ejpmr, 2024, 11(4), 96-102

SJIF Impact Factor 7.065

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

BENZAMIDE DERIVATIVES: A MULTIFACETED APPROACH TO TARGETING ALZHEIMER'S DISEASE PATHOLOGY

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Article Received on 14/02/2024 **Article Revised on 04/03/2024** **Article Accepted on 24/03/2024**

ABSTRACT

Alzheimer's disease (AD) remains a prominent neurodegenerative disorder characterized by progressive cognitive decline, memory loss, and behavioral changes. Pathologically, AD is marked by the presence of beta-amyloid plaques and neurofibrillary tangles in the brain, leading to synaptic and neuronal loss. Various hypotheses have been proposed to elucidate the underlying mechanisms of AD, including the Tau Hypothesis, Cholinergic Hypothesis, Amyloid Cascade Hypothesis, Mitochondrial Cascade Hypothesis, and Inflammation Hypothesis. These hypotheses provide insights into different aspects of AD pathology, ranging from protein aggregation to neurotransmitter dysregulation and inflammatory processes. In the search for effective treatments, numerous drug targets have been identified, including Aβ and Tau proteins, enzymes involved in Aβ production (BACE-1, γ-secretase), cholinergic pathways, serotonin receptors, and neuro-inflammatory pathways. Despite significant research efforts, developing effective therapies for AD remains challenging. Benzamide derivatives have emerged as potential candidates for AD treatment, with studies exploring their role as cholinesterase inhibitors, modulators of Aβ biosynthesis enzymes, inhibitors of tau aggregation, and antioxidants. These compounds offer a multifaceted approach to addressing different aspects of AD pathology, including enhancing cholinergic neurotransmission, reducing Aβ production, and mitigating oxidative stress and neuroinflammation. In conclusion, understanding the complex pathophysiology of AD and exploring novel therapeutic strategies, such as benzamide derivatives, holds promise for the development of effective treatments to alleviate the burden of this devastating disease. Further research is needed to fully elucidate the efficacy and safety of these compounds in clinical settings.

KEYWORDS: Alzheimer's disease (AD), Amyloid-beta peptide (Aβ), Tau Protein, Benzamide derivatives, Drug Targeting.

INTRODUCTION

Alzheimer's disease (AD) stands as the most prevalent form of dementia. It is named after the German psychiatrist Alois Alzheimer. It is characterized as a gradually advancing neurodegenerative disorder marked by the presence of neuritic plaques and neurofibrillary tangles. This pathology results from the accumulation of amyloid-beta peptide (Aβ) in the brain's most affected regions, namely the medial temporal lobe and neocortical structures.[1]

During his examination of the brain of his initial patient experiencing memory loss and personality changes, Alois Alzheimer observed the existence of amyloid plaques and a substantial neuronal loss. Describing the condition as a severe cerebral cortex disease, he laid the foundation for its understanding. It was in his 8th edition psychiatry handbook that Emil Kraepelin first coined the term "Alzheimer's disease" to characterize this medical condition.[2,3]

The progressive decline in cognitive functions can stem from cerebral disorders like Alzheimer's disease (AD) or various other factors, including intoxications, infections, abnormalities in pulmonary and circulatory systems leading to reduced oxygen supply to the brain, nutritional deficiencies, vitamin B12 deficiency, tumors, and other potential causes.[4,5]

Alzheimer's disease (AD) constitutes a form of dementia characterized by the distortion of memory, thinking, and behavior. Typically, symptoms manifest gradually and deteriorate over time, reaching a severity that disrupts daily life activities. An early sign often involves difficulty in recalling recent events, and the disease predominantly affects individuals in old age, typically beginning at 60 years or above.[6]

AD is marked by two pathological hallmarks

- Extracellular beta-amyloid deposits
- Intracellular neurofibrillary tangles.

These changes contribute to the loss of synapses and neurons, leading to significant atrophy in affected areas of the brain. The mechanisms underlying the formation of beta-amyloid peptides and neurofibrillary tangles remain incompletely understood, with various theories currently under investigation.

Two prominent theories concerning AD are the amyloid hypothesis and tau hypothesis. These theories aim to elucidate the processes that lead to the formation of beta-amyloid peptides and neurofibrillary tangles, providing critical insights into the understanding of Alzheimer's disease.[7]

HYPOTHESES POSTULATED RELATED TO ALZHEIMER'S DISEASE

1. The Tau Hypothesis of Alzheimer's disease

The pathophysiology of Alzheimer's disease (AD) is significantly influenced by the tau protein. Central to the tau hypothesis is an emphasis on the microtubule-binding tau protein, a key constituent of neurofibrillary tangles (NFTs) in AD. The hyperphosphorylation of the tau protein is implicated in the formation of NFTs. This hypothesis puts forth a mechanism for neurotoxicity rooted in the loss of the stabilizing effect of the microtubule-associated tau protein, ultimately leading to cytoskeletal degradation.[8]

Majority of research groups support the alternative hypothesis that amyloid-β is the primary causative agent for AD.

2. The Cholinergic Hypothesis of Alzheimer's Disease

The cholinergic hypothesis, dating back over 30 years and regarded as the oldest Alzheimer's disease (AD) hypothesis, posits that a diminished synthesis of the neurotransmitter acetylcholine in neurons is the underlying cause of AD. This theory suggests that the dysfunction of acetylcholine-containing neurons in the basal forebrain significantly contributes to the cognitive decline observed in individuals with AD.

Beyond the dysfunction and neuronal loss observed in basal forebrain regions, evidence supporting cholinergic deficits is derived from studies reporting declines in the activity of acetylcholinesterase (AChE) and choline acetyltransferase (ChAT), diminished release of acetylcholine (ACh), and reduced levels of nicotinic and muscarinic receptors in the Alzheimer's disease (AD)-affected brain. This collection of findings prompted the development of the cholinergic hypothesis, recognized as the oldest hypothesis in AD research.[9,10]

3. Amyloid Cascade Hypothesis

The primary characteristic of Alzheimer's disease (AD) pathology is acknowledged to be the presence of amyloid plaques. Identified as the primary constituent of senile plaques, Aβ peptide is generated through the proteolytic processing of the amyloid-β protein precursor (AβPP) by β- and γ-secretases. Moreover, the cloning of the AβPP gene[35] has permitted the examination of the disease at molecular and biochemical levels. Subsequent mapping of mutations in the AβPP gene associated with familial forms of AD (fAD), the link between AD and Down's syndrome, and the increased prevalence of AD with elevated AβPP quantities have collectively underscored the pivotal role of AβPP in the pathogenesis of AD. Although the exact cause of AD is still a matter of debate, the amyloid cascade hypothesis is the best accepted and most studied hypothesis.[11,12]

4. The Mitochondrial Cascade Hypothesis

Swerdlow and Khan initially proposed the mitochondrial cascade hypothesis in 2004, suggesting that mitochondrial dysfunction serves as the primary instigator of Aβ deposition, neurofibrillary tangle (NFT) formation, and synaptic degeneration in Alzheimer's disease (AD).[13] This hypothesis takes several conceptual leaps, positing that common physiological mechanisms underlie both AD and brain aging. It argues that AD-related mitochondrial dysfunction is not merely a consequence of neurodegeneration because it is systemic in nature. Additionally, the hypothesis contends that non-Mendelian genetic factors play a role in no autosomal dominant AD. Furthermore, it asserts that mitochondrial dysfunction in the brain is a driving force behind amyloidosis, tau phosphorylation, and cell cycle re-entry.[14]

Mitochondrial dysfunction has been observed in various AD tissues, including platelets, fibroblasts, mitochondria, and the brain. Specifically, three mitochondrial enzymes exhibit defects, with reduced activities noted in the α-ketoglutarate dehydrogenase complex, cytochrome oxidase, and pyruvate dehydrogenase complex. Special analysis of AD brains reveals that the level of cytochrome oxidase is normal, but the enzyme itself undergoes structural alterations. Oxidative stress and proteasome dysfunction are hypothesized to facilitate mitochondrial dysfunction in AD. Additionally, studies on cytoplasmic hybrids (cybrids) suggest that mitochondrial DNA (mtDNA) at least partially accounts for the reduced cytochrome oxidase activity observed in AD.[14,15]

5. Inflammation Hypothesis

Reactive gliosis and neuroinflammation are distinctive features of Alzheimer's disease (AD). Recent genetic and transcriptomic studies have highlighted the pivotal role of microglia-related pathways in AD risk and pathogenesis.[16] Growing evidence underscores the significance of microglia as key contributors in AD. In the initial stages, microglia, along with TREM2 and the

complement system, play a crucial role in synaptic pruning.[17]

Recent progress in comprehending the mechanisms that contribute to microglial dysfunction in processes like pruning, plasticity regulation, and neurogenesis is creating new prospects for therapeutic interventions and diagnostics in Alzheimer's disease (AD). Exploring ways to address these irregular microglial functions and restore homeostasis could offer innovative approaches to AD therapies. Nevertheless, considering the intricate and varied functions of microglia in both health and disease, the development of new biomarkers that accurately reflect the functionality of specific microglial subtypes is imperative.[18,19]

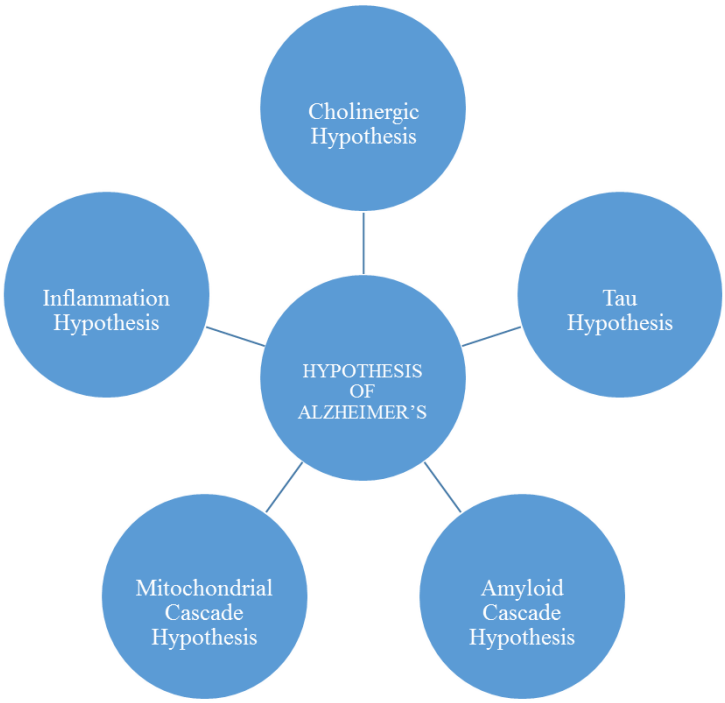

Fig. 1: Hypothesis of Alzheimer's.

POTENTIAL TARGET FOR DRUG DESIGN

1. Aβ and tau protein

The primary therapeutic targets investigated for Alzheimer's disease (AD) were either directly or indirectly associated with neurofibrillary tangles (tau protein) and senile plaques (Aβ protein). However, only aducanumab, an anti-Aβ antibody, received approval.[20]

The Aβ and tau proteins emerge as key drug targets, intricately linked to the pathogenesis of Alzheimer's disease (AD). The cleavage of amyloid precursor protein (APP) by β-secretases (BACE-1) or γ-secretases leads to the formation of insoluble Aβ protein, a distinctive hallmark of AD. Consequently, the therapeutic strategy revolves around chemically dismantling and degrading amyloid plaques or engaging microglia to activate phagocytosis. This approach aims to halt or reverse the neuronal damage triggered by the accumulation of these proteins.[21, 22]

2. BACE-1 and γ-secretases

Additional crucial targets associated with Alzheimer's disease (AD) pathogenesis include BACE-1 and γ-secretases, given their role in the development of Aβ, as discussed earlier in this study. Unfortunately, numerous studies on inhibitors for these enzymes were halted due to lack of efficacy and toxicity, which included cognitive impairment. Notably, severe toxicity was particularly prevalent in γ-secretase inhibitors, suggesting that inhibiting this enzyme cannot be safely accomplished due to its physiological impact on the Notch pathway.[23]

3. Cholinergic pathways

In accordance with the cholinergic hypothesis, Alzheimer's disease (AD) is associated with a decline in acetylcholine levels. Consequently, the most common pharmacologic approach for AD involves augmenting cholinergic pathways through the inhibition of acetylcholinesterase (IAch).[24]

A new strategy within the cholinergic framework for Alzheimer's disease involves adjusting α7 nicotinic receptors (nAChRs), which play a vital role in learning, memory, and executive function in the hippocampus and prefrontal cortex. Focusing specifically on α7 nAChR modulation, as opposed to the broader impact on all cholinergic receptors seen in acetylcholinesterase inhibition (IAch) drugs, is anticipated to decrease toxicity.[25]

4. 5-HT receptors

Serotonin receptors emerged as targets in cognitive impairment and AD. Serotonin receptors, including subtypes like 5-HT1A, 5-HT2A, and others, are widely distributed in the brain and are involved in various cognitive processes. In AD, alterations in the function of these receptors have been observed, contributing to cognitive decline and neuropsychiatric symptoms such as depression and agitation.

In this context, the serotonin receptors 5-HT6R and 5-HT7R have garnered significant attention for their thorough examination, primarily attributed to their prevalent distribution in the brain and notable cognitive characteristics observed in vivo.[26]

5. Neuroinflammation

Persistent inflammation in the brain represents another characteristic pathology of Alzheimer's disease (AD). The onset of neuroinflammation occurs as a response to the activation of glial cells by the neural environment or neuronal injury. Specifically, the signaling of tumor necrosis factor-α (TNF-α) assumes a pivotal role in this process, correlating with neuronal excitotoxicity, the loss of synapses, and the amplification of the inflammatory state. Additionally, TNF-α signaling contributes to the exacerbation of amyloidogenesis, leading to an increase in BACE-1 expression.[27,28]

BENZAMIDE DERIVATIVES IN ALZHEIMER'S

Benzamide is an organic compound identified by the chemical formula C_7H_7NO. It stands as the most basic amide derivative of benzoic acid. When in a powdered state, it presents as a white solid, while in its crystalline form, it manifests as colorless crystals. Its solubility characteristics include being slightly soluble in water and soluble in various organic solvents.

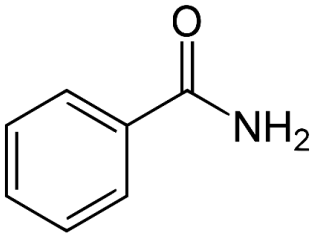

Fig. 2: Benzamide.

Table 1: Benzamide substituted commercial drugs.

CATEGORY	DRUGS
ANALGESICS	Ethenzamide, Salicylamide, Salverine, Procainamide
PROKINETICS/ ANTI-EMETICS	Batanopride, Bromopride, Cinitapride, Cisapride, Clebopride, Dazopride, Itopride, Metoclopramide, Mosapride
ANTI PSYCHOTICS	Azapride, Amisulpride, Levosulpiride, Nemonapride, Remoxipride, Sulpiride, Sultopride, Tiapride
ANTI DEPRASSANTS	Moclobemide
OTHERS	3-Aminobenzamide, Aminohippuric acid, Chidamide, Denipride, Entinostat, Eticlopride, Amatinib, Mocetinostat, Procarbazine

BENZAMIDE DERIVATIVES AS CHOLINESTERASE INHIBITORS

Benzamide derivatives have been explored for their potential as cholinesterase inhibitors, particularly in the context of Alzheimer's disease and related neurological conditions. Cholinesterase inhibitors are a class of compounds that target enzymes involved in the breakdown of acetylcholine, a neurotransmitter essential for cognitive function. By inhibiting these enzymes, cholinesterase inhibitors can increase acetylcholine levels in the brain, potentially improving cognitive function and alleviating symptoms in conditions like Alzheimer's disease.[29]

Some benzamide derivatives have shown promising inhibitory activity against cholinesterase enzymes, such as acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE). These enzymes are involved in the degradation of acetylcholine, and their inhibition can lead to increased acetylcholine levels in the synaptic cleft, enhancing cholinergic neurotransmission.[30]

The structure-activity relationship (SAR) studies of benzamide derivatives have helped in understanding the key structural features required for potent cholinesterase inhibition. Substituents on the benzamide scaffold, such as aromatic rings, alkyl groups, or other functional groups, can significantly influence the inhibitory activity.[30,31]

Researchers have synthesized various benzamide derivatives and evaluated their inhibitory potency against cholinesterase enzymes using in vitro assays. Computational modeling techniques have also been employed to predict the binding interactions between benzamide derivatives and the active sites of cholinesterase enzymes, providing valuable insights into their mechanism of action.[30,31]

Overall, benzamide derivatives hold promise as potential cholinesterase inhibitors, and further research in this area may lead to the development of novel therapeutic agents for neurodegenerative disorders like Alzheimer's disease.

BENZAMIDE DERIVATIVES DESIGNED TO TARGET ENZYMES INVOLVED IN AMYLOID- β BIOSYNTHESIS

Aβ is a peptide that plays a central role in the pathogenesis of Alzheimer's disease, and targeting enzymes involved in its production is a promising strategy for developing therapeutic interventions, where abnormal accumulation and aggregation of Aβ contribute to neuronal damage and cognitive decline. Benzamide derivatives have been investigated for their potential to target enzymes involved in amyloid-β biosynthesis, primarily in the context of Alzheimer's disease research.[32,33]

- **β-Secretase (BACE-1):** BACE-1 is an enzyme involved in the cleavage of amyloid precursor protein (APP), leading to the production of Aβ peptides. Inhibition of BACE-1 can reduce Aβ levels and is a major focus of drug development efforts.

- **γ-Secretase:** This enzyme complex is responsible for further cleaving the C-terminal fragment generated by BACE-1 cleavage, resulting in the release of various forms of Aβ peptides, including the pathogenic Aβ42 isoform.

BENZAMIDE COMPOUNDS DESIGNED FOR TAU AGGREGATION INHIBITION

Benzamide compounds have been explored for their potential in inhibiting tau protein aggregation, which is a hallmark of several neurodegenerative diseases, including Alzheimer's disease. Tau aggregation leads to the formation of neurofibrillary tangles, contributing to neuronal dysfunction and cell death.[32]

Methylene Blue is a well-known dye that has shown potential in inhibiting tau aggregation. Researchers have modified the MB scaffold to create benzamide derivatives with enhanced blood-brain barrier penetration and improved tau binding affinity. To target tau aggregation in the brain effectively, benzamide compounds with enhanced blood-brain barrier (BBB) penetration have been designed. These compounds are optimized to cross the BBB and exert their inhibitory effects on tau aggregation within the central nervous system.[34]

BENZAMIDE DERIVATIVES AS GLUTAMINYL CYCLASE INHIBITORS

Benzamide derivatives have indeed been investigated as potential inhibitors of glutaminyl cyclase (QC) in the context of Alzheimer's disease and related neurodegenerative disorders. Glutaminyl cyclase is an enzyme involved in the formation of pyroglutamate-modified amyloid-β peptides (pGlu-Aβ), which are known to be more neurotoxic and resistant to degradation compared to non-modified Aβ peptides. Targeting glutaminyl cyclase with inhibitors, including benzamide derivatives, is a strategy aimed at reducing the production of these toxic forms of Aβ.[35]

Glutaminyl cyclase catalyzes the conversion of N-terminal glutamate or glutamine residues into pyroglutamate in various peptides, including amyloid-β. Pyroglutamate-modified Aβ peptides are more prone to aggregation, exhibit increased neurotoxicity, and are resistant to degradation, contributing to the progression of Alzheimer's disease pathology.[36]

BENZAMIDE DERIVATIVES AS ANTIOXIDANTS

Benzamide derivatives have been explored for their potential as antioxidants in Alzheimer's disease (AD) due to their ability to scavenge reactive oxygen species (ROS) and mitigate oxidative stress, which is implicated in the pathogenesis of AD. Oxidative stress leads to neuronal damage and contributes to the progression of AD.

Several studies have investigated the antioxidant properties of benzamide derivatives and their potential therapeutic effects in Alzheimer's disease. Some benzamide derivatives exhibit anti-inflammatory properties, which can further contribute to their neuroprotective effects in AD. Inflammation is closely linked to oxidative stress in the brain, and reducing inflammation can help mitigate neuronal damage. Some benzamide derivatives have been shown to improve cognitive function in animal models of Alzheimer's disease. This improvement may be attributed to their antioxidant and neuroprotective effects, which help preserve synaptic function and neuronal integrity.[37]

Benzamide derivatives also demonstrated neuroprotective effects in various in vitro and in vivo models of AD. By scavenging ROS and reducing oxidative stress, these compounds can help preserve neuronal function and prevent neurodegeneration.[38]

BENZAMIDE DERIVATIVES IN 5-HT RECEPTORS

Benzamide derivatives targeting 5-HT receptors in AD offer a promising therapeutic approach. These compounds may act as agonists or antagonists, modulating the activity of serotonin receptors to restore neurotransmitter balance, improve cognitive function, and alleviate mood disturbances associated with AD. While preclinical studies provide valuable insights, clinical trials are necessary to evaluate the safety and efficacy of benzamide derivatives in humans with Alzheimer's disease. These trials would assess parameters such as cognitive function, mood, and overall disease progression in AD patients treated with benzamide derivatives targeting 5-HT receptors.[39,40]

CONCLUSION

Benzamide derivatives represent a diverse and promising class of compounds in the quest for effective therapies for Alzheimer's disease (AD). Through their multifaceted pharmacological properties, benzamide derivatives offer potential avenues for targeting various pathological mechanisms underlying AD, including cholinesterase

inhibition, amyloid-beta production, tau aggregation, glutaminyl cyclase inhibition, antioxidant activity, and modulation of serotonin receptors.

Their ability to inhibit cholinesterase enzymes holds promise for improving cognitive function by enhancing cholinergic neurotransmission. Moreover, benzamide derivatives designed to target enzymes involved in amyloid-beta biosynthesis and tau aggregation offer potential strategies for mitigating the accumulation of neurotoxic protein aggregates in the brain. Additionally, their antioxidant properties may help alleviate oxidative stress, while modulation of serotonin receptors could address mood disturbances associated with AD.

However, while preclinical studies have provided encouraging results, further research, including rigorous clinical trials, is needed to fully evaluate the safety and efficacy of benzamide derivatives in humans with AD. Additionally, optimizing their pharmacokinetic properties, enhancing blood-brain barrier penetration, and minimizing off-target effects are crucial considerations for the development of benzamide-based therapeutics.

In conclusion, the exploration of benzamide derivatives in AD research represents a promising frontier in the search for effective disease-modifying treatments. With continued investigation and collaboration across multidisciplinary fields, benzamide derivatives may offer new hope for patients and families affected by this devastating neurodegenerative disorder.

REFERENCES

1. De-Paula, V.J.; Radanovic, M.; Diniz, B.S.; Forlenza, O.V. Alzheimer’s disease. Sub-Cell. Biochem, 2012; 65: 329–352.
2. Cipriani, G.; Dolciotti, C.; Picchi, L.; Bonuccelli, U. Alzheimer and his disease: A brief history. Neurol. Sci. Off. J. Ital. Neurol. Soc. Ital. Soc. Clin. Neurophysiol, 2011; 32: 275–279.
3. Blass, J.P. Alzheimer’s disease. Dis. A Mon. Dm 1985, 31, 1–69.
4. Terry, R.D.; Davies, P. Dementia of the Alzheimer type. Annu. Rev. Neurosci, 1980; 3: 77–95.
5. Rathmann, K.L.; Conner, C.S. Alzheimer’s disease: Clinical features, pathogenesis, and treatment. Drug Intell. Clin. Pharm, 1984; 18: 684–691.
6. Reisberg B, Borenstein J, Salob SP, Ferris SH. Behavioral symptoms in Alzheimer's disease: Phenomenology and treatment. J Clin Psychiatry, 1987; 48(5): 9–15.
7. Kumar A, Singh A. A review on Alzheimer's disease pathophysiology and its management: an update. Pharmacol Rep., 2015; 67(2): 195-203.
8. Kametani F, Hasegawa M. Reconsideration of amyloid hypothesis and tau hypothesis in Alzheimer's disease. Frontiers in neuroscience. Jan 30, 2018; 12: 328460.
9. Hampel H, Mesulam MM, Cuello AC, Khachaturian AS, Vergallo A, Farlow MR, Snyder PJ, Giacobini E, Khachaturian ZS, Cholinergic System Working Group, and for the Alzheimer Precision Medicine Initiative (APMI). Revisiting the cholinergic hypothesis in Alzheimer’s disease: emerging evidence from translational and clinical research. The journal of prevention of Alzheimer's disease. Jan., 2019; 6: 2-15.
10. Fotiou D, Kaltsatou A, Tsiptsios D, Nakou M. Evaluation of the cholinergic hypothesis in Alzheimer’s disease with neuropsychological methods. Aging clinical and experimental research. Oct., 2015; 27: 727-33.
11. Hardy JA, Higgins GA. Alzheimer's disease: the amyloid cascade hypothesis. Science. Apr 10, 1992; 256(5054): 184-5.
12. Reitz C. Alzheimer's disease and the amyloid cascade hypothesis: a critical review. International journal of Alzheimer’s disease. Mar 17, 2012.
13. Swerdlow RH, Burns JM, Khan SM. The Alzheimer's disease mitochondrial cascade hypothesis: progress and perspectives. Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease. Aug 1, 2014; 1842(8): 1219-31.
14. Swerdlow RH, Burns JM, Khan SM. The Alzheimer's disease mitochondrial cascade hypothesis. Journal of Alzheimer's Disease. Jun 3, 2010; 20(s2): S265-79.
15. Wu T, Lin D, Cheng Y, Jiang S, Riaz MW, Fu N, Mou C, Ye M, Zheng Y. Amyloid cascade hypothesis for the treatment of alzheimer’s disease: progress and challenges. Aging and Disease. Dec 12, 2022; 13(6): 1745.
16. Zhang B, et al. Integrated systems approach identifies genetic nodes and networks in late-onset Alzheimer's disease. Cell, 2013; 153(3): 707–20.
17. Colonna M, Wang Y. TREM2 variants: new keys to decipher Alzheimer disease pathogenesis. Nat Rev Neurosci, 2016; 17(4): 201–7.
18. McGeer PL, McGeer EG. The amyloid cascade-inflammatory hypothesis of Alzheimer disease: implications for therapy. Acta neuropathologica. Oct, 2013; 126: 479-97.
19. Kinney JW, Bemiller SM, Murtishaw AS, Leisgang AM, Salazar AM, Lamb BT. Inflammation as a central mechanism in Alzheimer's disease. Alzheimer's & Dementia: Translational Research & Clinical Interventions. Jan 1, 2018; 4: 575-90.
20. Tolar M, Abushakra S, Sabbagh M. The path forward in Alzheimer's disease therapeutics: Reevaluating the amyloid cascade hypothesis. Alzheimers Dement. Nov., 2020; 16(11): 1553-1560.
21. Da Mesquita S, Papadopoulos Z, Dykstra T, Brase L, Farias FG, Wall M, Jiang H, Kodira CD, de Lima KA, Herz J, Louveau A. Meningeal lymphatics affect microglia responses and anti-Aβ immunotherapy. Nature. May 13, 2021; 593(7858): 255-60.

22. Troutwine BR, Hamid L, Lysaker CR, Strope TA, Wilkins HM. Apolipoprotein E and Alzheimer's disease. Acta Pharmaceutica Sinica B. Feb 1, 2022; 12(2): 496-510.
23. McDade E, Voytyuk I, Aisen P, Bateman RJ, Carrillo MC, De Strooper B, Haass C, Reiman EM, Sperling R, Tariot PN, Yan R. The case for low-level BACE1 inhibition for the prevention of Alzheimer disease. Nature Reviews Neurology. Nov., 2021; 17(11): 703-14.
24. Recio-Barbero M, Segarra R, González-Pinto A. Cognitive enhancers in schizophrenia: a systematic review and meta-analysis of alpha-7 nicotinic acetylcholine receptor agonists for cognitive deficits and negative symptoms. Frontiers in Psychiatry. Apr 6, 2021; 12: 631589.
25. Yakel JL. Cholinergic receptors: functional role of nicotinic ACh receptors in brain circuits and disease. Pflügers Archiv-European Journal of Physiology. Apr., 2013; 465(4): 441-50.
26. Kucwaj-Brysz K, Baltrukevich H, Czarnota K, Handzlik J. Chemical update on the potential for serotonin 5-HT6 and 5-HT7 receptor agents in the treatment of Alzheimer's disease. Bioorganic & Medicinal Chemistry Letters. Oct. 1, 2021; 49: 128275.
27. Craft JM, Watterson DM, Van Eldik LJ. Neuroinflammation: a potential therapeutic target. Expert opinion on therapeutic targets. Oct 1, 2005; 9(5): 887-900.
28. Fu WY, Wang X, Ip NY. Targeting neuroinflammation as a therapeutic strategy for Alzheimer's disease: mechanisms, drug candidates, and new opportunities. ACS chemical neuroscience. Sep 17, 2018; 10(2): 872-9.
29. Drozdowska D, Maliszewski D, Wróbel A, Ratkiewicz A, Sienkiewicz M. New Benzamides as Multi-Targeted Compounds: A Study on Synthesis, AChE and BACE1 Inhibitory Activity and Molecular Docking. International Journal of Molecular Sciences. Oct 4, 2023; 24(19): 14901.
30. Koca M, Güller U, Güller P, Dağalan Z, Nişancı B. Design and synthesis of novel dual cholinesterase inhibitors: In vitro inhibition studies supported with molecular docking. Chemistry & Biodiversity. Jun, 2022; 19(6): e202200015.
31. Wajid S, Khatoon A, Khan MA, Zafar H, Kanwal S, Choudhary MI, Basha FZ. Microwave-assisted organic synthesis, structure–activity relationship, kinetics and molecular docking studies of non-cytotoxic benzamide derivatives as selective butyrylcholinesterase inhibitors. Bioorganic & Medicinal Chemistry. Sep 15, 2019; 27(18): 4030-40.
32. Peng DY, Sun Q, Zhu XL, Lin HY, Chen Q, Yu NX, Yang WC, Yang GF. Design, synthesis, and bioevaluation of benzamides: novel acetylcholinesterase inhibitors with multi-functions on butylcholinesterase, Aβ aggregation, and β-secretase. Bioorganic & medicinal chemistry. Nov 15, 2012; 20(22): 6739-50.
33. Panek D, Więckowska A, Wichur T, Bajda M, Godyń J, Jończyk J, Mika K, Janockova J, Soukup O, Knez D, Korabecny J. Design, synthesis and biological evaluation of new phthalimide and saccharin derivatives with alicyclic amines targeting cholinesterases, beta-secretase and amyloid beta aggregation. European journal of medicinal chemistry. Jan 5, 2017; 125: 676-95.
34. Oz M, Lorke DE, Petroianu GA. Methylene blue and Alzheimer's disease. Biochemical pharmacology. Oct 15, 2009; 78(8): 927-32.
35. Hoang VH, Tran PT, Cui M, Ngo VT, Ann J, Park J, Lee J, Choi K, Cho H, Kim H, Ha HJ. Discovery of potent human glutaminyl cyclase inhibitors as anti-Alzheimer's agents based on rational design. Journal of medicinal chemistry. Mar 23, 2017; 60(6): 2573-90.
36. Ngo VT, Hoang VH, Tran PT, Van Manh N, Ann J, Kim E, Cui M, Choi S, Lee J, Kim H, Ha HJ. Structure-activity relationship investigation of Phe-Arg mimetic region of human glutaminyl cyclase inhibitors. Bioorganic & Medicinal Chemistry. Jul 23, 2018; 26(12): 3133-44.
37. Kilic B, Bardakkaya M, Sagkan RI, Aksakal F, Shakila S, Dogruer DS. New thiourea and benzamide derivatives of 2-aminothiazole as multi-target agents against Alzheimer's disease: Design, synthesis, and biological evaluation. Bioorganic Chemistry. Feb 1, 2023; 131: 106322.
38. Taj MB, Tirmizi SA, Raheel AA, ALI HM, Qureshi S, Alshatir H. Benzamide derivatives as potential candidates for anti-alzheimer, anti-fatigue, anti-urease and anti-oxidant activity. Journal of the Chilean Chemical Society. Mar., 2017; 62(1): 3342-4.
39. Donnier-Marechal M, Carato P, Larchanché PE, Ravez S, Boulahjar R, Barczyk A, Oxombre B, Vermersch P, Melnyk P. Synthesis and pharmacological evaluation of benzamide derivatives as potent and selective sigma-1 protein ligands. European journal of medicinal chemistry. Sep 29, 2017; 138: 964-78.
40. Jankowska A, Satała G, Kołaczkowski M, Bucki A, Głuch-Lutwin M, Świerczek A, Pociecha K, Partyka A, Jastrzębska-Więsek M, Lubelska A, Latacz G. Novel anilide and benzylamide derivatives of arylpiperazinylalkanoic acids as 5-HT1A/5-HT7 receptor antagonists and phosphodiesterase 4/7 inhibitors with procognitive and antidepressant activity. European Journal of Medicinal Chemistry. Sep 1, 2020; 201: 112437.