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Review Article

Acetylcholine Esterase Inhibition in Alzheimer's Therapy: Spotlight on Quinzolinone Derivatives.

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Abstract

As the most prevalent type of dementia with a high rate of mortality and disability, Alzheimer's disease (AD) poses serious and growing global issues. Its etiology is complex, serious and multifaceted, resulting from a confluence of environmental, genetic, and age variables. The cholinergic, amyloid, tau protein, oxidative stress, and inflammatory hypotheses are some of the theories that now underlie our understanding of AD pathology. However, more clarification and verification are needed to identify the main reasons causing AD and to understand how these clinical features interact. The cholinergic hypothesis states that Alzheimer's disease impairs the brain's cholinergic function, which results in decreased levels of the neurotransmitter acetylcholine (ACh) in the cortical and hippocampus areas. Thus, ACh level elevation is one of the main goals of current pharmaco-therapeutic strategies for decreasing progression of AD. Based on the aforementioned findings, this article provides an overview of the latest progress in the development of powerful novel AChE inhibitors.

Keywords Alzheimer's disease, AChE inhibitors, inflammation, Quinzolinone, Therapeutic strategies.

Introduction

Dementia causes a substantial reduction in cognitive function that impacts a person's ability to perform everyday tasks. The most prevalent type of dementia, affecting at least two-thirds of cases in those 65 and older, is Alzheimer disease (AD). The primary symptom of AD, an irreversible progressive neurological disease, is memory loss, which

interferes with day-to-day functioning. [1,2] AD exerts a significant impact on patients as well as on their caregivers and society in both developed and developing nations. AD is one of the biggest healthcare challenges of the twenty-first century because of its high rates of morbidity and mortality and the financial strain it places on the healthcare system.[2-4] AD is considered as an age-dependent neurodegenerative disorder with prevalence of about 24 million people worldwide. [5, 6]

By the end of 2030, World Health Organization (WHO) predicts that this number will be increased by more than 100%.[5] Historically, Alois Alzheimer, a German psychiatrist, is the inspiration behind the name AD.[7] Alois Alzheimer discovered amyloid plaques and significant neuronal deterioration in the brain of his first patient, who had memory loss and a personality shift before to death. Consequently, he labeled this affliction as an exceedingly distressing disorder of the cerebral cortex.[8]

Risk factors of AD

There is numerous established risk factors linked to Alzheimer's disease, making it a complex disease. The most significant factor includes increasing age, environmental factors, infections, circulatory vascular diseases, and head traumas, and genetic factors for example, trisomy 21, is a risk factor associated with early-onset dementia **Figure 1**.[8]

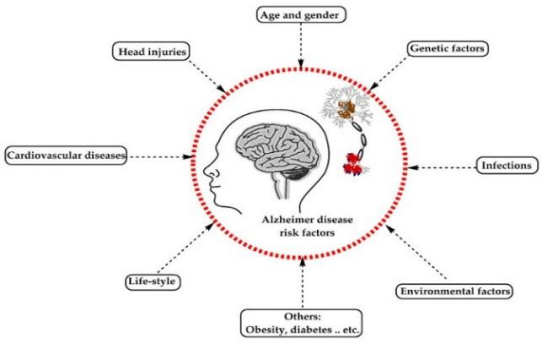


Figure 1. Major risk factors for Alzheimer's disease.[8]

Pathogenesis of Alzheimer's disease

Based on neuropathology, histopathological characteristics of AD pathogenesis are amyloid-beta plaques extracellular aggregates in extracellular voids and on the blood vessels walls. Also, clusters of neurofibrillary tangles (NFTs) inside cells made of hyper phosphorylated tau protein linked to microtubules. These characteristics emerge and proliferate in the brain's neocortex and hippocampus.[3,9,10,11] Following β-secretase's processing of transmembrane protein amyloid protein precursor (APP), the N terminus of Aβ and membrane-bound C-terminal fragment C99 are produced. Subsequently, the mature Aβ peptide is released when γ-secretase cleaves C99. Aβ production is prevented by APP being cut within the Aβ domain by α-secretase, a third protease.[12] Although the precise origin of AD is unknown, it is thought to be a complicated multifactorial disease brought on by sophisticated interplay between various pathophysiological processes. Amyloid β cascade, inflammation, tau, oxidative stress hypotheses and injury in the cholinergic neuron are among the primary hypotheses for the pathogenesis of AD.[13]

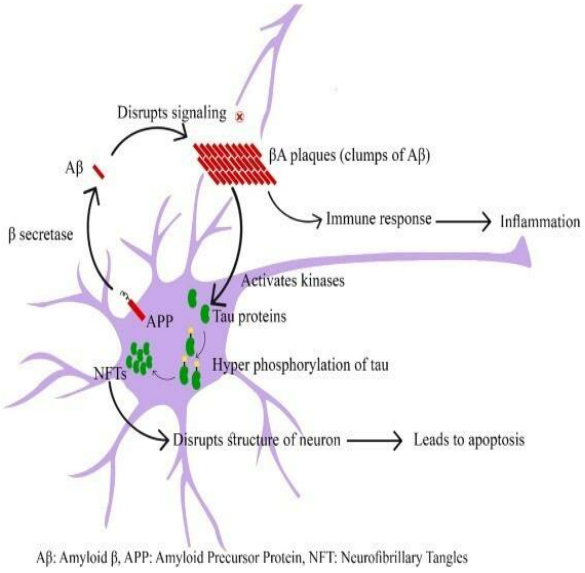
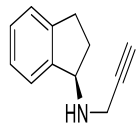


Figure 2. Pathophysiology of AD.[11]

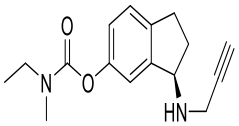
Aβ cascade theory

Aβ is mostly created by neurons and astrocytes under stressful situations that cause glial activation. As previously mentioned, the type 1 membrane protein APP is sequentially proteolyzed to generate Aβ. One of the primary therapeutic goals for reducing cerebral Aβ concentrations in Alzheimer's patients is believed to be the reduction or control of both β and γ secretases, as their activity is necessary for the formation of Aβ. On the other hand, therapeutic Aβ reduction may also be made possible by α secretase activation.[14] Aβ is eliminated from the CNS through the glymphatic and perivascular circulation, via different proteins like P-glycoprotein, SORLA and LRP-1 (low-density lipoprotein receptor-related protein 1) .[15-17] However, vascular issues like cerebral amyloid angiopathy are brought on by synaptic failure and inflammation, as well as the proteins like interleukins, MCP-1, Apo-E, etc.[12,18] Furthermore, hyper phosphorylation of tau proteins results in the production of neurofibrillary tangles (NFTs), which are crucial for the early identification of AD symptoms. These ideas work together through protein interactions, and the development of AD pathogenesis is typically greatly aided by this vast network of protein interactions.[19,20] Apart from the essential proteins that hasten the onset of AD, like tau, presenilins, and the amyloid precursor protein (APP), numerous other proteins either worsen or lessen the disease's pathology. According to the Aβ and tau (τ) theory, for example, proteins including mitoferrin-1, interleukin-1, GO protein, and C-reactive protein either directly or indirectly contribute to the development of Alzheimer's disease (AD). On the other hand, proteins such as neurogranin, P-glycoprotein, ubiquitin, insulin, calbindin-D28K, calretinin, parvalbumin, and a number of others are thought to have neuroprotective functions. Additionally, via increasing Aβ synthesis through presenilin-dependent γ-secretase cleavage of APP, some proteins, including mutant presenilin-1, contribute to neurodegeneration.[21-25] However, to lessen neurodegeneration, proteins such as calmodulin-like skin protein interact with heterotrimeric humanin receptors (htHNR).[26,27] The most straightforward way to lower Aβ production is targeting γ- and β–secretase.[12,28] Additionally, the presence of monoamine oxidase (MAO) can affect the activity of γ-secretase, which cleaves APP.[29] Rasagiline **(1)** and Ladostigil **(2)** are two monoamine oxidase inhibitors (MAOI) that have been licensed for the treatment of AD and have shown neuroprotective effects.[30,31] By combining the pharmacophores of rasagiline **(1)** and rivastigmine **(3)**, a dual inhibitor of acetylcholinesterase (AChE) and butyrylcholinesterase (BChE), Ladostigil **(2)** was created. Ladostigil has demonstrated multi-target therapeutic activity thanks to its distinctive design. Researchers have found via the study of MAOI that the structure's capacity to permanently inhibit MAO can be improved by the propargyl N-terminal substituent.[32]

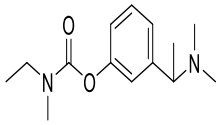
Based on this theory as a basis, the approach to medication development centered on limiting the amount of Aβ by suppressing the expression of the APP gene. This notion was the focus of Posiphen **(4)**, which has been proven in experiments to decrease APP mRNA translation. Posiphen **(4)** has been shown in mouse models to efficiently reduce the levels of APP, Aβ42, and related products.[33]



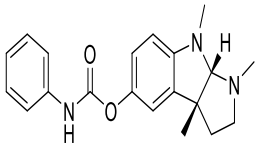
Rasagiline (**1**)



Ladostigil (**2**)



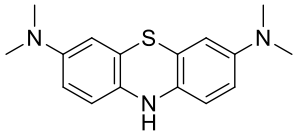
Rivastigmine (**3**)



Posiphen (**4**)

Tau hypothesis

Another intracellular characteristic linked to AD is neurofibrillary tangles, of which tau is a component. Tau is a microtubule-associated scaffolding protein that is mostly found in axons for support. Tau hyper phosphorylation will enhance the protein's susceptibility to aggregation, reduce its affinity for microtubules, and thus impact brain plasticity.[34,35] Neurodegeneration results from tau accumulation under pathological conditions that damage neurons' axons.[36,37] Tau aggregates to produce insoluble form as a result of mutations that change Tau's soluble form, which causes this hyper phosphorylation. The insoluble state disrupts axonal transport and severely damages the cytoplasmic functions of the nerve cells, leading to dementia and neuronal death.[38,39] In order to hyper phosphorylate Tau and induce neuronal cell death, GlaxoSmithKline (GSK)-3 must be activated. The primary kinase implicated in Tau phosphorylation is GSK-3β. Previous studies have shown that inhibition of GSK-3β reduces Tau phosphorylation.[40,41] GSK-3 facilitates the intracellular aggregation of Aβ, which may also be a factor in the hyper phosphorylation of Tau. The PI3K/Akt signaling pathway controls GSK. When PI3K activates Akt/protein kinase B, it kinase B, it phosphorylates GSK-3β, rendering it inactive and suppressing Tau Phosphorylation Figure 2.[42] Following the repeated failures of Aβ-targeted medications for AD, the therapeutic potential of targeting Tau is receiving more consideration, particularly as biomarker studies indicate that Tau pathology is more closely linked to the course of AD.[35] Following the recurrent failures of Aβ-targeted medications for AD, there is growing interest in the therapeutic potential of targeting Tau, particularly as biomarker studies indicate that Tau pathology is more closely linked to the progression of AD.[35] Therefore, strategies to counteract Tau include limiting Tau's ability to aggregate, employing Tau vaccinations, stabilizing microtubules, and altering kinases and phosphatases that regulate Tau changes. However, most of these efforts have failed in clinical research. In phase III trials for Tau aggregation blockers, the second-generation Tau protein aggregation inhibitor TRx0237 **(5)** did not show any therapeutic effects.[36]



TRx0237 (**5**)

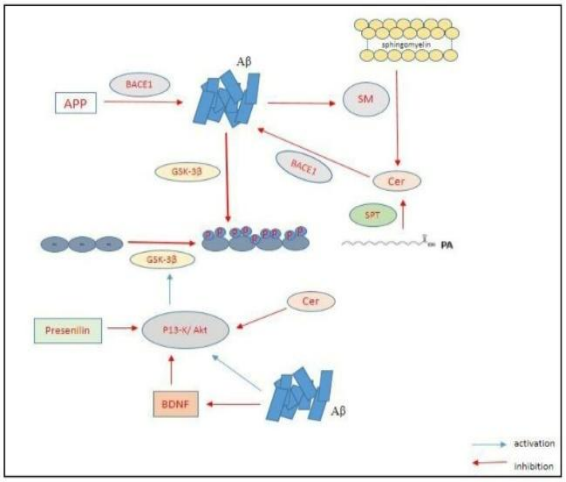
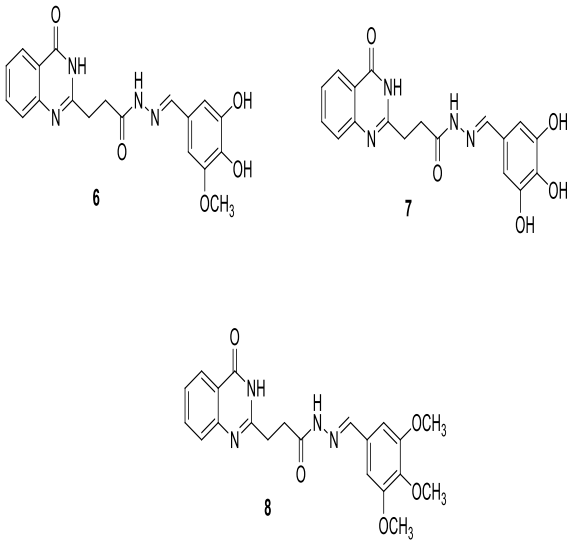


Figure 3. Interactions take place between hyper phosphorylated tau, ceramides (cer), glycogen synthase kinase 3β, and amyloid beta.[42]

Oxidative Stress Hypothesis

According to the oxidative stress theory, brain aging is accelerated by a redox imbalance that is typified by the generation of reactive oxygen species (ROS) or the breakdown of the antioxidant system.[43] The mitochondrial electron transport chain at the cytochrome oxidase complex consumes over 98% of the molecular oxygen, with the remainder being transformed into superoxide (O_2•) and hydrogen peroxide radicals. Among other things, regular metabolism produces the O2 and hypochlorous acid.[44] By generating the extremely reactive hydroxyl radical (OH•), an excess of O_2• and H_2O_2 can harm tissue.[45] [Abnormally high levels of Aβ buildup and the formation of NFTs are signs of severe oxidative brain damage seen in AD patients.[46] Biometals like as iron, zinc, and copper are implicated in Aβ and neurodegeneration, according to mounting evidence.[47] The N-terminal metal-binding domains of Aβ and its precursor APP have high affinity copper and zinc binding sites, based on those studies.[48,49] The extremely reactive OH• is strongly mediated by copper, which together raises the oxidative stress that is a hallmark of AD brain.[50] The high copper content of amyloid plaques.[51] lends credence to this. Significant zinc concentrations were also found in the neocortex, amygdala, and hippocampus—regions primarily affected by AD pathology. Memory and cognition are related to these areas of the brain.[52,53] Because Aβ is in a highly structured conformational state, this binding of zinc causes poisonous, fibrillary Aβ aggregates to form. Therefore, oxidative stress is characterized by the disruption of zinc homeostasis and the subsequent uncontrollable release of zinc from the brain as part of the immune/inflammatory response to non-soluble Aβ plaques. Zinc and Aβ-mediated oxidative stress and cytotoxicity are thus the outcomes of excessive zinc or Aβ accumulation.[54] Because of this, the brain is more vulnerable to damage from free radicals, even though the phospholipids in the brain membrane are composed of polyunsaturated fatty acids. Increased lipid peroxidation, which is caused by their double bonds, is the most obvious feature in which degenerative change is most significant in the AD brain.[55,56] Furthermore, free radical-induced protein oxidation may play a role in AD by changing enzymes crucial for brain glial and neuronal activity. This is especially pertinent to glutamine synthetase and creatine kinase, two enzymes that are greatly reduced in AD brains and are highly susceptible to oxidative change.[57,58] Therefore, oxidative stress, which is caused by excessive ROS formation, may be harmful and a major contributor to cell structure destruction, which in turn causes aging and a number of disease states. However, antioxidant treatments have demonstrated that AD is a more complex disease since it is associated with oxidative stress.[59] Antioxidants are essential for preventing oxidative damage brought on by ROS and free radicals. For mammalian cells to remain healthy overall, the production and detoxification of ROS must be balanced. Several physiologically active Schiff's bases have been found in recent research, including compounds **(6)**, **(7)**, and **(8)**, which exhibit antioxidant qualities and IC50 values of 104±1.41, 85±1.28, and 81±1.69, respectively. Because hydroxyl is present on the aromatic ring, hydroxyl-substituted Schiff's bases are especially strong antioxidants that may be used as therapeutic agents to combat disorders like AD that are linked to free radical damage.[60,61]



Inflammation hypothesis

According to a number of recent studies, neuroinflammation is a key factor in the development of the neuropathological changes seen in AD. AD is characterized by neuroinflammation and reactive gliosis. Microglia-related pathways were considered to be important for AD pathogenesis and risk based on transcriptome and genetic studies.[62-65] In addition to increased levels of cytokines and chemokines in the patients' blood and cerebrospinal fluid, other investigations have reported the presence of inflammatory markers in the patients' brains.[66-69] Furthermore, microglia are thought to be important in AD. Notably, the complement system is in charge of synaptic pruning in the very early stages of late onset Alzheimer disease (LOAD), and the innate immune system receptor triggering receptor expressed on myeloid cells 2 (TREM2) has been shown to increase the risk of LOAD by 2-4 times.[70-72] In this environment, amyloid plaques are surrounded by astrocytes and reactive microglia, which also generate a lot of pro-inflammatory cytokines. These events are thought to have played a significant role in the early development of AD.[64,73] The pathophysiology of AD involves a number of pro-inflammatory proteins, including TNF-α, NF-κB, IL-1β, and IL-6.

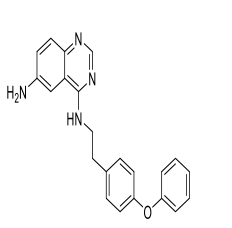
Tumor necrosis factor- α (TNF-α)

One of the most important pro-inflammatory cytokines in AD is tumor necrosis factor-α. In response to an inflammatory stimulation, it is essential for initiating and regulating the cytokine cascade.[74,75] TNF-α binds to the TNFR1 and TNFR2 receptors to produce its pharmacological actions.[76] In mouse hippocampal tissue, it was found that overexpression of TNFR1 was necessary for the stimulation of nuclear factor kappa B (NF-κB) and Aβ-induced neuronal death.[77] Conversely, mice with the APP23 transgenic AD model and TNFR1-deficient mice exhibit improved cognitive function, reduced plaque deposition, and diminished hippocampal microglial activation.[78] According to a study, soluble TNFR1 and TNFR2 levels were elevated in patients with moderate cognitive impairment (MCI) who developed AD following a 6-year follow-up. High levels of soluble TNFR1 and TNFR2 were found in the cerebrospinal fluid (CSF) of individuals with moderate cognitive impairment (MCI) who developed AD following a 6-year follow-up, according to a study.[79] It has been discovered that AD patients' brains and plasma have increased levels of TNF-α.[80] Aβ may directly boost microglia's production of TNF-α by activating the transcription factor NF-k.[81] Furthermore, TNF-α can increase the burden of Aβ by boosting γ-secretase activity and upregulating β-secretase production.[82,83] TNF-α blocking medications such as etanercept, adalimumab, and infliximab may help reduce the elevated risk of AD brought on by elevated TNF-α levels.[84] Soluble TNF receptor 2 and the Fc region of mouse immunoglobulin G1 are fused to produce etanercept (Enbrel®). Adalimumab (Humira®) is an entirely human anti-TNF monoclonal antibody, whereas infliximab (Remicade®) is a chimeric mouse-human

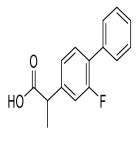
monoclonal antibody in which the antigen combining region of a mouse anti-TNF monoclonal antibody is fused to a human Fc domain.[85]

Nuclear factor kappa B

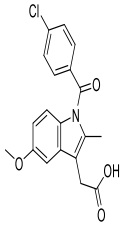
Considered a basic regulator of inflammatory responses, nuclear factor kappa B (NF-κB) is a transcriptional factor that responds to pro-inflammatory stimuli such as TNF-α or IL-1.[86] Activated NF-κB, which is usually seen in neurons and glial cells around Aβ plaques, is the main cause of reactive gliosis observed in AD brains.[87] Furthermore, it has been shown that Aβ promotes the production of cytokines through the NF-kB-dependent pathway, resulting in a vicious loop that makes illness worse.[81] Near the β-site APP cleaving enzyme 1 (BACE1) promoter, numerous NF-kB binding sites have been discovered. This indicates that NF-kB plays a critical role in regulating the transcription of BACE1, which is detected by higher levels in the brain of some sporadic AD patients.[88] Furthermore, it has been shown that Aβ triggers the production of cytokines through the NFκB-dependent pathway, resulting in a vicious loop that makes illness worse.[81] According to both in vitro and in vivo studies, using an NFκB inhibitor, such as 6-amino-4-(4-phenoxyphenylethylamino) quinazoline **(9)** with an IC50 of 7 nM, may reduce TNF-α-induced BACE1 transcription, which in turn reduces Aβ stress.[78,89] A number of NSAIDS have been shown to reduce NF-kB activity, which in turn reduced levels of Aβ1–40 and Aβ1–42.[90] Examples of these medications are flurbiprofen **(10)** and indomethacin **(11)** with an IC50 of 0.6 µM .[91]



6-Amino-4-(4-phenoxyphenylethylamino) quinazoline (**9**)



Flurbiprofen (**10**)



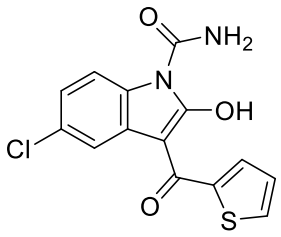
Indomethacin (**11**)

Interleukin-1 beta

Because of its critical role in regulating the release of other pro-inflammatory cytokines, including TNF-α and IL-6, and because changes in IL-1β can delay the onset of neuroinflammation and neurodegeneration, interleukin-1 beta has been referred to as a "master regulator" within the brain inflammatory cascade.[92] Early in the course of AD, the pro-inflammatory cytokine IL-1β is elevated and plays a crucial role in the development of amyloid plaques.[74] IL-1β levels are elevated in both AD and MCI patients when compared to controls, suggesting that increased IL-1β production begins early and continues as the disease progresses.[93] IL-1β has been observed to be increased in the hippocampus and prefrontal cortex of AD patients.[94] IL-1β must first attach to the IL-1β receptor, which is found throughout the brain but is particularly prevalent in the dentate gyrus and hippocampal pyramidal cells, two crucial areas in the early stages of AD pathogenesis, before it can start to have an effect.[95]

Interleukin-6 (IL-6)

A vital, multipurpose cytokine, IL-6 can be categorized as either pro- or anti-inflammatory based on the amount released and the situation.[95] The normal homeostasis of neural tissue depends on IL-6, and microglial activation is decreased when this signaling route is blocked. However, overproduction of IL-6 leads to chronic neuro-inflammation and neurodegeneration.[96] The neuro-inflammation that takes place in LOAD is believed to be mostly caused by IL-6, which is elevated in the blood and CSF of AD patients.[68,97] Tenidap **(12)** (NSAID), which inhibits the creation of IL-6 proteins and influences the levels of IL-6 mRNA, has been found to be an effective anti-inflammatory medication in AD.[98]



Tenidap **(12)**

The cholinergic hypothesis

The fields of neurochemistry, neuropharmacology, and neuroanatomy provide support for the idea that cholinergic activity is a major factor in the pathophysiology of Alzheimer's disease. A few of these foundations were aware of the impact scopolamine has on memory functions. Pazzagli and Pepeu's earlier rodent studies revealed a link between scopolamine's amnesic effects and the brain's acetylcholine levels.[99] Animals with cholinergic lesions and related learning problems were referred to as models of AD, and it was found that the degree of cholinergic depletion positively correlated with the severity of dementia in AD.[100-102]

Nature and effect of the cholinergic lesion

Acetylcholine, a major neurotransmitter in the brain, is active in the basal forebrain, basal ganglia, and cortex.[103] Figure 4 illustrates the key steps involved in the synthesis, release, and absorption of the neurotransmitter acetylcholine.[103,104] Cholinergic loss is caused by the degeneration of cholinergic neurons in the nucleus basalis magnocellularis (NBM) and the axons that these neurons send to the cerebral cortex. The cerebral cortex's muscarinic (metabotropic) and nicotinic (ionotropic) receptors are both changed as a result of the cholinergic lesion. The majority of research indicates that the cerebral cortex's nicotinic receptors are being lost. For instance, there are less postsynaptic nicotinic receptors in cortical neurons.[104,105] Nonetheless, there might be a sizable presynaptic component based on the loss of nicotinic receptors on the degenerating cholinergic axons originating from the NBM.[106]Additionally, there is data that suggests the remaining postsynaptic M1 receptors in the cerebral cortex may be impaired.[107] The upregulation of cortical choline acetyltransferase neuronal expression in early Alzheimer's disease patients raises the possibility that these neurochemical events could make up for the loss of basal cholinergic neurons.[108] Additionally, research has shown that nicotinic gene expression is higher in AD patients than in healthy controls.[109] The two sister cholinesterase enzymes present in mammalian brains are acetylcholinesterase (AChE) and butyrylcholinesterase (BChE). Although BChE has the ability to hydrolyze ACh, AChE primarily contributes to cholinergic neurotransmission by doing so. The body's first line of defense against dangerous compounds that could interfere with AChE's function is BChE, an endogenous bioscavenger. Glia and white matter in the brain contain BChE. But the protein is also connected to neurons, including those in the hippocampus, amygdala, and thalamus. BChE was also found in amyloid plaques and NFTs, suggesting that the protein may be involved in the pathogenesis of AD.[110,111]

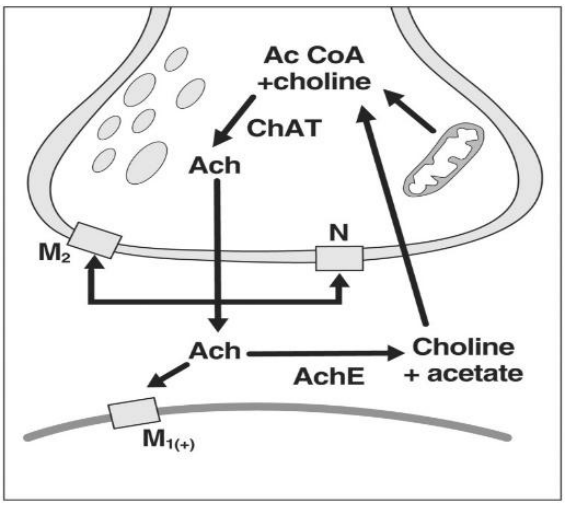


Figure 4. Physiology of the cholinergic synapse.[111]

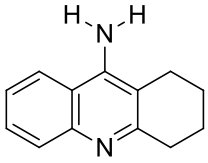
Cholinesterase (ChE) is a primary enzyme target for AD therapy. The loss of neurotransmission and the degradation of cholinergic neurons in the brain are the primary causes of the decline in cognitive performance in AD patients.[112] According to the cholinergic theory, AD is primarily caused by a decline in ACh production. Therefore, increasing the brain's cholinergic levels by blocking the AChE enzyme from carrying out its biological job is one of the potential treatment strategies. Therefore, AChE inhibitors are used to limit ACh breakdown. By increasing the quantity of ACh, AChE inhibitors can enhance the function of neuronal cells.[113]

Acetylcholinesterase enzyme

The levels of the enzyme AChE have a significant impact on the cholinergic nervous system, which includes the central nervous system and peripheral nervous system. AChE catalyzes the hydrolysis of ACh to provide choline and acetate ions (Figure 4). The active site of AChE is located in a sizable hydrophobic cavity. Two crucial elements are present in the AChE and BChE active sites: 1) the catalytic anionic site (CAS), which is composed of two parts: 1) the catalytic triad (CT), located 20 Å from the enzyme surface at the bottom of a narrow gorge that opens up towards the base and contains the amino acid residues His447, Glu334, and Ser203; 2) the peripheral anionic site (PAS), which contains the amino acid residues Asp72, Tyr121, and Tyr334; and 3) the anionic site (AS), which comprises the amino acid residues Phe330, Phe331, Phe329, Trp84, Trp82, Trp84, Trp82, and Tyr128. The therapeutic effects of cholinesterase inhibitors are significantly influenced by their interactions with both CAS and PAS components.[114-117]

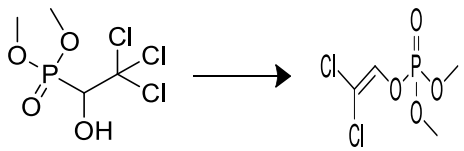
Conventional AChE inhibitors

Many AChE inhibitors have been developed including tacrine **(13)** which is the first medication approved to treat AD symptoms. Tacrine interacts with amino acid residues Trp84 and Phe330 found in AChE's anionic site. However, it was restricted due to its hepatotoxicity.[112,118] It was introduced to the market in 1993, tacrine is a centrally acting, reversible and non-selective AChEI with IC50 of 125 ± 23 nM.[119]



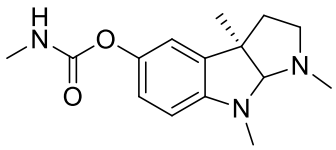
Tacrine (**13**)

Metifonate **(14)**, physostigmine **(16)**, galantamine **(17)**, and donepezil **(18)** are the four AD drugs now available on the market.[118,120] With a long half-life, the organophosphate AChE inhibitor metrifonate (14) has also been investigated for the treatment of mild to severe AD. It functions by enhancing cholinergic neurotransmission via 2,2-dichlorovinyl dimethyl phosphate **(15)** [112], a pharmacologically active metabolite.



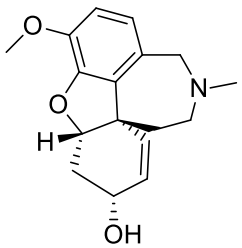
Metrifonate (**14**) 2,2-dichlorovinyl dimethyl phosphate (**15**)

Physostigmine **(16)** is a tricyclic carbamate. It was the first alkaloid with reversible acetylcholinesterase inhibitory activity with IC50 of 0.15 µM, initially discovered in Calabar beans in 1864.[121,122] The structure of physostigmine is made up of a carbamate ester connected to an indole alkaloid.[123]



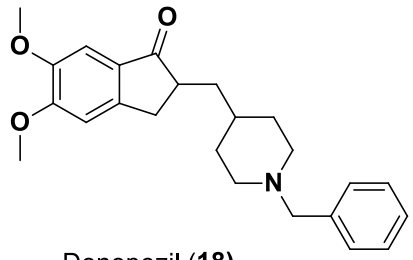
Physostigmine (**16**)

Several plants contain galantamine **(17)**, an alkaloid. Galantamine **(17)**, a reversible acetylcholinesterase inhibitor and allosteric nicotinic receptor modulator, has an IC50 of 360±10 nM and decreases cognitive and functional decline in mild to moderate AD-induced dementia.[124,125] Galantamine, which was developed in 1950 and is marketed under the name Nivalin(R), is used to treat a variety of neurological diseases because it inhibits ChE.[112]



Galantamine (**17**)

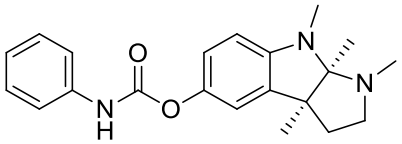
The medication donepezil **(18)** has been authorized for the treatment of mild to moderate AD.[118] With an IC50 of 5.7 ± 0.2 nM, this class of AChE inhibitors is more selective and has a longer half-life.[126] It is composed of an N-benzylpiperidine and an indanone moiety. The anti-AChE activity was increased by adding a methoxy group to the indanone molecule at positions 5 and 6. The indanone moiety's carbonyl group is necessary for its anti-AChE properties.[127] Donepezil operates at the molecular and cellular levels in addition to the neurotransmitter level in nearly every stage of the pathophysiology of AD. This includes the reduction of early expression of inflammatory cytokines, the induction of a neuroprotective isoform of AChE, the suppression of several aspects of glutamate-induced excitotoxicity, and the mitigation of oxidative stress-induced consequences [128]. Both the active and peripheral anionic sites (PAS) of AChE are concurrently inhibited by donepezil's unique chemical structure.[129]



Donepezil (**18**)

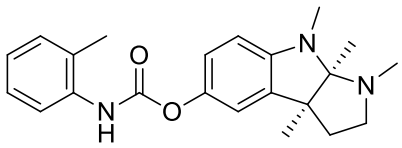
Next generation AChE inhibitors

Physostigmine derivatives such phenserine **(19)**, tolserine **(20)**, and eseroline **(21)** have been used to make ChE inhibitors. As alternative substrates, carbamoyl ester linkages in phenserine, eseroline, and tolserine attach to active centers in a manner akin to that of ACh and choline esters.[130] Phenserine **(19)** is a non-competitive, selective AChE inhibitor that decreases APP production both in vitro and in vivo and inhibits AChE more selectively than BChE.[131,132] Moreover, phenserine is less poisonous than physostigmine and tacrine. With an IC50 of 0.045 µM, phenserine was clinically studied for AD; however, the initial phase II clinical trials were only moderately successful.[132] Its combined anti-Aβ and anti-AChE properties were discovered, which makes it a promising medication for the development of novel AD treatment approaches.[133]



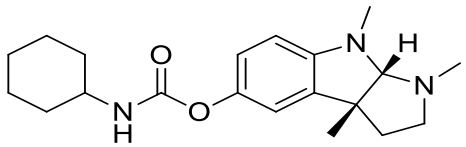
Phenserine (**19**)

Tolserine **(20)** differs from phenserine in structure due to the presence of a 2-methyl group in the phenylcarbamoyl moiety.[134] Tolserine has an IC50 value of 8.13 nM, making it 200 times more selective than BChE against human AChE (hAChE), according to preclinical studies published in 2000. Tolserine is more potent against hAChE than either phenserine or physostigmine.[112,134] In human erythrocytes, tolserine has an inhibitory concentration of 0.01 µM against AChE.[135]



Tolserine **(20)**

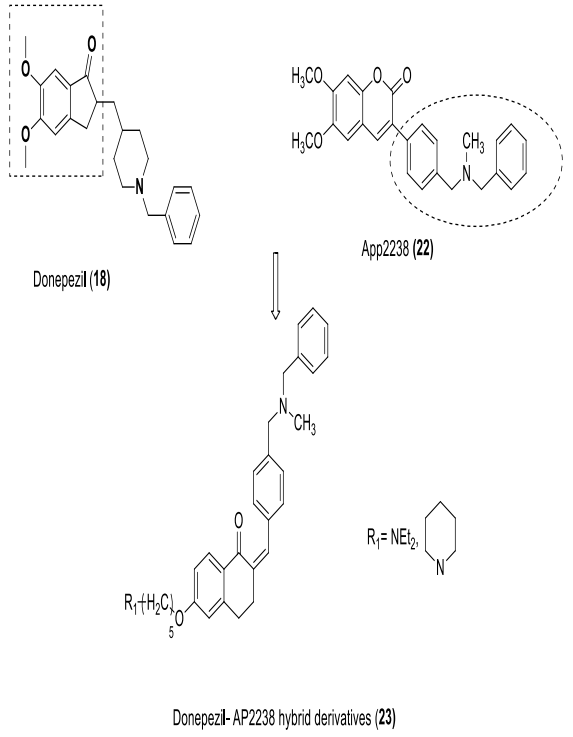
A derivative of eseroline **(21)** possesses opioid agonist properties. It has been demonstrated to be a metabolite of physostigmine; however, it has a milder and more reversible effect on AChE inhibition than physostigmine.[136] Several physostigmine analogues have been investigated for ChE inhibition. A cyclic alkyl carbamate **(21)** derived from eseroline was reported to have good selectivity against AChE in comparison to BChE.[131] Eseroline derivative **(21)** is 65 times more potent and selective than AChE compared to BChE, with IC50 values of 1.5 µM of -21 and 7.0 µM of +21.[130,137]



Eseroline derivative **21**

Hybrid AChE inhibitors

The first drug to be created with two coupled pharmacophores was donepezil-AP2238 hybrid derivatives **(23)** which can interact with both of the anionic sites of AChE. Donepezil's **(18)** and AP2238's **(22)** actions on AChE are comparable. On the other hand, AP2238 is more effective at preventing Aβ-mediated toxicity.[134] reports on several hybrids of donepezil with AP2238, where the donepezil indanone core has been joined to the Phenyl-N-methylbenzylamino moiety of AP2238. The most potent derivatives have converted donepezil's indanone ring to a tetralone scaffold in conjunction with the AP2238 Phenyl-*N*-methylbenzylamino moiety.[138] With IC50 values of 0.056 ± 0.003 for the NEt2 derivative and 0.052 ± 0.002 for the piperidine derivative, the two molecules have shown strong activity. Additionally, the combination of both moieties showed a higher affinity with the PAS of AChE because of an extended five-carbon alkyl chain that is connected to a terminal alkyl or amino group.[138]

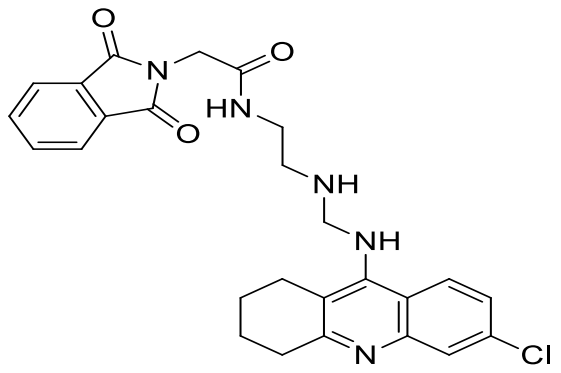


Donepezil (**18**)

App2238 (**22**)

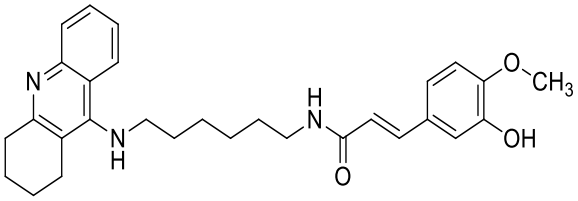
Donepezil- AP2238 hybrid derivatives (**23**)

AChE, BChE, and Aβ-aggregation generated by AChE were reported to be inhibited by donepezil-tacrine hybrid derivative **(24)**. Compound **(24)** was created to interact with the active, peripheral, and mid-gorge binding sites of AChE.[139] It is a donepezil-tacrine hybrid derivative with an IC50 value of 2.8 nM.



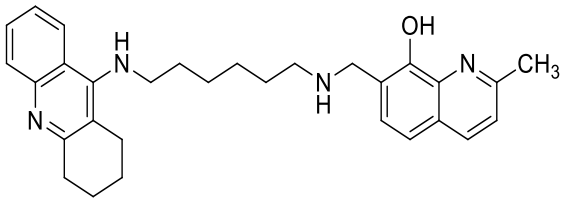
24

With a percent inhibition of 20.23% at 50 µM and 50.27% at 100 µM, the tacrine-ferulic acid (T6FA) hybrid derivative **(25)** shows stronger AChE-inhibitory effects than tacrine. T6FA has shown great efficacy in inhibiting Aβ-mediated AD-associated pathologies both in vitro and in vivo.[140]



T6FA (**25**)

By forming complexes with redox-active metals, tacrine and 8-hydroxyquinoline hybrid derivatives **(26)** are drugs that inhibit cholinesterase and reduce Aβ aggregation. Compared to tacrine alone, these hybrids have been shown to have improved CNS permeability, reduced toxicity, antioxidant properties, and copper complexing properties. Additionally, it was discovered that this hybrid was a more effective AChE inhibitor than tacrine alone, as seen by compound 26's IC50 value of 75 ± 3 nM against the AChE enzyme.[141]



26

Quinazolinone based AChE inhibitors

Quinazolinone and its derivatives have garnered significant attention due to their medical and pharmacological properties, including their anti-inflammatory, antibacterial, anticancer, antifungal, and antitubercular effects.[142,143] Furthermore, quinazolinone scaffolds have been extensively documented as AChE inhibitors used to treat AD.[144,145] *Pedrood et al.*[116] assessed how various substituents affected the activity of compounds based on quinazolinones against the enzymes AChE and BChE. According to the data, 1-naphthalene derivative **(27)**, 4-phenoxyphenyl derivative **(28)**, and 4-chloro derivative **(29)** were the most potent newly synthesized compounds against AChE and BChE, with respective IC50 values of 0.95±0.9721 nM, 1.0±0.9325 nM, and 1.87±0.9637 nM. With IC50 values of 3.78±0.9735 nM, 4.06±0.9037 nM, and 3.87±0.9310 nM, respectively, the 3-bromo derivative **(30)**, 4-methyl derivative **(31)**, and 2-nitro-3-methoxy derivative **(32)** demonstrated good inhibitory activity against AChE, while the remaining compounds showed moderate anti-AChE activity in contrast to compounds **(30)**, **(31)**, and **(32)**.[116]

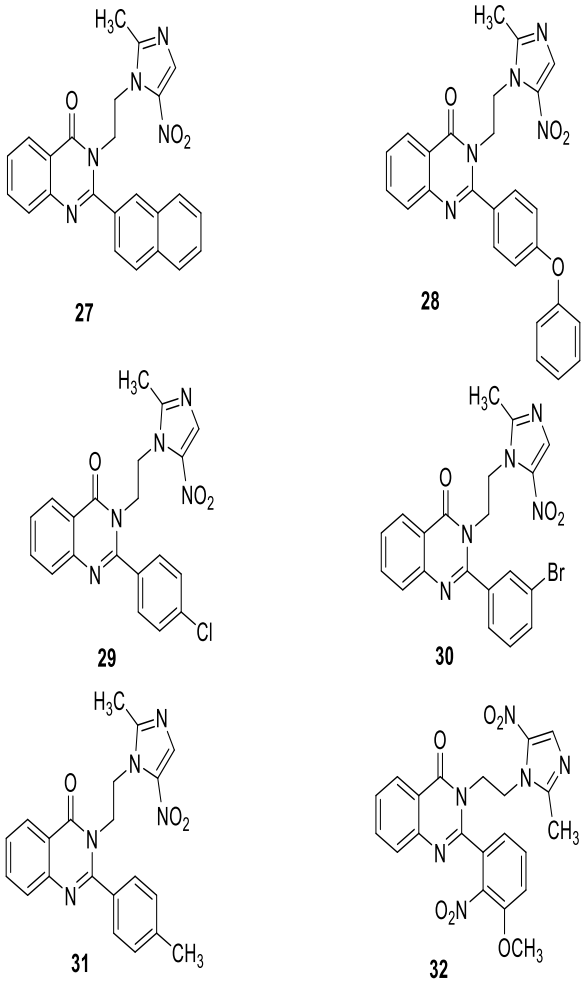


Figure 5. Reported quinazoline based AChE inhibitors

Besides the compounds mentioned above, a new series of quinazolinone-based inhibitors, compounds **(33)**, **(34)**, **(35)**, **(36)** and **(37)**, demonstrated good inhibitory activity against AChE, with inhibitory percentages of 36%, 31.3 %, 32%, 49%, and 49.59%, respectively, in comparison to donepezil, which inhibited AChE by 63.3%.[146]

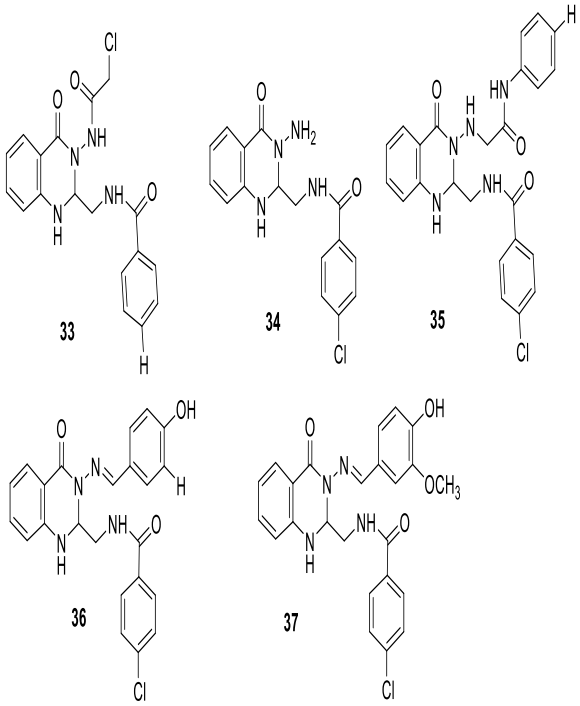


Figure 6. New series of active quinazoline based AChE inhibitors

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Declaration of competing interest

The author declares that they have no known competing financial interests or personal relationships that could influence the work reported in this article.

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