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Review of Various Approaches to Alzheimer's Disease Treatment Have Focused Solely on ß-Secretase (BACE) As A Ligand's Target in The Last Two Decades

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ABSTRACT

AD is the most common type of dementia, characterized by advancing memory deterioration that ultimately leads to the complete loss of intellectual and mental abilities leading to loss of the ability to carry on a conversation and respond to the environment. It can seriously affect a person's ability to carry out daily activities. The morphological and biochemical characteristics of AD are central to modern strategies for developing new medical approaches. Amyloid plaques, which are primarily made of Ab, progressively form in the brains of AD patients, and mutations in three genes (APP, PS1, and PS2) cause FAD by increasing the synthesis of the toxic Ab42 peptide. Given the strong link between Ab and AD, therapeutic strategies that lower Ab concentrations in the brain should be useful in the treatment of AD. For over the past years, the molecular identities of these proteases remained unknown. ß-secretase has been identified as the novel transmembrane aspartic protease, ß-site APP Cleaving Enzyme 1 (BACE1, also known as Asp2 and memapsin 2). BACE2, a novel protease similar to BACE1, was also discovered, and the two BACE enzymes form a new family of transmembrane aspartic proteases. BACE1 has all of the properties of a ß-secretase, and as the key enzyme that initiates the formation of Ab, it is a promising drug target for AD. This review summarizes AD treatment from a medicinal chemistry perspective, as well as the development of novel AD remedies (BACE inhibitors).

KEYWORDS: Alzheimer's disease, beta-secretase, medical approaches, BACE inhibitors.

1. INTRODUCTION

Alzheimer's disease is a degenerative neurological condition that primarily impacts the brain, resulting in a deterioration of memory, cognitive abilities, and overall mental function. It is the predominant cause of dementia, comprising around 60-80% of all cases. The disease typically initiates with mild symptoms, such as memory lapses and verbal retrieval challenges, but progressively deteriorates over time, significantly impairing an individual's capacity to perform routine tasks. The etiology of Alzheimer's disease remains incompletely elucidated, but it is hypothesized to entail a multifaceted interplay of genetic, environmental, and lifestyle determinants. The defining features of the disease are the buildup of atypical protein formations known as amyloid plaques and tau tangles in the brain. These formations interfere with the regular operation of neurons and ultimately result in their deterioration and demise. Alzheimer's disease not only impacts the individuals who are diagnosed, but also imposes a substantial burden on their families and carers. At present, there is no known remedy for Alzheimer's disease, and the treatments that are currently available solely focus on symptom management and the deceleration of the disease's advancement. Current research endeavors are concentrated on comprehending the fundamental mechanisms of Alzheimer's disease,

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formulating more efficient therapies, and investigating potential preventive approaches [1]. Alzheimer's disease is associated with five stages. Preclinical Alzheimer's disease is one of them. mild Alzheimer's disease-related cognitive impairment, mild Alzheimer's disease-related dementia, moderate Alzheimer's disease-related dementia, severe Alzheimer's disease-related dementia [1] [2]. This review summarizes the compounds that have been published in the last 20 years and could serve as a foundation for future medications that treat AD.

2. MATERIAL AND METHODS

Data Collection; A thorough literature search was conducted using electronic databases, including PubMed, Embase, and PsycINFO. The search terms used were "Alzheimer's disease," "AD," "therapeutic strategies," "treatment options," and "clinical trials." Articles published between January 2002 and September 2002 were included to capture the most recent developments. Both preclinical and clinical studies were considered.

- *Study Selection*; Full texts of potentially relevant articles were retrieved and assessed for eligibility. Inclusion criteria; Studies focusing on therapeutic strategies for Alzheimer's disease. Exclusion criteria; Studies not directly related to Alzheimer's disease and Articles published in languages other than English.
- *Data Analysis*; The extracted data were synthesized and analyzed thematically. Similarities and differences among the included studies were identified. Key findings were summarized, highlighting the efficacy and limitations of different therapeutic approaches. Emerging trends and potential future directions were discussed.
- *Ethical Considerations*; No ethical approval was required for this review article as it is based on the analysis and interpretation of previously published studies.
- *Limitations*: The review is limited by the availability and quality of the included studies. The scope of the review focuses on therapeutic strategies for Alzheimer's disease and does not cover other aspects, such as diagnostic approaches or pathophysiological mechanisms. The cutoff date for article selection may have excluded recent publications**.**

3. RESULTS AND DISCUSSION

3.1. Ligands Approach for the Treatment of AD

3.1.1. Current Available Treatment of AD

The cholinergic hypothesis is the foundation of the traditional and most popular theory of AD treatment, having been applied to treat this ailment for nearly twenty years. The cholinergic theory, which is predicated on the finding that the CNS lacks adequate amounts of A.Ch. It has been demonstrated that cognitive dysfunctions are closely associated with cholinergic functions and levels (1). Furthermore, it has been noted that individuals with early onset AD exhibit aberrant and reduced activity of the enzyme Ch.AT, which is in charge of synthesising A.Ch [1]. Aberrantly high levels of enzymes like Bu.ChE and A.ChE, which break down A.Ch, were seen in AD patients. Based on these results, the cholinergic replacement strategy was selected as the main therapeutic approach to treat AD. A.ChEI and Bu.ChEI were used in an attempt to try this strategy. FDA approved Tacrine 1 (Fig. 1), an A. ChEI, for clinical use against AD in 1993. Later, the FDA approved three more A.ChEI, named Donepzil 2 (Fig. 1), Galantamine 3 (Fig. 1), and Rivastigmine 4 (Fig. 1), for the same use. Due to the severe

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adverse peripheral effects caused by the over-activation of cholinergic systems, the use of these A.ChEIs is largely limited [1].

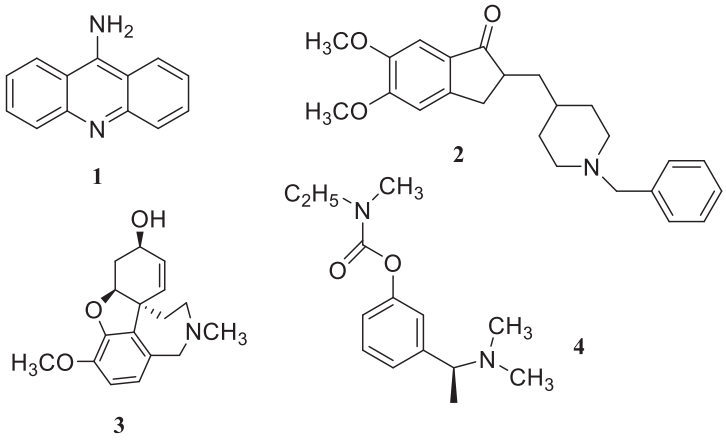

Fig. 1: A.ChEI analogous

3.1.2. Dual Binding A.ChEI

The 3D crystallographic structure of A.ChE by Sussman *et al*. (1991) and the crystallographic structure of the Donepzil-A.ChE complex served as the foundation for the development of dual inhibitors of A.ChE. A.ChE had catalytic and PAS binding sites where Donepzil 2 (Fig. 1) could interact. The connection between PAS and Aβ has been further elucidated by interactions with other PAS ligands that have been shown to have an impact. Additional advancements in the inhibition of dual biding sites focused on modifying the structure of donepzil to reserve the dual binding and improve its pharmacological action. Using this method, a large variety of N-benzylpiperidine analogues were created, including homodimers and heterodimers of well-known inhibitors like Tacrine 1 (Fig. 1) and Donepzil 2 (Fig. 1) [2].

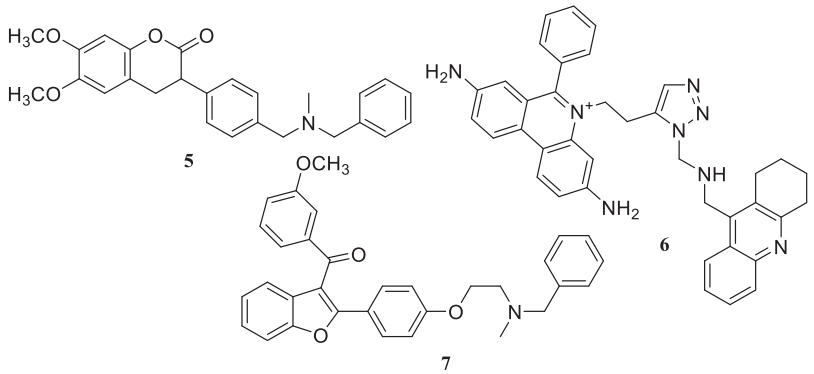

Fig. 2: Dual binding A.ChEI analogous

Based on the analysis of the x-ray crystallographic structures of various A.ChE-Ligand complexes and molecular modelling studies, a novel molecule known as compound (5) (Fig. 2) was created. It was created by combining two of the best binders for the catalytic and PAS binding sites of A.ChE, in which a coumarin (2H-2-chromene) and benzylamino were fused together with a linker to interact with the enzymatic residue. Compound (6) (Fig. 2) was designed using the same methods as by Sharpless *et al*. (2002), and it was realized to be one of

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the most potent inhibitors in this class. A huge fact indicated that Bu.ChE is a co-regulator of A.Ch neurotransmission, which is an evidence of what formerly mentioned that Bu.ChE showed a significant high levels in AD patients, these findings lead to the evolution of selective inhibitors of Bu.ChE. Like, Compound 7 (Fig. 2) which was designed as a selective potent Bu.ChE inhibitor [3].

3.1.3. Dual binding A.ChE and β-Secretase Inhibitors

As previously mentioned, Aβ deposits play a role in the aetiology of AD and have a sharp impact on the decline in cerebral cortex cognitive functions in AD patients. Thus, it makes sense to target the enzymes A.ChE and β-secretase in order to find new AD treatments. It has been reported that bis(7)-tacrine 8 (Fig. 3) is a selective inhibitor of the β-secretase enzyme. Administration of bis(7)-tacrine was found to decrease the production of intracellular and secreted Aβ deposits. Based on compound 5 (Fig. 2), Piazzi *et al*. (2008) reported the first dual inhibitor for both enzymes, Compound 9 (Fig. 3) [4].

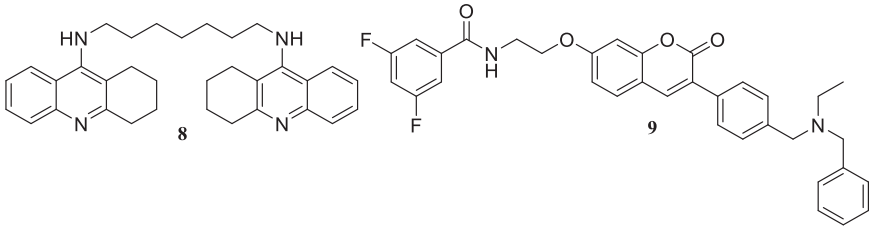

Fig. 3: Dual binding A.ChE and β-secretase Inhibitors analogous

3.1.4. A.ChEI and Antioxidants

Oxidative stress, which is brought on by AD patients' abnormally high production of ROS, is one of the primary causes of neuronal cell death. The interaction of hydrogen peroxide with metal ions (iron) can result in the production of free radicals when abnormal ROS production occurs. In AD patients, these free radicals lead to lipid peroxidation in the membranes of their neuronal cells [5].

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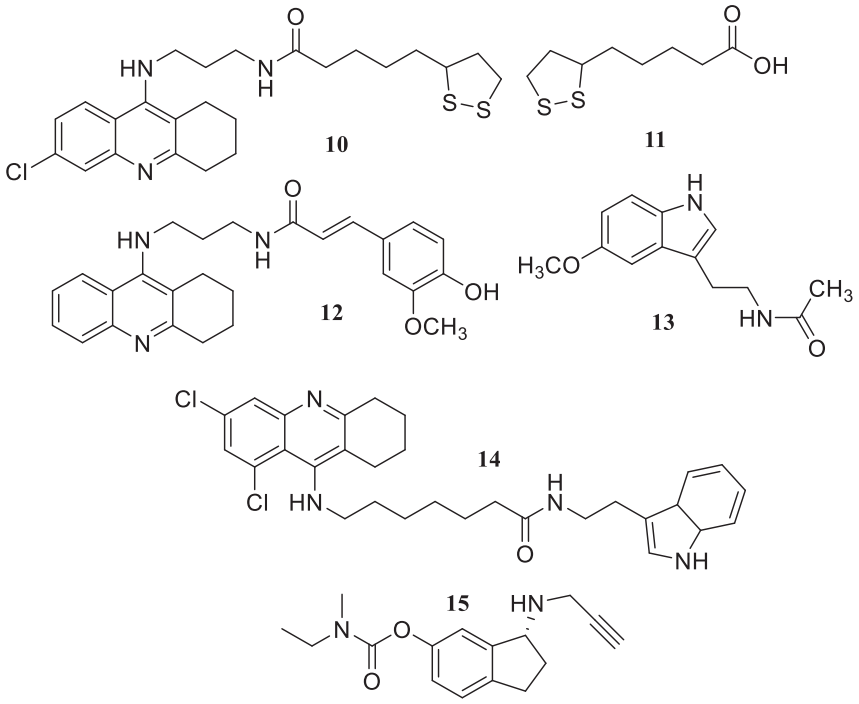

Fig. 4: A.ChEI and Antioxidants analogous

Additionally, certain proteins can be oxidised by free radicals to produce protein carbonyl species, which are found in specific brain regions in AD patients. Based on this data, Lipocrine 10 (Fig. 4) was created as an antioxidant to lower the concentration of free radicals and, in turn, lessen their harmful effects; its structure is derived from that of Lipoic acid 11 (Fig. 4), an effective antioxidant with a variety of neuroprotective properties [6]. Compound 12 (Fig. 4), which was created using the same methodology and was based on lipoic acid, demonstrated strong neuroprotective properties. A fascinating design of compound 14 (Fig. 4) was also inspired by the neurohormones melatonin 13 (Fig. 4) and tacrine 1 (Fig. 1), which have potent antioxidant and free radical-scavenging abilities [7]. During the catalytic deamination of neurotransmitters (norepinephrine, dopamine, and serotonin), the MAO enzymatic family releases reactive oxygen species (ROS). Consequently, in AD patients, MAO inhibition will lessen ROS and the consequences of oxidative stress. Propargylamine moieties were introduced to target the dual inhibition effect of A.ChE and MAO. Modelled as a novel multifunctional inhibitor of both A.ChE and MAO, Ladostigil 15 (Fig. 4) was developed [8].

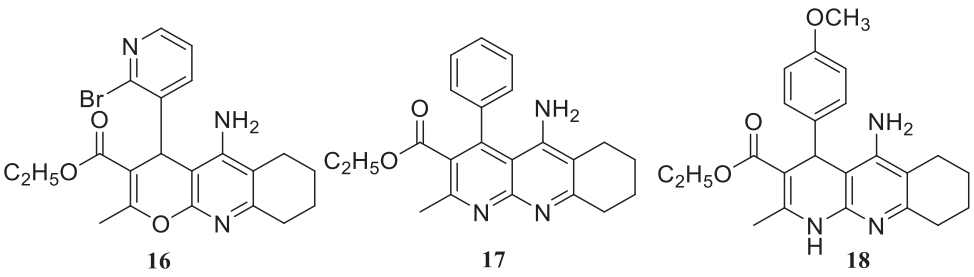

Fig. 5: A.ChEI and Ca+2 Channel Blocking analogous

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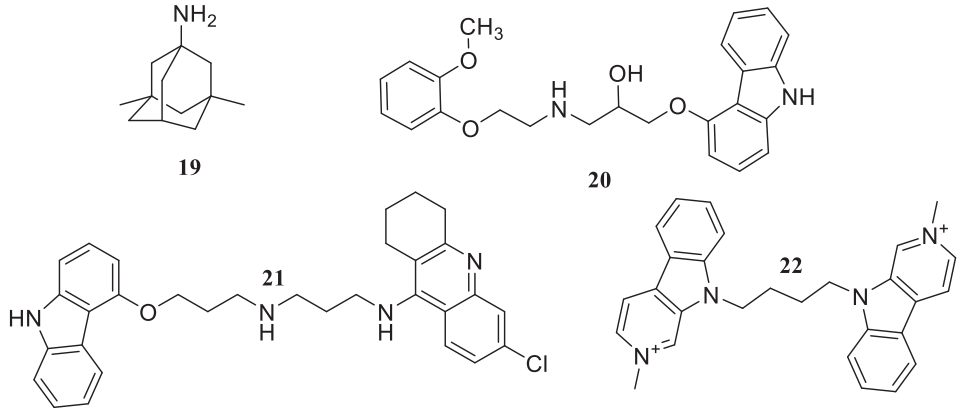

Fig. 6: A.ChEI and and Other modifying targets analogous

3.1.5. A.ChEI and Calcium Channel Blockers

Calcium disruption can cause cell death, leading to increased Aβ deposits and hyperphosphorylation of tau protein. Calcium overload in pathological circumstances disrupts mitochondria and initiates a cascade of neuronal apoptosis. Neuronal cell death can be prevented by manipulating intracellular calcium levels through specific calcium channels. Compounds 16 (Fig. 5), 17 (Fig. 5) and 18 (Fig. 5) were developed to target calcium disruption in the pathological progression of Alzheimer's disease [9]. This is accomplished by modulating VDCCs. They can modulate calcium levels and act as A.ChEI [10].

3.1.6. A.ChEI and Other Modifying Targets

Mitochondrial abnormalities are known to be markers for AD. Also, cerebral cortex of AD patients showed diminished activity of crucial enzymes such as COX (Antioxidant), α-Ketoglutarate dehydrogenase and Pyruvate dehydrogenase. Mitochondrial abnormalities are found mainly in neurons that lack pathological Aβ deposits, indicating that these abnormalities occur only at very early stages of AD these abnormalities may induce also intracellular calcium dyshomeostasis, which have deleterious effects in the progression of AD as mentioned before [11]. The overload activation of NMDAR also could cause bigger neurotoxicity. Compound 19 Memantin (Fig. 6), was only A.ChEI and NMDAR antagonist, which was able to minimize the toxicity caused by Aβ deposits. Rosini *et al*. (2008) deigned a new multi-target ligand based on the structure of Carvedilol 20 (Fig. 6), Carbacrine 21 (Fig. 6) showed effective anticholinesterase activity and found to be more potent than tacrine. Compound 22 (Fig. 6) was designed among several bivalent β-carboline analogues, which were potent NMDAR blockers [12].

3.1.7. Non-Cholinergic Multi-Target Developments

A lot of research has been done on non-cholinergic-based drug discovery because AD pathogenesis involves a variety of pathways and mechanisms. Studies have focused on the processing of Aβ deposits and the hyperphosphorylation of tau proteins [13]. SL-65.0155 (Sanofi-Aventis, Paris, France) and VRX-03011 (EPIX Pharmaceuticals, Lexington, MA) have reached phase II clinical trials for the treatment of AD. Modulation of APP cleavage pathways was observed with some NSAIDs such as Ibuprofen 23 (Fig. 7) and Indomethacin 24 (Fig. 7). They are not responsible for this action because they inhibit COX 1 and 2. however connected

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to the antagonistic relationship with the PPAR [14]. Ample evidence and data suggested that PPAR antagonistic actions could be advantageous in AD in a number of ways. A series of molecules was designed by Heike *et al*. (2010) based on the integration of PPAR activity and α-secretase modulation activity. Compound 25 (Fig. 7) was created to be a strong 5-HT4 receptor agonist, and 5-HT4 agonists are of interest in AD medication development [15]. HDAC enzyme inhibition is another novel strategy. One of the benzolactam derivatives created by Kozikowski *et al*. (2009) that exhibits good HDAC enzyme inhibition activity is compound 26 (Fig. 7). One of the most significant pathological elements in AD is oxidative stress. An innovative method was employed to create an anti-inflammatory antioxidant molecule. This approach was chosen because inflammation may be taken into account when analysing the pathophysiology of AD [16]. Quinolones have a wide range of biological activity and are present in many synthetic and natural products. Detsi *et al*. (2007) created a series of analogous compounds using quinolone structures; compound 27 (Fig. 7) demonstrated strong antioxidant properties and good anti-inflammatory activity [17]. The pathophysiology of AD was clearly impacted by the formation of tau-protein aggregates, and tau-protein is only harmful when it is hyperphosphorylated. Glycogen synthase kinase-3β (GSK3β), casein kinase-1 (CK-1), and cyclin-dependent kinase-5 (CDK-5) phosphorylate tau protein. Based on the inhibition of protein kinase enzymes, tau-protein was the target of drug design [18]. Compound 28 (Fig. 7) is a trisubstituted purine that has shown promise in preventing tau-protein aggregations and is thought to be one of its analogous compounds' most potent CK-1 inhibitors [19].

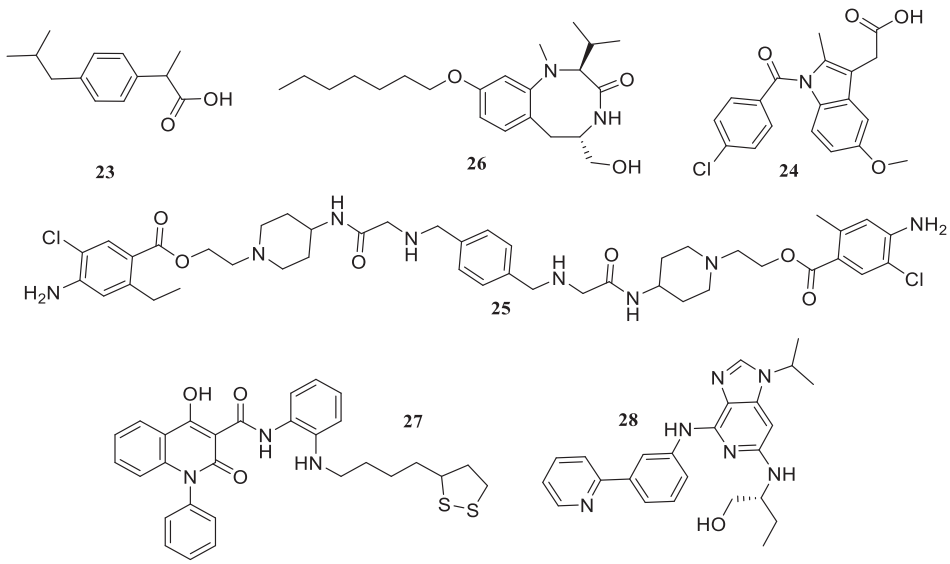

Fig. 7: Non-Cholinergic Multi-Target developments

3.2 Evolution of B-Secretase Inhibitors

It was believed that the principles of inhibitor design for other aspartic protease drugs could be applied to the development of β-secretase inhibitors because the catalytic properties of β-secretase are nearly identical to those of other catalytic enzymes (HIV protease and renin). Based on the history of HIV protease and renin drug development, it is probable that effective β-secretase inhibitor medications will imitate substrate conformation at transition state, providing high potency β-secretase inhibitor. Since the endosomes of brain neurons are the

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primary location of APP and its products (Aβ-40, Aβ-42) a clinically effective β-secretase inhibitor must be able to cross both the neuronal membranes and the BBB. Approximately 550 Da is the maximum molecular size that can cross the BBB. Furthermore, these inhibitors ought to possess favourable drug-like properties related to. ADME. Since 2002 until the present, over 600 publications and patents pertaining to β-secretase inhibition have been published [20].

3.2.1. Pseudo-Peptide Inhibitors

Based on a HE transition-state isostere (57), OM99-2 29 (Fig. 8) was developed as the first highly potent inhibitor. A statine-derived inhibitor of cell β-secretase 30 (Fig. 9) demonstrated selective inhibition of Aβ formation. There has been information on another compound 31 (Fig. 9) that has a phenyl-norstatine moiety as the transition-state isostere. Tetrazole rings were shown to be a suitable bio-isosteric substitute for the carboxylic acids in compounds 32 and 33 (Fig. 9), which were later reported to be strong β-secretase inhibitors based on phenyl-norstatine. By examining the bioisosteres of the acidic tetrazole ring, another study attempted to create pharmaceutically useful compounds. This resulted in compound 34 (Fig. 9), which maintained optimal enzymatic inhibition activity, by adding a fluoroorotyl group at the P4 position and an L-cyclohexylalanine residue at the P2 position. Another design was reported that used α-phenyl-norstatine or α-benzyl-norstatine as the central core and involved a series of new tetra-alcohol. Compound 35 (Fig. 9) and β-secretase co-crystallized. For this class of inhibitors, a novel binding mode was found in which the TS-isostere was the N-terminal amine group [21].

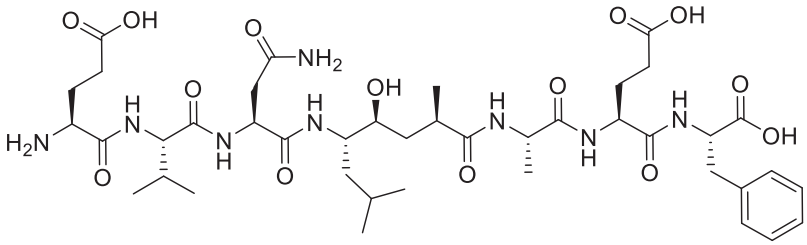

Fig. 8: OM99-2 29

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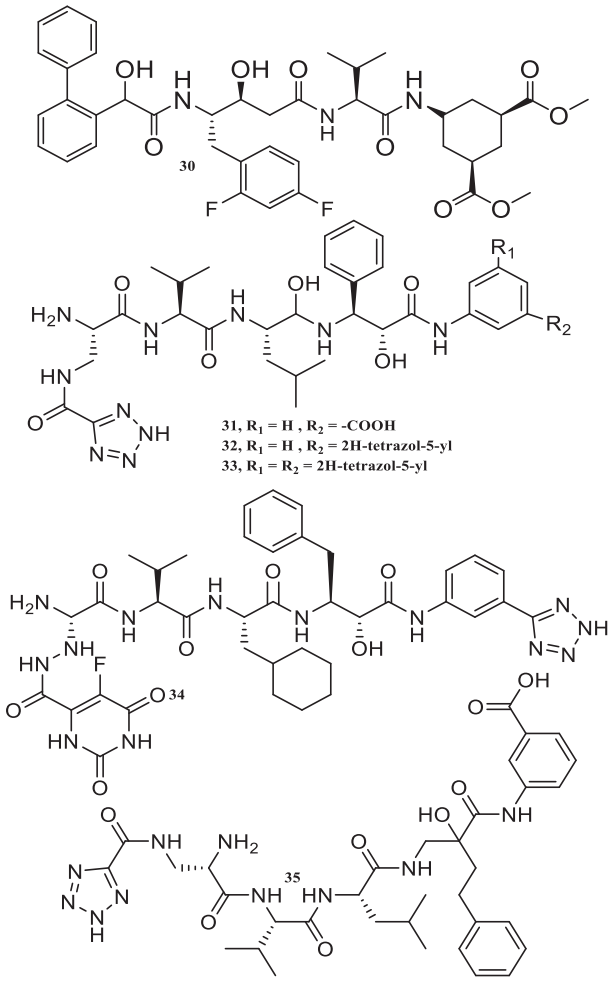

Fig. 9: Pseudo-peptide inhibitors

3.2.2. Hydroxy-Ethylene-Based Inhibitors

Compound 36 (Fig. 10) with the N-terminal iso-phthalamide group shown to be a potent, small molecule inhibitor with improved cell penetration was investigated using hydroxyethylene transition state isostere as a scaffold. Compound 37 (Fig. 10) emerges as a result of the hydroxy-ethylene-based peptidomimetic inhibitors' P1 position having an oxygen atom substituted [22].

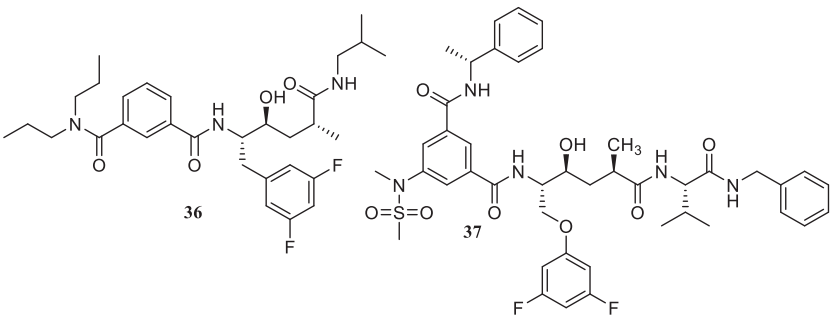

Fig. 10: Hydroxy-ethylene-based inhibitors

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3.2.3. Hydroxy-Ethylamine-Based Inhibitors

One of a class of hydroxyethylamine (HEA)-based inhibitors, compound 38 (Fig. 11), is a powerful and cell-permeable peptidomimetic inhibitor that combines the isophtalamide moiety with a HEA isostere. Similar to inhibitor compound 39 (Fig. 11), which increased affinity for the enzyme by functionalizing the isophthalamide ring's C-5 position with a polar primary amide, high enzymatic potency was also observed [23]. It was demonstrated that Compound 40 (Fig. 11) is an oral bioavailable inhibitor with BBB-passing ability. A tricyclic indole derivative was then found to be able to mimic the important non-primed side interactions of compound 40 (Fig. 11) through molecular modelling. It was supported by the argument that binding to the protein would be significantly more effective if the active conformation was constrained in this manner. Compound 41's bioavailability was increased by the introduction of 4-pyranyl amine, which demonstrated enhanced permeability and clearance (Fig. 11) [24].

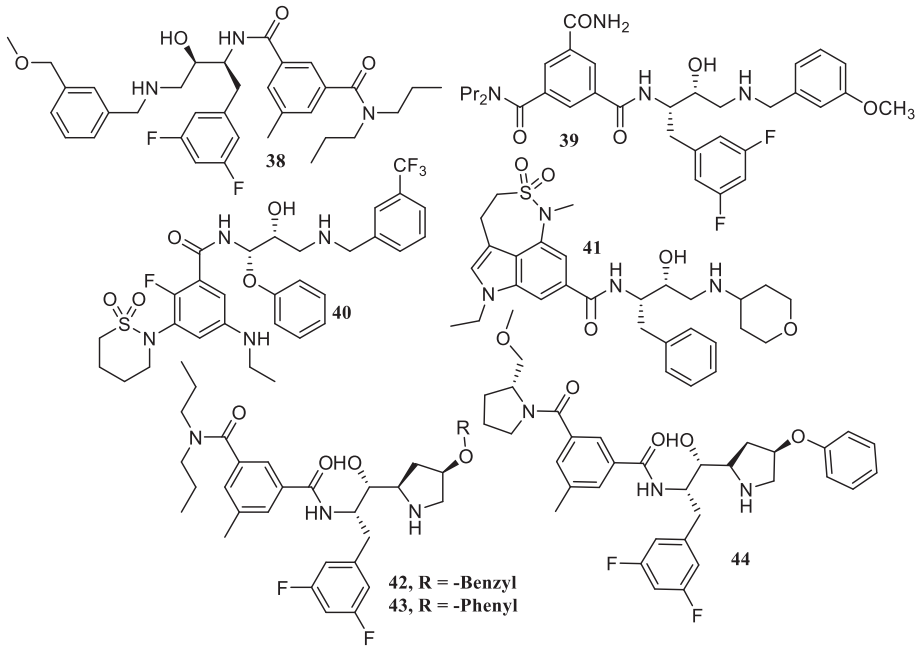

Fig. 11: Hydroxy-ethylene-based inhibitors

Compounds 42 and 43 (Fig. 11) representing the development of 4-benzyloxypyrrolidine and 4-phenoxypyrrolidine inhibitors, with insufficient pharmacokinetic properties. Compound 44 (Fig. 11) was produced by substituting a 2-(R)-methoxymethylpyrrolidine amide for the N,N-dipropylamide found in compounds 42 and 43 (Fig. 11) [25].

3.2.4. Carbinamine-Based Inhibitors

Compound 45 (Fig. 12), one of a series of tertiary carbinamine-derived inhibitors, has been studied in which the catalytic Asp of β-secretase is interacting with the primary amine; it was reported that this compound has high potency. Compound 46 (Fig. 12) is one of several intriguing inhibitors that have been developed. They are based on a 2,6-diamino-isonicotinamide core linked to a truncated reduced amino isostere as the aspartate binding element [26].

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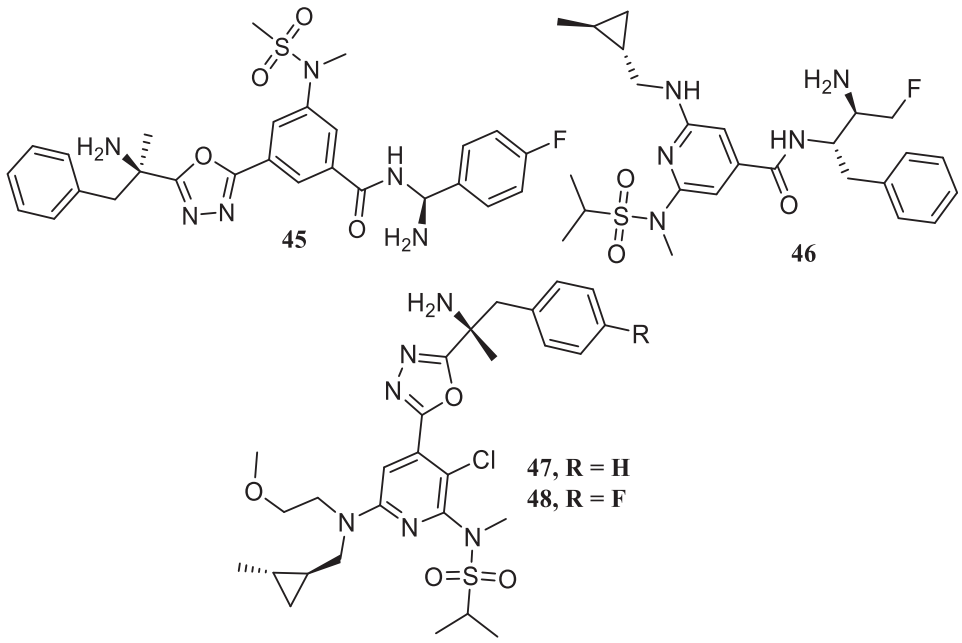

Fig. 12: Carbinamine-based inhibitors

Compound 47 (Fig. 12) is the product of the reaction between the oxadiazolyl tertiary carbinamine and the isonicotinic core, which contains a methylcyclopropyl group. It proved to be a highly effective inhibitor with good performance. Compound 47 (Fig. 12) was found to have pharmacokinetic liabilities due to its low oral bioavailability in various species. Comparing compound 48 (Fig. 12) to compound 47 (Fig. 12), the addition of a 4-fluoro substituent resulted in a 2-fold enhancement in both in vitro and cell-based assays [27].

3.2.5. Macrocyclic-Based Inhibitors

The stabilization of active conformations served as the foundation for the macrocyclization strategy, which has been supported by the emergence of numerous inhibitors. The possibility of boosting potency by stabilising the bioactive conformation of the acyclic series with the preparation of macrocyclic ethers and macrolactones was suggested by the close spatial proximity of the P1 aryl group and the P3 methyl of carbinamine-based inhibitors. Compound 49, macrolactone (Fig. 13), demonstrated good potency and was found to be hydrolytically stable at physiological pH [28].

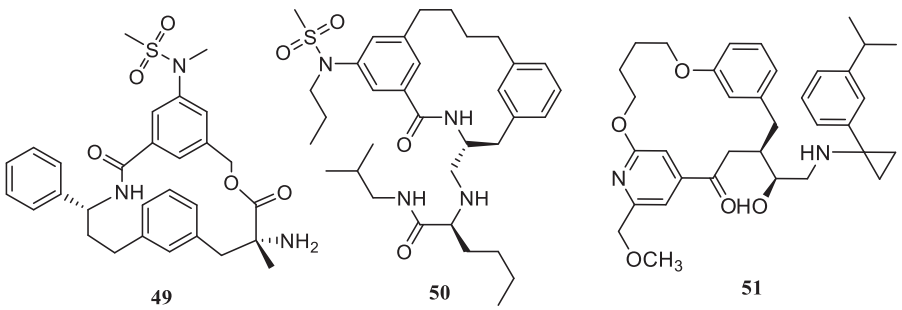

Fig. 13: Macrocyclic-based inhibitors

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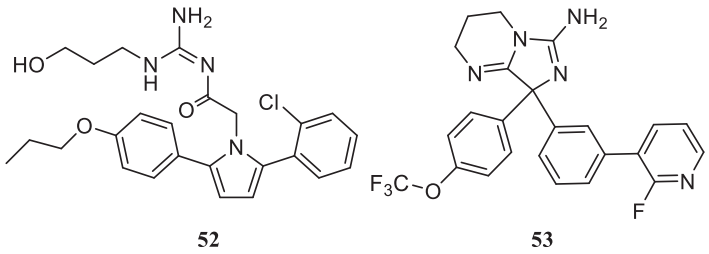
Compound 50 (Fig. 13) consisted of a reduced amide isostere coupled to an isophthalamide scaffold. It demonstrated enhanced permeability of the membrane. Compound 51 (Fig. 75) is one of the macrocyclic peptidic inhibitors that were created using the same methodology in a different study [29].

3.2.6. Acyl-Guanidine-Based Inhibitors

Compound 52 (Fig. 14) was the result of high-throughput screening (HTS) for low molecular weight acyl-guanidine inhibitors. The X-ray structure of β-secretase complexed with a closely related analogue of compound 52 (Fig. 14) showed that the substituents on the acyl-guanidine nitrogen extend into the S1' pocket, forming hydrogen-bonding interactions with Arg235 and Thr329 via bridging water molecules, while the N-acyl-guanidine moiety forms hydrogen bonding interactions with the important catalytic aspartates. Little strain, the p-propyl-oxyphenyl group goes from the S1 to the S3 pocket, and the pyrrole ring interacts with the flap Tyr71 through p-stacking. Furthermore, the inhibitor maintains the enzyme in an open conformation, as demonstrated by the crystal structure. This is different to most peptidomimetic inhibitors which bind to β-secretase in a closed-flap form [30].



52 53

Fig. 14: Acyl-guanidine, Amino-imidazole and amino-hydantoin-based inhibitors

3.2.7. Amino-Imidazole and Amino-Hydantoin-Based Inhibitors

Amino-imidazole-based inhibitor, compound 53 (Fig. 14) was derived from the addition of either a pyridine or a pyrimidine ring on a previously identified compound 52 (Fig. 14) [31].

3.2.8. Amino-Quinazoline-Based Inhibitors

Amino-quinazoline was introduced to be combined with the catalytic Asp. One of these synthetic analogous compounds was compound 54 (Fig. 15). Structure-based optimisation of compound 54 (Fig. 15) produced compound 55 (Fig. 15) with moderate potency. A series of inhibitors that included particular heterocycles to interact with residues in the active site was compound 56 (Fig. 35) [32].

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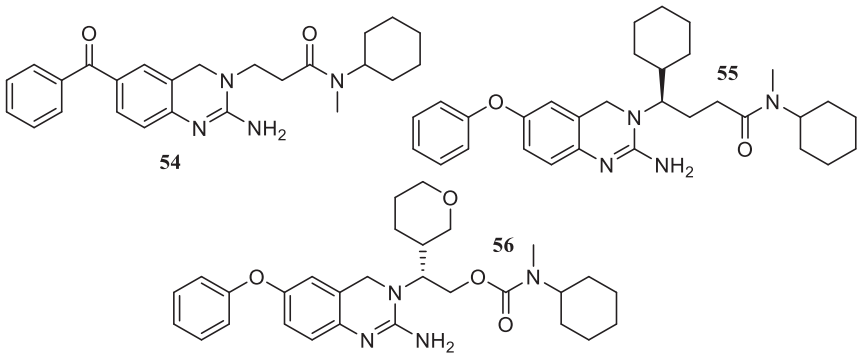

Fig. 15: Amino-quinazoline-based inhibitors

3.2.9. Miscellaneous Non-Peptidic Scaffolds

Compound 57 (Fig. 16), a novel non-peptidic inhibitor based on an isatin motif, was created through virtual screening. It was discovered that these compounds have two primary problems: their relatively low solubility in combination with the nitro and phenolic functionalities [33]. Several new non-peptide inhibitors were identified through virtual screening in conjunction with bioassay. Compound 58 (Fig. 16) is one of the most potent molecules found in this class. A benzothiazole ring found in compound 58 (Fig. 16) docks into the enzyme's S1' pocket and spans the interaction through nearly all β-secretase substitutes [34].

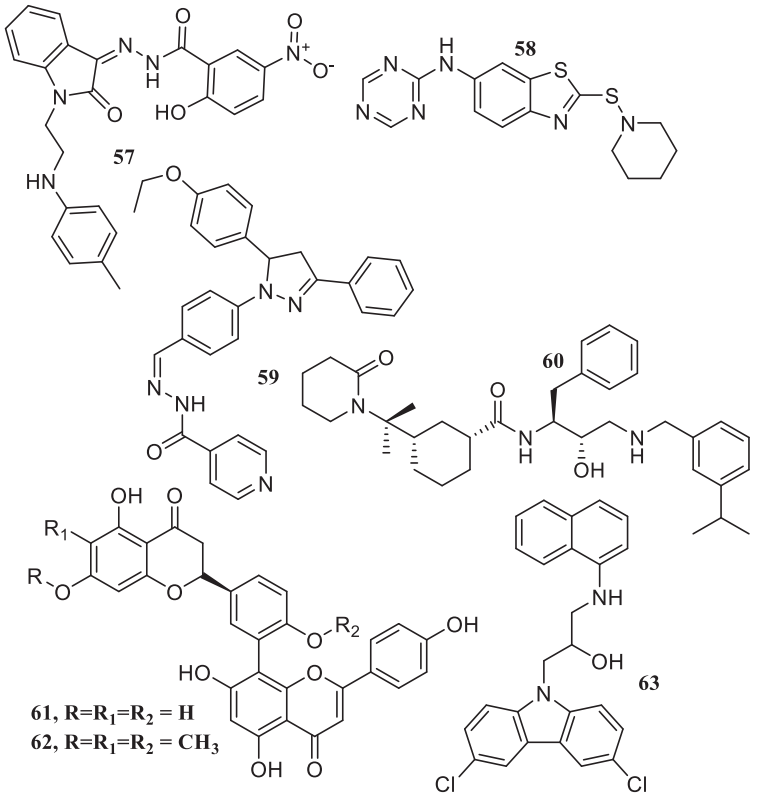

Fig. 16: Miscellaneous non-peptidic scaffolds

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An in silico virtual screening of the commercial database SPECS chemical library led to the identification of compound 59 (Fig. 16) [35]. In a different study, a rigid 3-aminomethyl cyclohexane carboxylic acid was used in place of the P2 amino acid, including the P2/P3 peptide bond, to create a series of inhibitors. The series' most active compound was compound 60 (Fig. 16). The P3/P4 amide bond was positioned into the S3 pocket by co-crystallization, revealing an unexpected binding mode and creating a novel hydrogen bond interaction pattern [36]. Amentoflavone-type bi-flavonoids have been shown in studies to exhibit strong neuroprotective properties as well as β-secretase inhibitory activity. Two of these naturals showed strong inhibitory effects: 2,3-di-hydroamentoflavone (compound 61 (Fig. 16)) and 2,3-dihydro-6-methylginkgetin (compound 62 (Fig. 16)) [37]. Using an HTS fluorescence assay, Compound 63 (Fig. 36) was found to be a promising new lead compound [38].

3.2.10. Multi-Target-Directed Ligand (MTDL)

The goal of MTDL is to improve efficacy and safety by addressing multiple targets for a specific disease. The complexity and multiple aetiologies of Alzheimer's disease make the MTDL approach a potentially effective strategy for AD treatment. In recent years, MTDLs with improved pharmacological profiles have been reported, including β-secretase inhibitors with A.ChE inhibitory activity and metal chelating properties [39]. Compound 64 (Fig. 17) was developed by incorporating a 1,4-benzoquinone functionality as a free radical scavenger into the polyamine skeleton series of cholinergic derivatives. Recently, dual inhibitors of A.ChE and β-secretase were designed using the MTDL strategy. Compound 65 (Fig. 17) was one of them. To address the importance of β-secretase and metal ions in Alzheimer's disease, a new class of 1,3-diphenylurea derivatives were created by combining a metal chelator and a β-secretase inhibitor. All compounds in this class were able to chelate metal ions, with compound 66 (Fig. 17) being the most effective inhibitor [40].

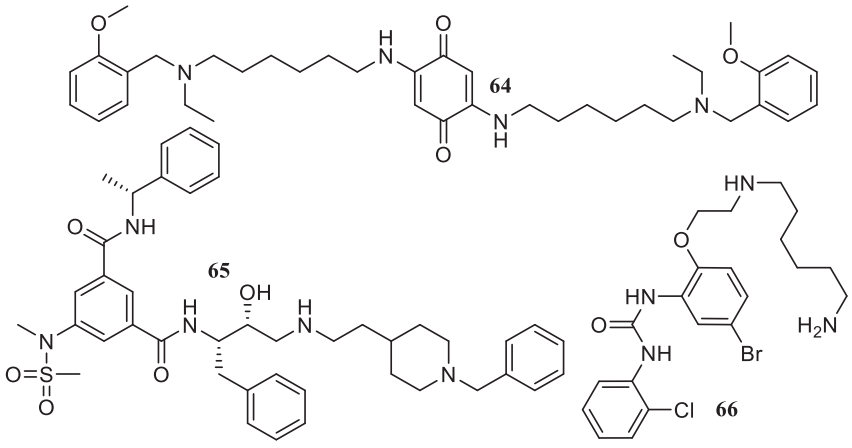

Fig. 17: Multi-target-directed ligands

4. CONCLUSION

A brief review of the literature on potential mechanisms of the development of Alzheimer's disease-type pathology demonstrates that the pathology's complex nature suggests a wide range of approaches for its pharmacological correction. Indeed, the development of this neurodegenerative disorder is characterized by the involvement of various intra- and extracellular biological systems, which may be medicinally affected by potential therapeutic

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agents. In addition to the direct effect on AD pathogenesis, the pathology can be corrected by activating compensatory mechanisms in the CNS, significantly expanding the range of AD treatment options.

Research into BACE1 (and BACE2) and its role as a drug target in Alzheimer's disease is still in its early stages. As an extension of this line of reasoning, BACE1 inhibitors should reduce amyloid plaque formation. Despite recent advances in understanding the molecular and cellular properties of BACE1 and BACE2, little is known about their substrates (aside from APP) and biological functions. Regarding BACE2 function, the intriguing pattern of BACE2 expression in the brain indicates that BACE2 plays an important role in specific neuronal populations. To date, no mutations in the BACE1 gene have been identified as strongly associated with Alzheimer's disease. Still, mutations in the BACE1 gene may escalate the risk of Alzheimer's disease by increasing either BACE1 gene expression or enzyme activity. Such BACE1 mutations are expected to increase Ab production, potentially contributing to AD pathogenesis. A 50% increase in Ab levels in DS is sufficient to cause early-onset AD, and even much smaller Ab increases may have profound effects over time, resulting in some forms of late-onset AD. In this regard, the use of modern computational approaches based on the analysis of QSAR for the focused design of novel efficient neuroprotectors and cognition enhancers for Alzheimer's disease therapy appears to be particularly promising. Finally, as the key enzyme that initiates Ab formation in vivo, BACE1 is an ideal drug target for inhibiting Ab production. Although developing BACE1 inhibitors will be difficult, BACE1 drugs are likely to become available in the future. Drugs that inhibit other therapeutically important aspartic proteases, such as renin and HIV protease, have been successfully developed, and these drugs serve as models for the rational design of BACE1 inhibitors for AD.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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APPENDIX A: LIST OF ABBREVIATIONS

ADME	Absorption, Distribution, Metabolism, and Excretion
A.Ch	Acetyl Choline
A.ChE	Acetylcholinesterase
A.ChEI	Acetylcholinesterase enzyme inhibitors
AD	Alzheimer's disease
BBB	Blood Brain Barrier
Bu.ChE	Butyrylcholinesterase
Bu.ChEI	Butyrylcholinesterase enzyme inhibitors
CNS	Central Nervous System
Ch.AT	Choline Acetyl Transferase
FAD	Early-onset familial
FDA	Food and Drug Administration
HDAC	Histone deacetylase
HT	Hydroxy tryptamine
MAO	Monoamine Oxidase Enzyme
NMDAR	N-Methyl-D-Aspartate
PAS	Per-Arnt-Sim
PPAR	Peroxisome Proliferator-Activated Receptor
QSAR	Quantitative Structure Activity Relationship
ROS	Reactive Oxygen Species
VDCCs	Voltage Dependent Calcium Channels

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