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Exploring New Vista for Alzheimer's Disease Drug Targets-Part II

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Alzheimer's disease (AD) is a degenerative neurological condition that progressively impairs cognitive function, memory retention, and daily functioning.[1] AD is the predominant type of dementia, comprising 60–70% of the total cases among the estimated 55 million individuals affected globally.[2] AD's economic and social impact is significant, which cost the U.S. economy an estimated $321 billion in 2022 and an estimated $271 billion in unpaid caregiving responsibilities, placing a tremendous strain on healthcare systems and families. By 2050, the number of individuals affected by AD is expected to triple, bringing the total cost to over $1 trillion yearly, heightening the urgent need to develop effective therapeutic strategies. Despite extensive research efforts, developing effective treatments remains challenging as AD is a complex neurodegenerative disease with multifactorial underlying pathological mechanisms, such as the formation of amyloid-beta (Aβ) plaques and neurofibrillary tangles, which has made it difficult to find efficacious targeted therapies.[3–4] Significant progress has been made in recent years, with researchers making remarkable strides in comprehending the molecular intricacies underlying AD. This enhanced understanding has paved the way for the discovery of novel therapeutic targets, offering promising prospects for the development of effective treatments. FDA-approved cholinesterase inhibitors, like Galantamine (Razadyne®), Rivastigmine (Exelon®), and Donepezil (Aricept®), result in higher concentrations of acetylcholine, leading to increased communication between nerve cells, which in turn, temporarily improve or stabilize the symptoms of mild to moderate AD.[5] Lecanemab (Lequembi®) and Aducanumab (Aduhelm®) received approval through the Accelerated Approval pathway, a regulatory process that allows the FDA to grant approval for drugs targeting severe conditions with unmet medical needs. These drugs demonstrated an impact on a surrogate endpoint that reasonably predicts clinical benefits for patients.[6] Support for the Accelerated Approval of Leqembi and Aducanumab are based on their observed reduction of Aβ plaque.[7] At present, the FDA has approved Memantine (Namenda®) as the sole medication for treating symptoms associated with moderate to severe stages of AD.[8] Memantine functions as an

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CONFLICT OF INTEREST

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antagonist of the NMDA (N-Methyl-D-Aspartate) receptor subtype of glutamate receptors, reducing the accumulation of glutamate in the brain that can lead to neuronal death.[9] Other emerging approaches include immunotherapy and tau proteins, as well as exploring the role of inflammation, synaptic dysfunction, and vascular factors in disease progression.[10–11] Additionally, advancements in diagnostic techniques, such as biomarkers and neuroimaging, have improved early disease detection and monitoring.[12–13] Although significant challenges remain, these new developments provide hope for future breakthroughs in preventing and treating AD.

This Current Topics in Medicinal Chemistry issue features a comprehensive review of the anti-Alzheimer's potential of herbal remedies and heterocyclic derivatives, highlighting recent advancements and future therapeutic directions. The issue begins with a comprehensive review by experts in the field, summarizing the literature reports on the anti-Alzheimer's potential of heterocyclic derivatives.[14] It illuminates the recent advancements in the medicinal chemistry of heterocyclic compounds and the progress made in understanding the role of heterocyclic compounds as potential agents for treating and managing AD. Correlations between heterocyclic compounds' structure-activity relationship (SAR) and their pharmacological responses are also discussed. Including investigating the molecular interactions, mechanisms of action, and *in silico* studies that contribute to understanding how specific structural features of heterocyclic derivatives affect their therapeutic efficacy in Alzheimer's disease. By exploring the SAR and pharmacological responses, the review aims to provide valuable insights and ideas for designing and developing novel lead molecules with enhanced therapeutic properties for Alzheimer's disease. Another review in this issue explores the acridine scaffold as a promising framework for the development of anti-Alzheimer's drugs.[15] This review explores the therapeutic potential of acridine derivatives, emphasizing their ability to target multiple pathways implicated in AD pathogenesis. Notably, these derivatives have shown activity against key enzymes such as acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE), which are involved in the breakdown of acetylcholine, a neurotransmitter crucial for memory and cognition. Additionally, the review highlights their interactions with dual specificity tyrosine kinase 1A (Dyrk1A) and Aβ and prion proteins, which play significant roles in forming plaques and neurofibrillary tangles.[16] Within the field of acridine derivatives, this review underscores this versatile framework's potential for designing novel multi-target inhibitors for AD. However, it acknowledges that further research is necessary to evaluate the effectiveness of acridine derivatives with various substitutions in the treatment of AD. A third review delves into the potential of plants from the genus *Mahonia,* used in Traditional Chinese Medicine (TCM) for preventing and treating AD.[17] TCM and herbal treatments have a long history of improving symptoms of aging-associated conditions by targeting multiple underlying mechanisms associated with a disease.[18] In this context, *Mahonia* emerges as a potential candidate for the treatment of AD. The anti-inflammatory activity of these plants can help reduce neuroinflammation, a common feature of AD. Additionally, their antioxidant properties can counteract oxidative stress, a key contributor to neuronal damage in AD. The inhibition of acetylcholinesterase activity can enhance cholinergic neurotransmission, while the ability to target Aβ can potentially prevent the accumulation of amyloid plaques. The multifaceted nature of their therapeutic properties, combined with their long-standing use

in TCM, suggests that these plants hold promise as an alternative therapeutic approach for AD, potentially offering new avenues for disease management and intervention. The fourth review highlights piperidine as a promising scaffold for developing drugs targeting AD.[19] Piperidine derivatives have demonstrated significant pharmacological properties against AD, and the review provides a comprehensive overview of the advancements in this field. It explores the SAR and presents the promising activities these piperidine-based scaffolds exhibit. This valuable information serves as a solid foundation for future research and the development of innovative therapies for AD, ultimately offering hope for improved treatment options for patients affected by this devastating neurodegenerative disease.

As the Guest Editors, we would like to thank all the authors for their tremendous effort, dedication, and excellent contribution to this special issue of *Current Topics in Medicinal Chemistry*. This issue provides an exciting collection of reviews focusing on recent advances in the development of nitrogen-containing heterocyclic anti-Alzheimer's agents as well as the potential of natural sources of inspiration. These contributions will serve as valuable references for medicinal chemists, chemical biologists, and researchers dedicated to the discovery and development of effective drugs to combat this challenging neurodegenerative disease.

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Biographies

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