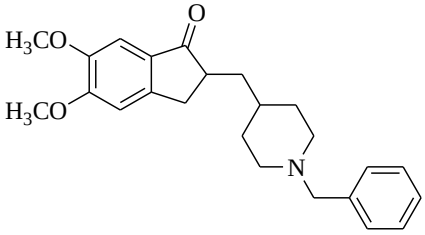
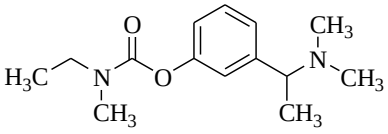
2. LITERATURE REVIEW

2.1 FDA approved drugs for the treatment of AD

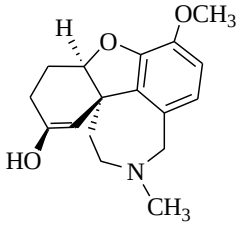
Currently, there are five FDA-approved drugs for the treatment of AD. These drugs work by either increasing the levels of neurotransmitters in the brain or slowing down the breakdown of these neurotransmitters. The five drugs are Donepezil **(I)**, Rivastigmine **(II)**, Galantamine **(II)**, Memantine **(IV)** and Memantine/donepezil combination therapy[1] **(Figure 2.1)**. These drugs have modest and temporary benefits in improving cognitive function and delaying the progression of AD, but they cannot reverse or cure the disease process, and they do not work for all individuals with AD[2,3].



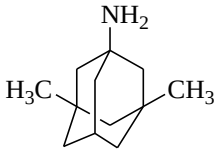
(**I**)



(**II**)



(**III**)



(**IV**)

Figure 2.1: Currently marketed drugs for the treatment of AD

The mechanism action of drug and use are following:

- Donepezil (brand name: Aricept): This drug is an AChE inhibitor, which increases the levels of the neurotransmitter acetylcholine in the brain. Donepezil is approved for mild to moderate AD[4].
- Rivastigmine (brand name: Exelon): Rivastigmine is also an AChE inhibitor. It is approved for mild to moderate AD[5].
- Galantamine (brand name: Razadyne): Galantamine is an AChE inhibitor and also works by modulating nicotinic receptors in the brain. It is approved for mild to moderate AD[6].
- Memantine (brand name: Namenda): Memantine is an N-methyl-D-aspartate (NMDA) receptor antagonist, which blocks the activity of the neurotransmitter glutamate in the

brain. Glutamate is involved in learning and memory, but excess levels of glutamate can be toxic to brain cells. Memantine is approved for moderate to severe AD[7].

- Memantine/donepezil (brand name: Namzaric): Namzaric is a combination of memantine and donepezil. It is approved for moderate to severe AD[8].

Tacrine was the first AChE inhibitor approved by the FDA for the treatment of AD[9]. It works by increasing the levels of the neurotransmitter acetylcholine in the brain, which is important for memory and learning[10,11]. However, its use is limited due to a high incidence of side effects, including hepatotoxicity (liver damage) and gastrointestinal disturbances, and the availability of newer, safer medications[12]. Therefore, tacrine is no longer widely used for the treatment of AD.

2.2 FDA approved antibodies for the treatment of AD

The FDA has approved two antibodies for the treatment of AD:

- Aducanumab (brand name: Aduhelm): Aducanumab is a monoclonal antibody that targets beta-amyloid plaques in the brain. Aducanumab is designed to help remove beta-amyloid from the brain and slow the progression of the disease. It was approved in 2021 for the treatment of early AD[13,14].
- Solanezumab (brand name: Eli Lilly): Solanezumab is also a monoclonal antibody that targets beta-amyloid plaques in the brain. It was approved in 2021 for the treatment of mild AD[15,16].

Both of these antibodies have shown some benefit in clinical trials, but their effectiveness is still being studied and debated. It is important to note that these drugs are expensive and require regular infusions, and their long-term effects on cognitive function and disease progression are still unknown[17].

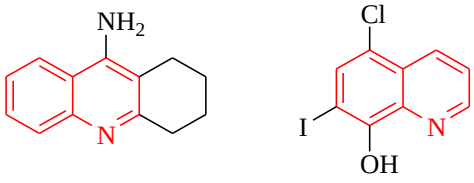
2.3 Reported Multi-targeted directed ligands (MTDLs) for treatment for AD.

Multi-targeted directed ligands (MTDLs) are a promising class of drugs for the treatment of AD[18]. Unlike traditional drugs that target a single receptor or pathway, MTDLs act on multiple targets involved in the disease process, including the beta-amyloid protein, tau protein, inflammation, and oxidative stress[19,20]. This MTDLs approach has the potential to be more effective in slowing or halting the progression of AD. MTDLs are still in the early stages of development and testing, but initial results have shown promise in preclinical and early clinical

trials[21,22]. In the following section, various recently developed MTDLs with different scaffolds have been summarized.

2.3.1 Quinoline based anti-AD agents

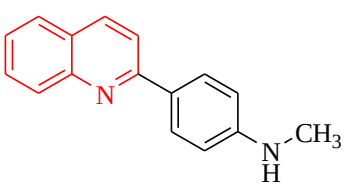
Quinoline is a heterocyclic organic compound that contains a benzene ring fused to a pyridine ring[23]. It is an aromatic compound and is pale yellow in color. Quinoline has a wide range of applications, including in the production of dyes, as a solvent, and as a building block for the synthesis of various drugs and other organic compounds[24]. It also has biological activity and has been studied for its potential use as an antimalarial and anticancer agent[25,26]. Additionally, quinoline derivatives have been investigated for their potential therapeutic applications in various neurological disorders, including AD and Parkinson's disease[27]. Quinoline is considered a classic privileged structure due to its ability to serve as an easily modifiable scaffold for the development and synthesis of drugs, making it a valuable tool in drug discovery for various diseases, including Alzheimer's disease[28]. Some of the approved anti-Alzheimer containing quinoline moiety shown in **Figure 2.2**. Many quinoline based MTDLs were reported in the literature for the treatment of AD as described below.



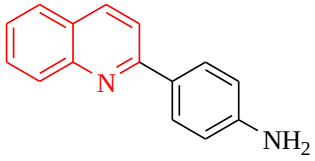
Tacrine Clioquinole

Figure 2.2: Approved quinoline moiety containing anti-AD agent[29,30].

Okamura *et al.* designed and synthesized compounds **(1)** and **(2)**, which contained a quinolone moiety with a phenyl ring at the 2-position. These compounds demonstrated a higher binding affinity to tau fibrils and a lower binding affinity to Aβ fibrils. The Ec_{50} value of compound **(1)** and **(2)** against Aβ fibrils was 659 ±2.04 nM and 786 ± 1.79 nM, respectively. These findings suggest that the quinolone moiety has the potential to be used in the development of anti-Alzheimer's agents[31].

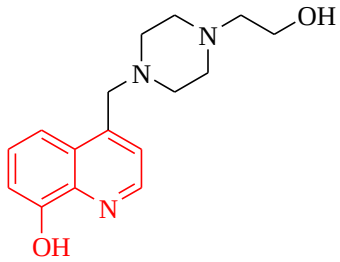


(1)



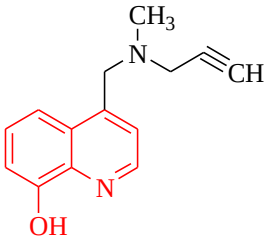
(2)

According to the study by Shachar *et al.*, compound **(3)** has the potential to act as a neuroprotective agent by inhibiting mitochondrial membrane lipid peroxidation induced by Fe/ascorbate and substrate. It was also observed to have a protective effect against 6-hydroxydopamine-induced damage to striatal dopaminergic neurons. Moreover, compound **(3)** could act as a brain-penetrating iron chelator, exhibiting its neuroprotective effects. The study suggests that compound **(3)** could be a promising candidate for the development of therapeutic agents for neurodegenerative diseases[32].



(3)

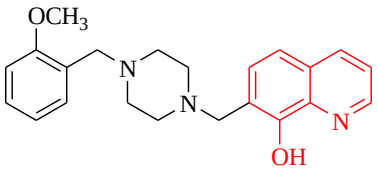
Youdim *et al.* reported that compound **(4)** had properties of a brain-penetrating iron chelator, a selective MAO inhibitor, and a propargyl alcohol neuroprotective agent. It was shown to effectively reduce the expression of amyloid precursor protein (APP) and secretion of Aβ peptide while activating α-secretase and releasing the neuroprotective neurotrophic solution APP alpha. Based on these findings, compound **(4)** was considered a potential therapeutic agent for the treatment of Alzheimer's disease[33].



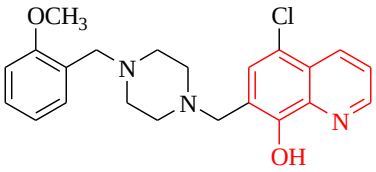
(4)

Prati *et al.*, synthesized two categories of 8-hydroxyquinoline derivatives and assessed their

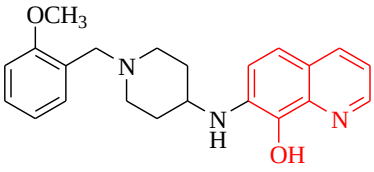
potential as anti-Alzheimer agents by evaluating their inhibition of human cholinesterase (*h*AChE). The findings demonstrated that one group of compounds was either inactive or had weaker inhibition rates against *h*AChE (with inhibition rates ranging from 9.0% to 63.8% for compound **(6)**. However, both series of compounds exhibited a significant inhibitory effect on human butyrylcholinesterase (*h*BChE) at 40 µM (with inhibition rates ranging from 49.2% to 89.1% for 8-hydroxyquinoline derivatives). In particular, the elimination of the Cl atom from compounds **(5)** and **(6)** resulted in a fourfold increase in inhibitory activity, with IC_{50} values decreasing from 23.3 to 5.71 µM. Compound **(5)**, which lacked the Cl atom, exhibited the highest anti-*h*BuChE activity. Additionally, compound **(7)**, which had a bromine substitution, also exhibited good BuChE inhibition[34].



(5)

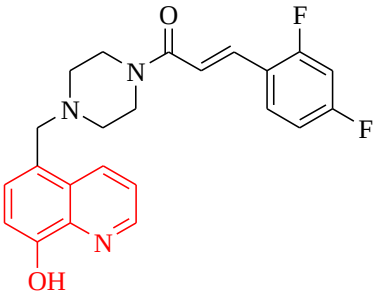


(6)

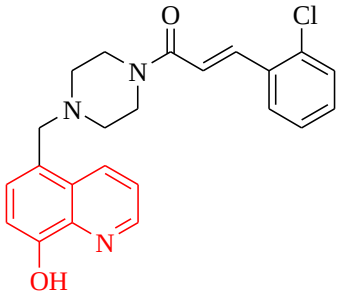


(7)

Yang *et al.* synthesized analogues of 8-hydroxyquinoline containing a piperazine ring and investigated their potential as anti-Alzheimer's disease (AD) agents. They found that three compounds **(8-10)** displayed better inhibition of $A\beta_{1-42}$ aggregation than clioquinol (25.72%) at 10 µM, with inhibition rates ranging from 32.46% to 73.41%. Among them, compound **(8)**, which had a 2,4-difluorobenzene ring, exhibited the strongest $A\beta_{1-42}$ aggregation inhibition activity, with an IC_{50} value of 5.05 µM. Additionally, compounds **(9)**, which contained a 2-chlorobenzene ring, demonstrated greater inhibitory effects against $A\beta_{1-42}$ aggregation than resveratrol (IC_{50} = 12.43 µM) with IC_{50} values of 5.64 µM[35].

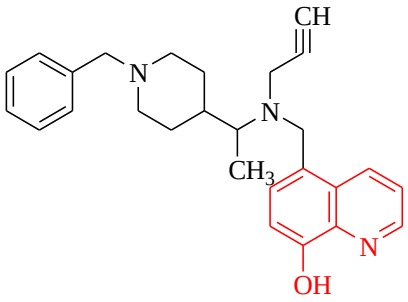


(8)



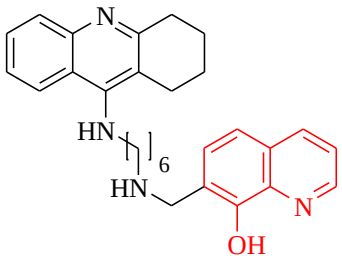
(9)

Li wang *et al.* reported the novel scaffold of donepezil, propargylamine and 8-hydroxyquinoline hybrid as a new multifunctional metal-chelator, AChE inhibitor and MAO inhibitors. Among the reported series, compound **(10)** showed highest MAO inhibitory activity with IC_{50} value of 6.2 ± 0.7 µM for MAO A and IC_{50} value of 10.2 ± 0.9 µM for MAO B. Additionally, compound **10** showed good AChE inhibition and BuChE inhibition with IC_{50} value of 1.8 ± 0.1 µM and 1.6 ± 0.25 µM)[36].



(10)

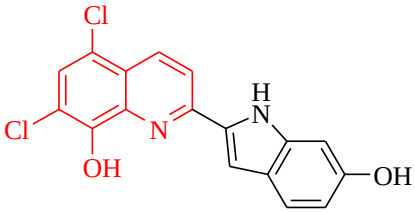
Maria and research group developed new tacrine-8-hydroxyquinoline hybrids that could serve as multifunctional agents for treating AD. These hybrids possess neuroprotective, cholinergic, antioxidant, and copper-complexing properties. Among the synthesized compounds, compound **(11)** displayed significant activity with an IC_{50} value of 20 nM for AChE and 5 nM for BuChE. Furthermore, these compounds exhibited superior antioxidant properties compared to Trolox[37].



(11)

Wang *et al.* developed orally bioavailable quinoline-indole derivatives as MTDLs for the treatment of AD by promoting cell proliferation in the adult murine hippocampus. Among the compounds in the series, Compound **(12)** exhibited strong metal-chelating ability and potent neuroprotective effects through intracellular antioxidant activity (EC_{50} = 0.1 µM). It also showed significant inhibition of self- or Cu^{2+}-induced Aβ aggregation (71.6% and 85.8%, respectively)

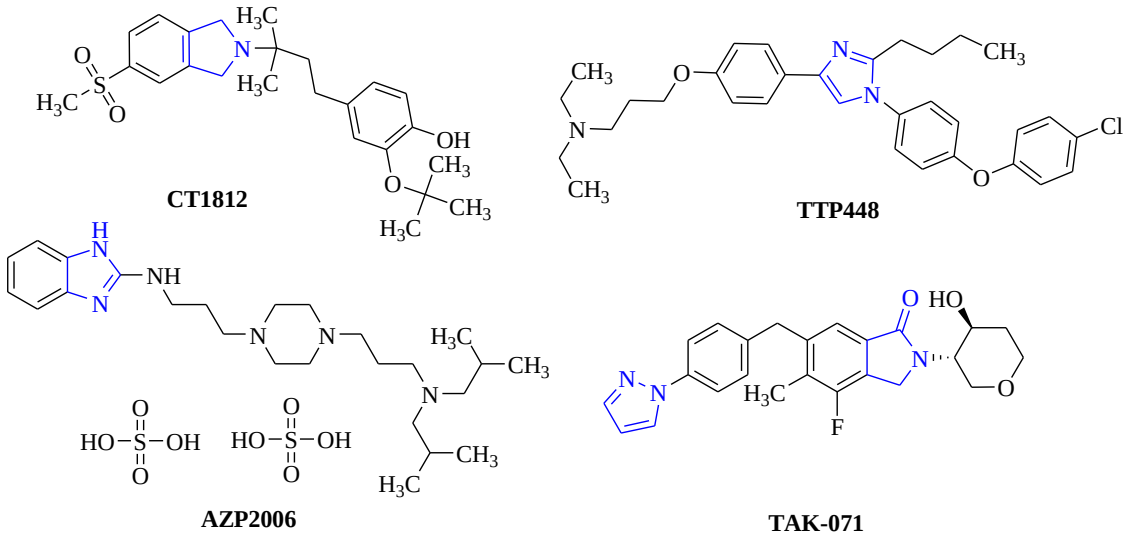
and effective disaggregation of preformed self- or Cu^{2+}-associated $A\beta_{1-42}$ aggregate fibrils (72.7% and 83.3%, respectively)[38].



(12)

2.3.2 Pyrazole based anti-AD agents

Pyrazole is a five-membered heterocyclic compound containing two nitrogen atoms at positions 1 and 2 of the ring[39]. It is an aromatic compound and is characterized by a planar structure due to resonance stabilization[40]. Pyrazole and its derivatives have a wide range of applications in the pharmaceutical and agrochemical industries due to their diverse biological activities such as anti-inflammatory, analgesic, antipyretic, antifungal, antibacterial, and antitumor properties[41,42]. Several pyrazole-based compounds have been developed and evaluated for their anti-AD activity *in-vitro* and *in-vivo*[42]. For example, some studies have shown that pyrazole derivatives can inhibit AChE activity, which can improve cognitive function in AD patients[43]. Other studies have shown that pyrazole compounds can inhibit the aggregation of *β*-amyloid, which is a hallmark feature of AD pathology[44]. Furthermore these type of compounds also investigated for MAO inhibition which is plays important role in progress of AD[45]. Some of the pyrazole based anti-AD agents in clinical trials shown in **Figure 2.3.**

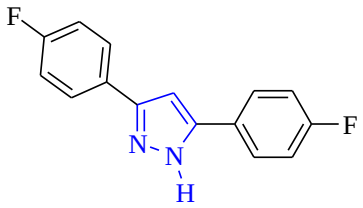


CT1812 **TTP448** **AZP2006** **TAK-071**

Figure 2.3: Pyrazole based anti-AD agents in clinical trials[46-49]

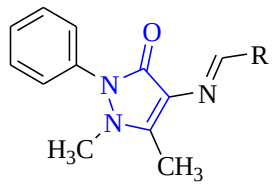
Overall, pyrazole-based anti-AD agents hold promise as a potential therapeutic approach for the treatment of AD. Some of the pyrazole based scaffolds as anti-AD agents mentioned below:

Chimenti F. *et al.* investigated a series of 3,5-diaryl pyrazoles for reversibly inhibit MAO-A and MAO-B. The results showed that several compounds exhibited inhibitory activity with concentration values in the nanomolar range. Compound **(13)**, which having fluoro substitution on both aryl rings, exhibited the most potent inhibitory activity with IC_{50} values of 5.20 nM and 4 nM for MAO-A and MAO-B, respectively[50].



(13)

Tok *et al.* synthesized several analogues and evaluated them for their potential as monoamine oxidase and cholinesterase inhibitors in the treatment of AD. The most potent derivatives in the series were found to be compounds **(14)** and **(15)**, with IC_{50} values of 0.285 µM and 0.057 µM, respectively. Moreover, compounds **(16)** (IC_{50} = 0.114 µM), compound **(17)** (IC_{50} = 0.049 µM), and compound **(18)** (IC_{50} = 0.054 µM) exhibited the highest activity against MAO-B enzyme activity[51].

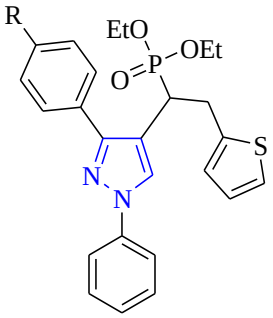


(14-18)

Comp Id	R
14	2,6-Dimethylphenyl
15	4-[3-(Dimethylamino)propoxy]phenyl
16	4-Hidroxyphenyl
17	4-Nitrophenyl
18	4-Nitrophenyl

Shaikh *et al.* developed novel *N*-substituted pyrazole-derived α-aminophosphonates as potential AChE inhibitors for AD treatment. Among the compounds synthesized, (19 and 20 exhibited greater AChE inhibitory activity than standard drugs tacrine, rivastigmine, and galantamine, with IC_{50} values ranging from 0.055 ± 0.143 µM to 0.017 ± 0.02 µM. However, the

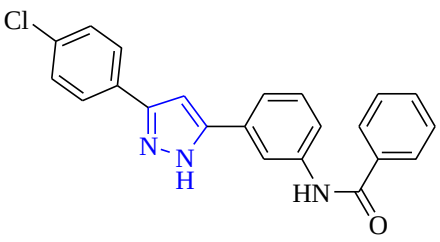
BuChE inhibitory activity of the synthesized compounds was moderate to weak. Compound 20 showed similar activity to rivastigmine against BuChE with an IC_{50} value of 6.331 ± 0.17. Additionally, the synthesized compounds showed promising antioxidant activities against DPPH and H_2O_2 scavenging[52].



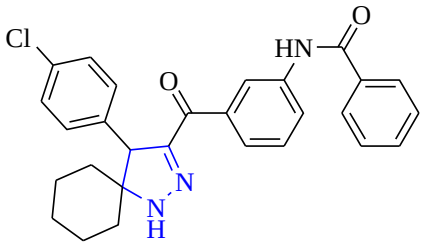
Comp id	R
19	H
20	Cl

(19-20)

Gutti *et al.* had reported a linear pyrazole derivatives as an AChE inhibitor. Among the series, compound **(21)** (AChE = 1.937 ± 0.066 µM; BuChE = 1.166 ± 0.088 µM; *h*AChE = 1.758 ± 0.095 µM; Pe = 9.491 ± 0.34 × 10-6 cm s^1) had exhibited positive results. This led to the development of compound **(22)** through further optimization, which showed improved activity as an AChE inhibitor with an IC_{50} value of 0.464 ± 0.166 µM. It also exhibited moderate inhibition of BuChE and *h*AChE with IC_{50} values of 0.754 ± 0.121 µM and 0.472 ± 0.042 µM, respectively[53]. The permeability coefficient (Pe) of compound **(22)** was determined to be 13.92 ± 0.022 × 10-6 cms^1.

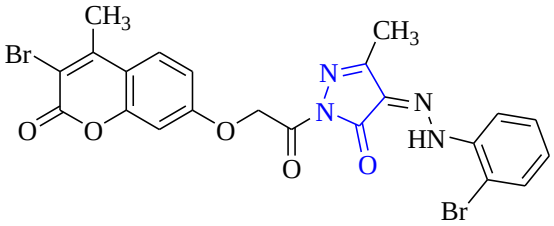


(21)



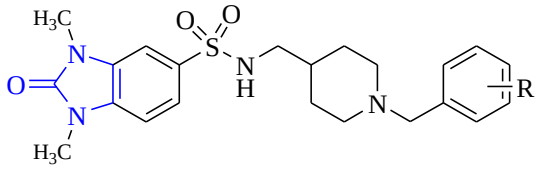
(22)

Narayanan *et al.* designed and synthesized a novel series of pyrazoles containing brominated 7-hydroxy 4-methyl coumarin derivatives with potential for the treatment of AD. Compound **(23)** demonstrated MAO inhibitory activity with an IC_{50} value of 3.9 nM for human MAO-A and 4.4 nM for human MAO-B, in addition to exhibiting antioxidant properties[54].



(23)

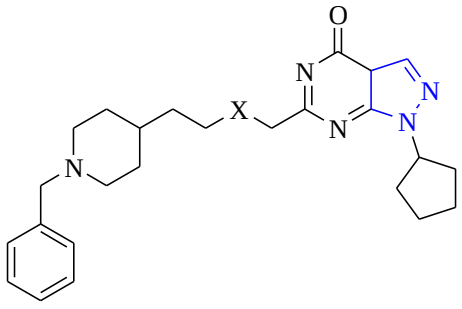
J. Mo *et al.* synthesized a series of 1,3-dimethylbenzimidazolinone derivatives as cholinesterase inhibitors. Among the synthesized compounds **(24)** and **(25)** showed submicromolar IC_{50} values towards AChE and BuChE, with **(24)** having an AChE IC_{50} of 0.39 ± 0.11 µM and **(25)** having a BChE IC_{50} of 0.16 ± 0.04 µM. Kinetic and molecular modeling studies showed that both compounds acted in a competitive manner. Additionally, **(24)** and **(25)**exhibited neuroprotective effects against H_2O_2-induced oxidative damage in PC12 cells, and their antioxidant activity was confirmed through a DPPH assay in vitro[55].



Comp Id	R
24	2-CH_3
25	4-Br

(24-25)

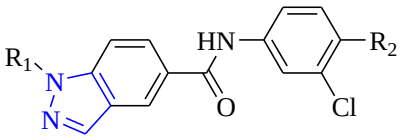
J. Hu *et al.* synthesized and evaluated a series of dual-target AChE/PDE9A inhibitors as anti-AD agents. The synthesized compounds included compound **(26)**, which exhibited good activity against AChE and PDE9A with IC_{50} values of 0.048 µM and 0.530 µM, respectively. Compound **(27)** also showed good activity against AChE and PDE9A with IC50 values of 0.223 µM and 0.285 µM, respectively, among the reported series. Additionally, both compounds were found to have strong BBB penetrability and low neurotoxicity[56].



Comp Id	X
26	CH_2
27	O

(26-27)

Tzvvetkov and colleagues developed three MAO-B inhibitors (**28-30**) that were potent, reversible, and competitive with high selectivity against the MAO-A isoform. The studies showed that all three inhibitors had the ability to bind to Fe(II) and Fe(III) through UV-Vis analysis. These inhibitors were also water-soluble and highly permeable through the blood-brain barrier, making them promising candidates for both diagnostic and therapeutic applications in the treatment of AD[57].



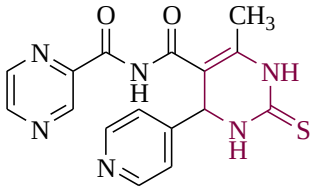
(28-30)

Comp Id	R_1	R_2
28	H	F
29	H	Cl
30	CH_3	F

2.3.3 Pyrimidine based anti-AD agents

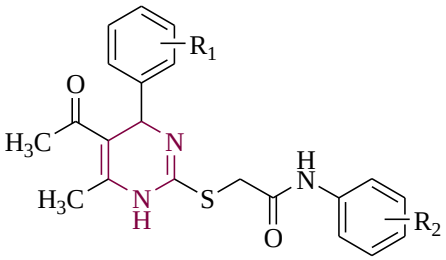
Pyrimidine is a medicinally active heterocyclic compound that has found numerous applications in the development of drugs[58]. Its aromatic nature, the presence of various functional groups, and the possibility of substitution at multiple positions make pyrimidine a versatile scaffold for designing compounds with a wide range of biological activities[59]. The pharmacological activity of pyrimidine derivatives can be attributed to their ability to interact with various biological targets[60]. Pyrimidine-containing compounds have shown promising activity as potential therapeutics for various diseases, including AD, cancer, anti-inflammatory, antioxidant and viral infections[61]. Overall, pyrimidine is an important heterocyclic scaffold with diverse medicinal applications[62,63]. Its ability to interact with various biological targets and the ease of synthesis of pyrimidine derivatives make it an attractive target for drug discovery and development[64].

Elumalai and colleagues had reported novel pyrazinamide condensed 1,2,3,4-tetrahydropyrimidine derivatives as inhibitors of AChE and BuChE. The synthesized compounds had demonstrated weak, moderate, or high AChE and BuChE inhibitory activity. Specifically, compound **(31)** had exhibited the most potent AChE and BuChE inhibition among all compouns, with an IC_{50} value of 0.11 mM and 3.4 mM[65].



(31)

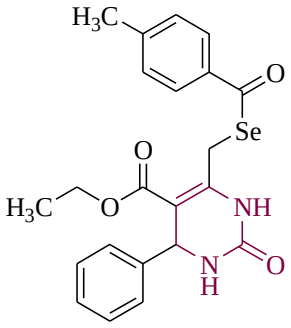
Substituted dihydropyrimidines linked with an acetamide linker to substituted aromatic anilines were synthesized by Ahmad et al. The compounds were tested for their ability to inhibit AChE and BuChE. The series showed promising AChE inhibitory activity, and compounds **(32)** and **(33)** were found to be the most potent with IC_{50} values of 0.17 ± 0.01 and 0.39 ± 0.04 μM, respectively[66].



Comp Id	R_1	R_2
32	H	H
33	4-OC_7H_7	H

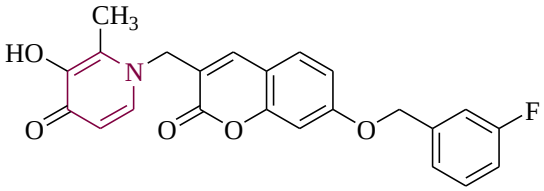
(32-33)

Flavio and his group had synthesized a group of selenoesters functionalized with electron donating or withdrawing groups on the DHPM aromatic portion, as well as bicyclic aromatic structures. The compounds were assessed for their ability to inhibit lipid peroxidation in the thiobarbituric acid reactive species (TBARS) assay and their efficacy as iron chelating agents. The most active compounds were screened for their inhibition of the enzyme AChE. Compound **(34)** exhibited significant activity with an IC_{50} value of 7.21 ± 0.48 μM[67].



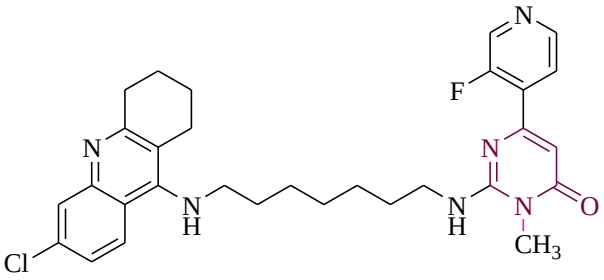
(34)

Changjun Zhang *et al.* designed a new series of hybrids that combined hydroxypyridinone and coumarin. These compounds were synthesized and subsequently subjected to biological evaluation in order to determine their ability to chelate iron ions and inhibit MAO-B. The majority of the compounds exhibited notable iron ion chelating effects and demonstrated moderate to good anti-MAO-B activities. Compound **(35)**, which was among the series of compounds that were evaluated, exhibited the most potent activity against MAO-B, with an IC_{50} value of 14.7 nM[68].



(35)

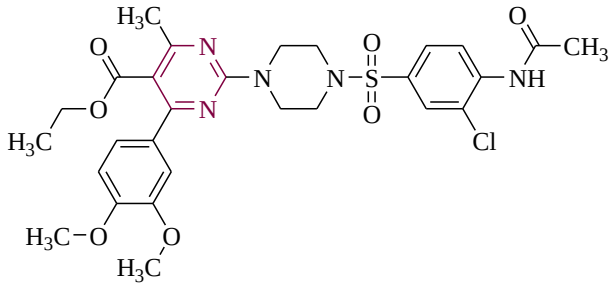
Hong Yao *et al.* found GSK-3β to be a promising target for new anti-AD drugs due to its involvement in tau protein phosphorylation. They synthesized and tested novel tacrine-Pyrimidone hybrids as dual AChE and GSK-3β inhibitors for AD treatment. Compound **(36)** from the series showed excellent dual inhibition activity with IC_{50} values of 51.1 nM and 89.3 nM for AChE and GSK-3β, respectively. It also exhibited suitable pharmacokinetic properties, kinase selectivity, and moderate neuroprotection against GA-induced cell viability reduction and neurite damage in SH-SY5Y-derived neurons. These results suggested that compound **(36)** should be further studied as a promising lead for the prospective treatment of AD. The paraphrase is strongly in past tense[69].



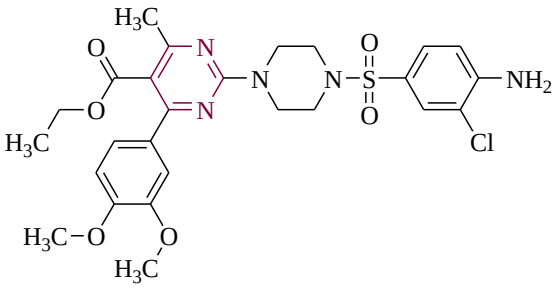
(36)

Shoaib M. *et al.* synthesized a series of MTDLs phenylsulfonyl-pyrimidine carboxylate derivatives for AD treatment and evaluated their potential as AChE and BuChE inhibitors through molecular docking. The compounds showed moderate to excellent inhibitory activity against both enzymes at nanomolar concentrations. Compounds **(37)** and **(38)** showed potential inhibition against AChE, with IC_{50} values of 47.33 ± 0.02 nM and 51.36 ± 0.04 nM, and moderate inhibition

against BuChE. Compound 37 exhibited non-competitive inhibition of AChE with a Ki value of 8 nM in the enzyme kinetics study. In thioflavin T-assay, both compounds inhibited AChE-induced $A\beta_{1-42}$ aggregation at 10 μM and 20 μM concentrations, with compound **37** showing greater potency. Additionally, both compounds significantly inhibited self-induced and AChE-induced $A\beta_{1-42}$ aggregation as indicated by dynamic light scattering. The compounds' effects on the viability of MC65 neuroblastoma cells and their ability to cross the blood-brain barrier (BBB) in PAMPA-BBB were also investigated. The results showed promising potential for these compounds as AD therapeutics[70].

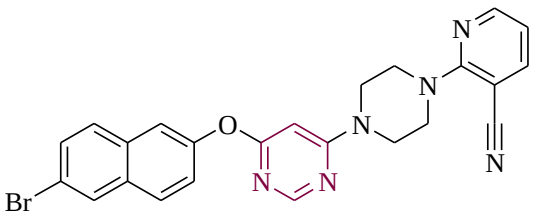


(37)



(38)

Kumar *et al.* synthesized pyrimidine derivatives conjugated with a triazolopyrimidine-based hybrid scaffold to develop new molecules for the treatment of AD. The study employed a combination of computational, chemical, and biological methods to identify the most effective AChE inhibitor. Compound **(39)** from the series demonstrated strong AChE inhibition in the nanomolar range, with an $_{IC50}$ value of 36 nM. The inhibitory effect of **(39)** was found to be stronger for human AChE in neuronal cell extract compared to eel AChE. The activity of **(39)** was comparable to donepezil, which is considered a good standard among AChE inhibitors. The study's findings suggest that compound **(39)** has potential as a lead compound for further development as a treatment for AD[71].

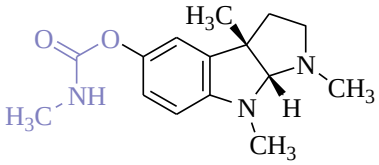


(39)

2.3.4 Carbamate Fragment based anti-AD agents

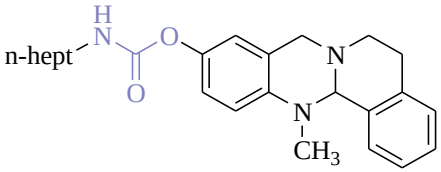
Carbamate is a functional group that consists of an ester of carbamic acid[72]. It is a type of amide derivative that has a nitrogen atom attached to a carbonyl group[73]. The carbamate fragment is widely used in pharmaceutical and agrochemical industries due to its ability to form reversible covalent bonds with biological targets[74]. Carbamate-containing compounds are used as pesticides, herbicides, and fungicides[75]. They are also used as drugs to treat diseases such as glaucoma, hypertension, and AD[76]. The carbamate group can act as an enzyme inhibitor by binding covalently to the active site of enzymes, resulting in the inhibition of enzyme activity[77]. Rivastigmine (**II**) carbamate-based drugs is approved by the FDA for the treatment of mild to moderate AD, as well as for the treatment of dementia associated with Parkinson's disease[78].

Physostigmine **(40)** was a cholinesterase inhibitor that was extensively studied in clinical trials and was the first carbamate-based cholinesterase inhibitor[79]. Its inhibitory activities on both AChE and BChE were found to be potent (*h*AChE IC_{50} = 28 nM; *h*BChE IC_{50} = 16 nM), and its tertiary amine fragments helped it to penetrate the blood-brain barrier (BBB) effectively. However, due to its short effective time and significant toxicity, it was not considered suitable for AD treatment[80].



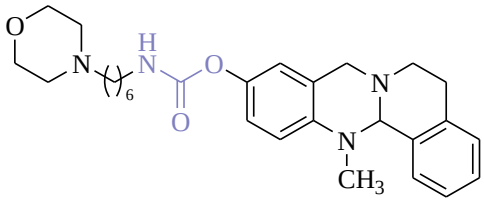
(40)

Darrs H. *et al.* synthesized a range of tri- and tetracyclic nitrogen-bridgehead compounds with diverse carbamate groups and evaluated them as inhibitors of cholinesterase. Compound **(41)**, which contained an n-heptyl carbamate residue, was identified as the most potent selective inhibitor of BuChE in the micromolar range. The systematic kinetic study confirmed its pseudo-irreversible inhibition. Additionally, compound **(41)** exhibited neuroprotective effects on HT-22 cells after glutamate treatment. However, further studies are needed to investigate the potential of this compound as a treatment for AD[81].

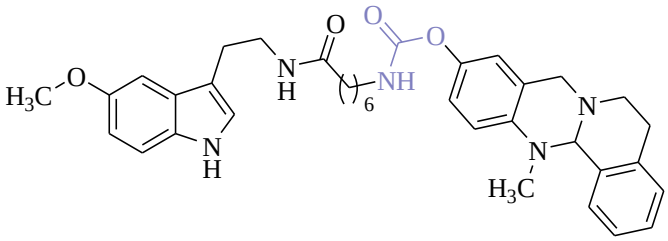


(41)

Hoffmann *et al.* investigated the effects of modifying carbamate structures with various heterocycles and alkylene spacers on BuChE binding. They synthesized a range of compounds with different heterocycles and alkylene spacers and evaluated them for their enzyme inhibition abilities[82]. Compound **(42)** was found to be the most potent among the series, with an IC_{50} value of 49.3 nM towards BuChE. In addition, the optimized compounds were observed to protect neuronal cells from glutamate treatment and alleviate Aβ-induced memory impairments. The researchers also incorporated antioxidants such as melatonin, ferulic acid, cinnamic acid, and Trolox into the carbamate residue to enhance the potential of MTDLs. Compound **(43)**, which contained a fused melatonin moiety with carbamate and tetrahydroisoquinoline, was the most potent among the synthesized compounds, with an IC_{50} value of 102 nM towards BuChE. Additionally, compound **(43)** exhibited antioxidant and neuroprotective activity in addition to its inhibitory activity[83].

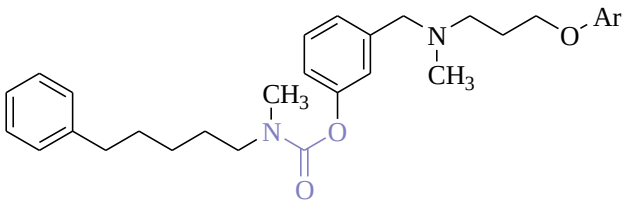


(42)

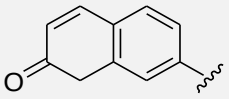
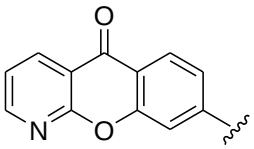


(43)

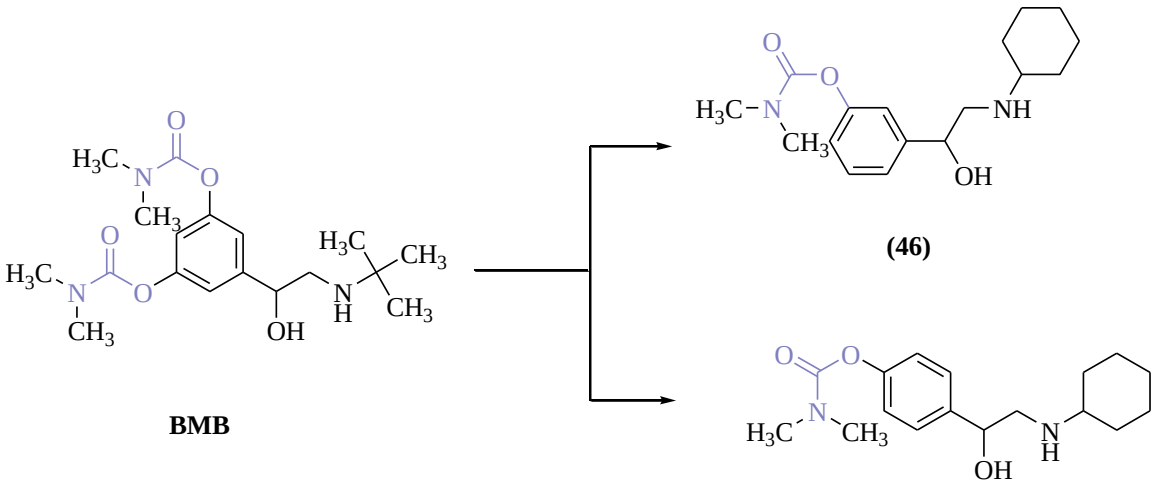
Rampa *et al.* designed carbamate-based coumarin derivatives to explore their potential as anti-AD agents due to coumarin's known AChE inhibition potency. The compounds were evaluated for their biological activity, and it was found that compounds **(44)** and **(45)** showed inhibitory activity on AChE, BChE, and FAAH (Fatty acid amide hydrolase) in the nanomolar range. They were also the first dual cholinesterase-FAAH inhibitors reported, suggesting a novel approach for developing anti-AD agents. Compound **(44)** displayed IC_{50} values of 74.9 nM towards *h*AChE and 1.57 nM against *h*BuChE, while compound **(45)** had IC_{50} values of 89.5 nM towards *h*AChE and 1.71 nM against *h*BuChE[84].



(44-45)

Comp Id	Ar
44	
45	

Bambuterol (BMB) is biscarbamate ester prodrug of the β_2-adrenergic receptor agonist terbutaline used to treat asthma, undergoes hydrolysis by BuChE to produce terbutaline. The hydrolysis process is believed to be mainly catalyzed by BuChE, and during this process, bambuterol acts as a strong pseudo-substrate inhibitor of BuChE with an IC_{50} of 3×10^{-9} M. However, it is a much weaker inhibitor of AChE, with an IC_{50} of 3×10^{-5} M[85]. Based on this observation, Jie Wu *et al.* synthesized and evaluated some carbamate derivatives as inhibitors of AChE and BuChE, and found that compounds **(46** and **47)** were the most potent with IC_{50} values of 792 nM and 2.2 nM fand 266 nM and 10.6 nM for AChE and BuChE, respectively[86].



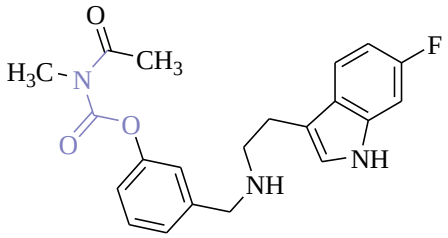
BMB

(46)

(47)

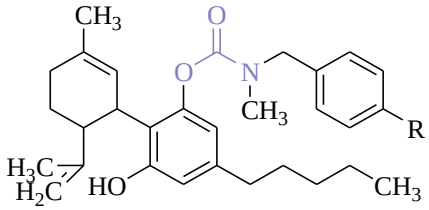
Toublet *et al.* carried out a study on serotonin, an endogenous neurotransmitter that plays a significant role in several physiological and pathological processes, including learning and memory. AD patients have reduced density of serotonin receptors (5-HTRs) in their cortex. The activation of 5-HTRs reduces cholinergic transmission, while the blocking of 5-HTRs can

stimulate the production of ACh. Thus, targeting both cholinesterase and 5-HTRs can be a potential strategy for treating AD. In this regard, the researchers developed pleiotropic prodrugs that act as dual inhibitors of BuChE and 5-HT6 receptor antagonists. Among the tested compounds, compound **(48)** exhibited covalent inhibition of BuChE with an IC_{50} value of 0.97 µM[87].



(48)

Jiang *et al.* synthesized 17 novel compounds using structural reassembly and evaluated their activity as BuChE inhibitors. Among the series, compound **(49)** showed highly selective and potent BuChE inhibition with an IC_{50} value of 5.3 nM and a selectivity index of >4000. Additionally, **(49)** demonstrated good BBB penetrating ability, safety, neuroprotection, antioxidant activity, and pseudo-irreversible BuChE inhibition. Moreover, compound **(50)** also exhibited nanomolar inhibition on *eq*BuChE with an IC_{50} value of 7.3 nM and a selectivity index of >4000. Both compounds showed better *h*BuChE inhibition than rivastigmine with IC_{50} values of 1.77 and 2.15 nM for *h*BuChE[88].

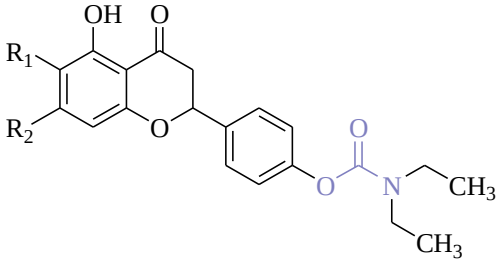


Comp Id	R
49	Cl
50	Br

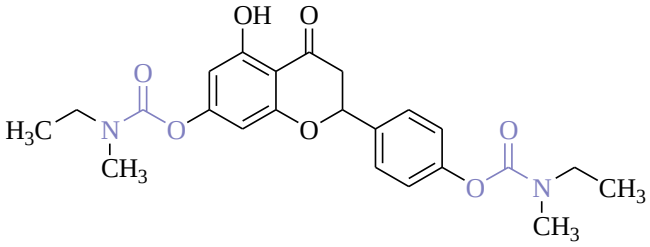
(49-50)

Sang D. *et al.* designed a series of carbamate-based flavone derivatives by incorporating various carbamate fragments into the flavone-carrier skeleton[89]. Among the series, compound **(51)** showed promising inhibitory activity against both AChE (IC_{50}= 1.2 µM) and BuChE (IC_{50}= 22.1 µM), as well as good neuroprotection, strong oxidant potency, and selective metal chelation potency due to the presence of hydroxyl and carbonyl groups in the skeleton[90]. Notably, compound **(51)** was found to significantly improve memory deficit and reduce AChE (IC_{50}= 0.57 µM) activity in the brain in vivo. In further optimization, methoxy groups in flavone ring to obtain compound

(52) which showed slightly weaker antioxidant efficacy but stronger inhibitory activity against AChE. Further modification done by introducing combined methyl-ethyl carbamate moieties in both the rings to get compound **(53)** exhibited fine inhibitory potency against both AChE (IC_{50}= 6.8 µM) and BuChE (IC_{50}= 16.1 µM) and was also capable of resisting self-, Cu2+- and *h*AChE-induced Aβ aggregation[91,92].



(51, 52)



(53)

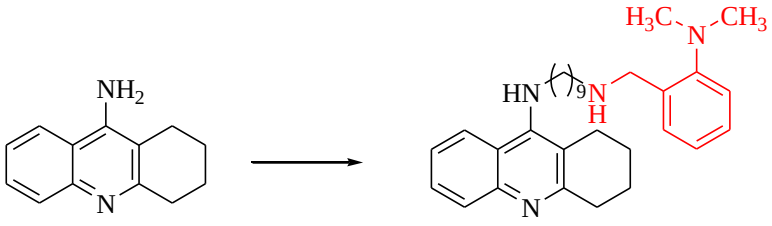
Comp Id	R_1	R_2
51	OH	OH
52	OCH_3	OCH_3

2.3.5. Amine Fragment based anti-AD agents

The presence of an amine-based fragment is essential for cholinesterase and MAO-B inhibitory activity, as it improves the interaction between the compound and the enzymes' active sites[93]. At physiological pH, the nitrogen of the amine is protonated, forming a strong cation-π interaction with amino acid residues in the active site of the enzymes[94]. A number of scaffold reported as novel anti-AD agents were attached with various suitable amine linker[95]. Some of the reports are discussed below:

Mao F. *et al.* modified a tacrine derivative by reacting *N*-(aminoalkyl)tacrine with salicylic aldehyde or derivatives of 2-aminobenzaldehyde to design novel hybrid molecules and evaluated as multifunctional anti-AD agents. All the synthesized hybrids exhibited potential as biometal chelators, and moreover, most of them demonstrated superior antioxidant and cholinesterase inhibitory properties, as well as the ability to inhibit amyloid-β aggregation, compared to the lead compound tacrine. Among the series of compounds that were reported, Compound **(54)** displayed inhibitory activity against AChE with an IC_{50} value of 0.55 nM, which was better than tacrine (IC_{50}

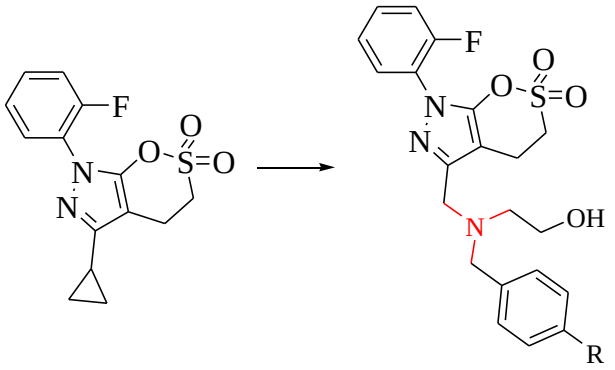
109 nM). It also exhibited good biometal chelation ability, the capacity to inhibit Aβ aggregation, and moderate antioxidant activity (1.22 Trolox equivalents)[96].



Tacrine

(54)

Z. Zhang *et al.* conducted a study to improve the potency and selectivity of BuChE enzymes by optimizing the structure of δ-sulfonolactone-fused pyrazole derivatives. From the series of compounds synthesized, compounds **(55)** and **(56)** were found to be highly selective for BuChE enzymes with IC50 values of 8.3 and 7.7 nM, respectively, due to the substitution of benzyl amines. These compounds also showed mild antioxidant activity, were non-toxic, lipophilic, and had neuroprotective properties. Additionally, kinetic studies demonstrated that compound **(56)** had mixed-type inhibition against BuChE with a Ki value of 24 nM, and > 2000-fold selectivity for BuChE over AChE[97].

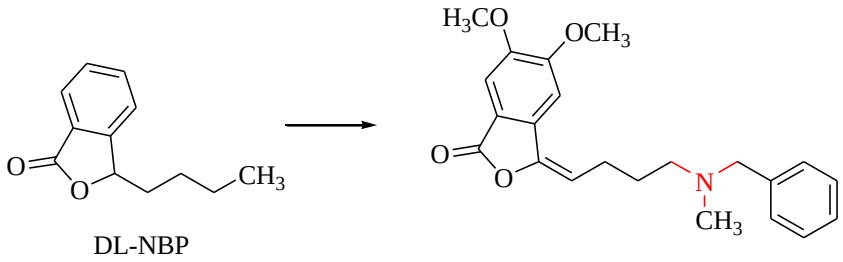


Comp Id	R
55	F
56	Br

(55-56)

Luo *et al.* synthesized a series of phthalide alkyl tertiary amine derivatives to develop multi-target agents against AD. The synthesized compounds exhibited significant and selective AChE inhibitory activities, and most of them showed improved self-induced $A\beta_{1-42}$ aggregation inhibitory activity compared to the lead compound DL-NBP. In addition, some of the derivatives demonstrated good antioxidant activity. Among the synthesized compounds, compound **(57)** showed the most potent AChE inhibitory activity with an IC_{50} value of 2.66 nM, which was

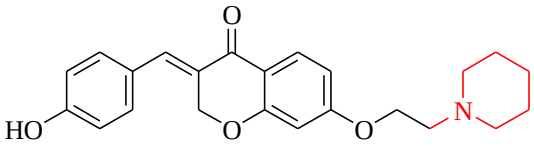
significantly better than Donepezil (IC_{50} = 26.4 nM). Molecular docking studies suggested that compound **57** could bind to both the catalytic active site and peripheral anionic site of AChE[98].



DL-NBP

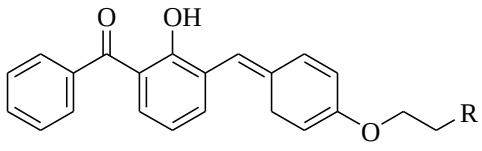
(57)

A series of chroman-4-one derivatives were synthesized by Shamsimeymandi R. *et al*. and their cholinesterase inhibitory activities were evaluated. Among the reported series, compound **(58)** with piperidinyl ethoxy side chains with 4-hydroxybenzylidene on the 3-position of chroman-4-one exhibited the most potent activity against AChE (IC_{50} = 1.18 µM)[99].

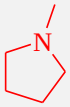
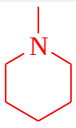


(58)

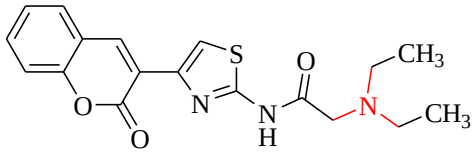
Leong *et al.* designed and synthesized diarylpentenedione analogs possessing heterocyclic amines as potent dual ChEIs. Among the reported series, compound **(59** and **60)** possessed the highest inhibitory activity against both AChE (IC_{50} =1.6 µM & 2.7 µM) and BuChE (IC_{50} = 3.5 µM & 0.6 µM). SAR study revealed that the basic scaffold diarylpentenedione was selective towards the AChE inhibition while the presence of bheterocyclic chain was critical for both AChE and BuChE inhibitory activity[100].



(59, 60)

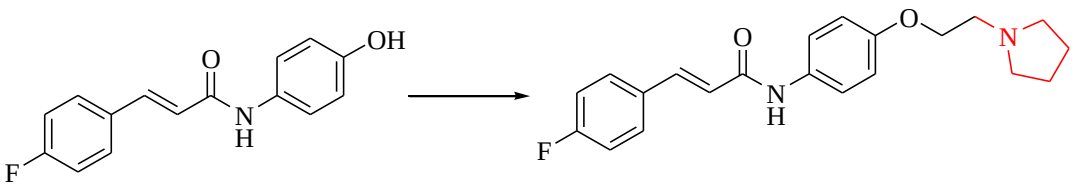
Comp Id	R
59	
60	

Sonzmen F. *et al.* reported novel series of coumarine-thiazole derivative as anti-AD agent. Among the reported series, compound **(61)** showed excellent selective AChE inhibitory activity (IC_{50}value of 43 nM, SI value of 4151.16). Kinetic study revealed that the compound showed mix-type AChE inhibition[101].



(61)

Gao X. *et al.* focused on developing new halo substituted cinnamic acid derivatives with tertiary amine side chains as potential ChEIs (Cholinesterase inhibitors) for the treatment of AD (AD). It was found that the presence of a tertiary amine side chain in the structure of the compounds led to moderate to good AChE inhibition, indicating their potential as therapeutic agents for AD. The study also revealed that the presence of alicyclic amines like pyrrolidine and piperidine in the side chain of the compounds resulted in better AChE inhibitory activity than aliphatic amines like diethylamine. The halogen group present in the structure had a significant effect on selectivity as well as on inhibitory activity on AChE. Out of all the compounds synthesized, compound **(63)** showed the best selective AChE inhibitory activity with an IC_{50} value



(62) **(63)**

of 1.11 µM and SI (selectivity index) value of 46.58. Interestingly, the parent compound **(62)** without the tertiary amine moiety exhibited poor inhibitory activity against AChE (IC_{50}= >500 µM). These findings suggest that the addition of a tertiary amine side chain to the cinnamic acid structure could enhance the AChE inhibitory activity of the compounds and improve their potential as ChEIs for the treatment of AD[102].

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