in order to improve potency and blood–brain barrier (BBB) permeability, medicinal chemistry concentrates on structural modification, which includes increasing lipophilicity, adding heterocycles, introducing metal-chelating groups, and improving metabolic stability. These improved synthetic analogues frequently exhibit multi- target activity and excellent pharmacokinetic characteristics, which makes them promising building blocks for the creation of potent Alzheimer's treatments [28].

6. **Computational Drug Design**

Drug discovery for Alzheimer's disease is accelerated in large part by computational drug design. For cholinesterase, secretase, and tau inhibitors, molecular docking, QSAR models, and pharmacophore modelling aid in ligand–target interaction prediction, structural feature optimization, and the identification of important binding motifs. Rapid identification of multi- target candidates is made possible by developments in AI and machine learning, which also improve virtual screening, de novo molecule generation, and ADMET prediction. These tools greatly advance medicinal chemistry efforts in Alzheimer's disease by lowering experimental workload, increasing hit-to-lead efficiency, and supporting the logical design of compounds with improved potency, selectivity, and blood–brain barrier permeability [29]

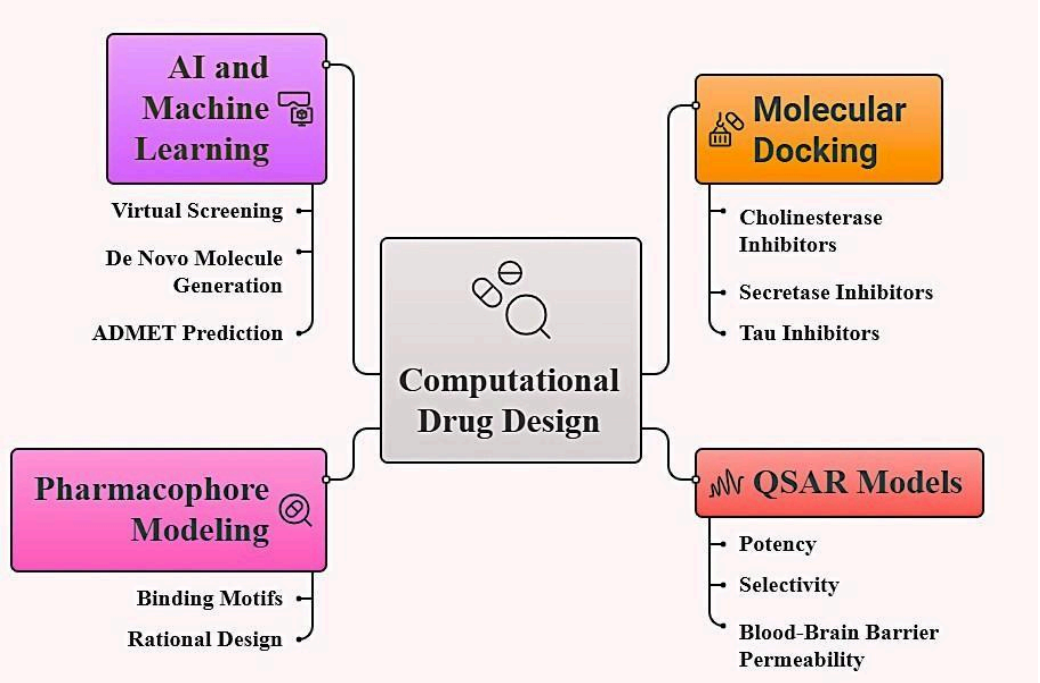

Figure 5. Computational Drug Design

7. Drug Delivery and BBB Penetration

For Alzheimer's treatment to be effective, the blood-brain barrier (BBB) must be broken down. Increasing lipophilicity, decreasing molecular weight, and optimizing pKa to favor passive diffusion are some medicinal chemistry techniques to enhance brain uptake. Transport efficiency is improved by prodrug strategies like amino acid conjugation and esterification. Brain penetration is further enhanced by incorporating P-glycoprotein evasion motifs and creating molecules that make use of carrier-mediated transport (such as glucose or amino acid transporters). When combined, these tactics improve the therapeutic effectiveness and CNS availability of Alzheimer's medication candidates [30,31].

7.1. Prodrugs, nanocarriers, lipophilic modifications

Prodrug strategies, which involve transforming inactive precursors into active drugs after they cross the blood-brain barrier and improve solubility and metabolic stability, are used in medicinal chemistry to improve CNS delivery. Liposomes, polymeric nanoparticles, and solid lipid nanoparticles are examples of nanocarriers that enable targeted brain delivery and shield medications from deterioration. Passive diffusion across the BBB is improved by lipophilic modifications, such as the addition of hydrophobic moieties or the reduction of polar surface area. When combined, these strategies greatly increase the therapeutic potential, brain absorption, and bioavailability of Alzheimer's medication candidates [32-34].

8. Emerging Directions

Targeting unknown mechanisms and incorporating cutting-edge technologies are key components of emerging directions in Alzheimer's drug discovery. Restoring the balance of gene expression associated with neurodegeneration is the goal of epigenetic modulators, such as HDAC and DNMT inhibitors. Therapeutics based on miRNA provide accurate control over the inflammatory, tau, and amyloid pathways. Precision medicine developments enable patient- specific treatment plans informed by genetic profiling and biomarkers. Furthermore, multi-target ligands, combination therapies, and AI-driven drug design are becoming more well-known and provide novel approaches to creating more potent, disease-modifying Alzheimer's treatments [35].

8.1. Precision medicine and personalized therapies

In Alzheimer's disease, precision medicine and personalized therapies place a strong emphasis on customizing care according to a patient's unique genetic variations, biomarker profiles, disease stage, and clinical phenotype. Personalized approaches increase therapeutic efficacy, improve patient stratification, and decrease side effects by combining genomics, neuroimaging, and fluid biomarkers, providing more focused and successful interventions.

9. Conclusion and Future Perspective

Alzheimer's disease is still a complicated, multifactorial illness with few available treatments, underscoring the continuous need for novel medicinal chemistry strategies. While recent developments like monoclonal antibodies and multi-target ligands offer promising but still insufficient solutions, current medications only alleviate symptoms. In order to simultaneously address the amyloid, tau, oxidative, and inflammatory pathways, future advancements will depend on combining structure-based design, computational tools, and multi-target strategies. More effective, selective, and brain-permeable candidates should be developed more quickly thanks to improved drug delivery systems, biomarker-driven patient selection, and AI-assisted discovery. The

development of successful, disease-modifying Alzheimer's treatments will depend on ongoing interdisciplinary cooperation.

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