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# Chalcone and its Analogs: Therapeutic and Diagnostic Applications in Alzheimer's Disease

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## Abstract

Chalcone [(E)-1,3-diphenyl-2-propene-1-one], a small molecule with α, β unsaturated carbonyl group is a precursor or component of many natural flavonoids and isoflavonoids. It is one of the privileged structures in medicinal chemistry. It possesses a wide range of biological activities encouraging many medicinal chemists to study this scaffold for its usefulness to oncology, infectious diseases, virology and neurodegenerative diseases including Alzheimer's disease (AD). Small molecular size, convenient and cost-effective synthesis, and flexibility for modifications to modulate lipophilicity suitable for blood brain barrier (BBB) permeability make chalcones a preferred candidate for their therapeutic and diagnostic potential in AD. This review summarizes and highlights the importance of chalcone and its analogs as single target small therapeutic agents, multi-target directed ligands (MTDLs) as well as molecular imaging agents for AD. The information summarized here will guide many medicinal chemist and researchers involved in drug discovery to consider chalcone as a potential scaffold for the development of anti-AD agents including theranostics.

## Graphical Abstract

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Declaration of competing interest

The authors declare no conflict of interest.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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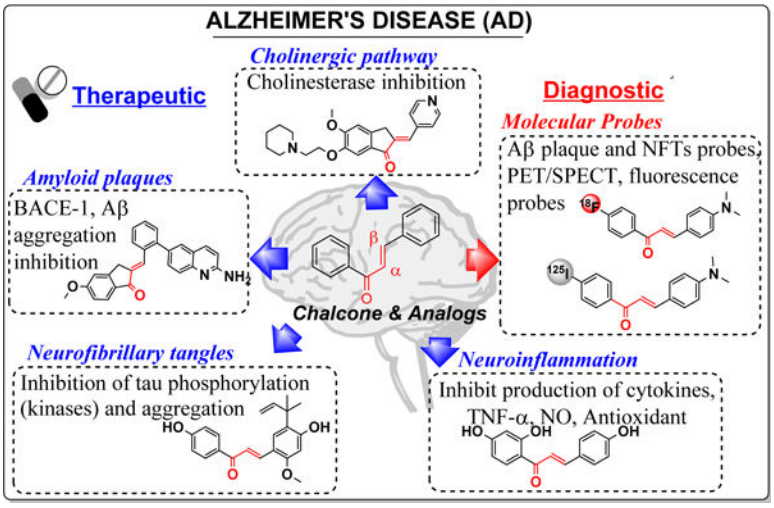


**Keywords**

Chalcone; Alzheimer's Disease; multi-target directed ligands; cholinesterase inhibitors; Amyloid beta inhibition; neuroinflammation; molecular probes; theranostic

## 1. Introduction

Chalcone [(E)-1,3-diphenyl-2-propene-1-one] is a simple molecule with two aryl rings (A and B) separated by α, β unsaturated carbonyl group (Figure 1). Chalcone found as the precursor or component of many naturally occurring flavonoids and isoflavonoids can exist in both *cis* or *trans* forms, although the *trans* form is thermodynamically more stable [1, 2].The chalcone skeleton is one of the privileged scaffolds studied for several medicinal applications such as anti-cancer, anti-ulcer, anti-tuberculosis, anti-inflammatory, and anti-bacterial[3–10]. Presence of α, β unsaturated carbonyl functional group, which acts as a potential Michael acceptor, allows the chalcone molecule to interact with sulfhydryl of cysteine residue or other thiol groups. This interaction is believed to be important for their biological activities [11–13]. Given the promise of chalcone in preclinical studies, some of the chalcone-based molecules such as metochalcone (choleretic drug), hesperidin methyl chalcone (vascular protective) and sofalcone (antiulcer and mucoprotective) have been approved for clinical applications (Figure 1) [1, 14, 15].

Because of chalcone's low molecular weight, convenient and efficient synthesis and easy optimization of lipophilicity (logP) with appropriate substituents, this scaffold has gained significant attention in drug discovery of central nervous system (CNS) diseases including Alzheimer's Disease (AD). This simple scaffold can be modified in several ways as shown in Figure 1. Among the possible modifications, most prominent ones are (i) substitution of ring A and B with different heteroaryls; (ii) substitution on phenyl ring with several functional groups such as hydroxyl, methoxy, halogens (Cl, F, Br), amine etc. (iii) fusion of ring A and α-carbon and various combinations of the above modifications. Synthetically, it can be prepared by acid or base-catalyzed condensation reactions. Claisen-Schmidt condensation is the most common classical reaction used for preparation of chalcone(s) [16,

17]. However, depending upon the substituents, this reaction occasionally gives a complex mixture of isomers and other side products. Several other name reactions such as Suzuki coupling reaction [18], Friedel-crafts acylation [19], Wittig reaction [20] etc have been optimized to prepare chalcones.

Naturally occurring flavonoids and isoflavonoids are derived from chalcones which are biosynthesized with the aid of chalcone synthase (CHS, EC 2.3.1.74). CHS exists as a homodimer of two 42kDa polypeptides and the key amino acid residues in active/catalytic site of CHS are Cys164, Phe215, His303, and Asn336 [21]. Chalcone biosynthesis occurs by the condensation of one molecule of p-coumaroyl-CoA and three malonyl-CoA catalyzed by CHS. First, a coumaroyl moiety from p-coumaroyl-CoA is transferred to cysteine (Cys164) at active site of CHS [22]. Thereafter, condensation of three acetates from 3 malonyl-CoA extend the polyketide intermediate to form thioester-linked tetraketide intermediate. The tetraketide subsequently undergoes regiospecific intramolecular Claisen-type condensation and forms a ring system to yield chalcone [23, 24]. Several flavonoids and isoflavonoids are produced from chalcone by the action of chalcone isomerase (CHI) [25]. Similarly, five membered cyclized products, aurones are biosynthesized from chalcone by the action of aurone synthase (AUS) (Figure2) [26].

This review will focus on providing comprehensive insight on recent development related to chalcone and its analogs as therapeutic or diagnostic agent(s) for treating or diagnosing AD. A brief description of AD and its significance will be followed by outline on current advances on potentially using chalcones as new clinically useful compounds.

## 2. Alzheimer’s Disease (AD)

Alzheimer’s disease (AD), a progressive neurodegenerative disorder is a complex multifactorial disease characterized by formation and deposition of extracellular amyloid β (Aβ) plaques and intracellular neurofibrillary tangles (NFTs), oxidative stress, mitochondrial dysfunction and neuroinflammation. The underlying mechanisms lead to neuronal loss with associated progressive decline in cognitive functions including memory loss. AD is the most common cause of dementia in elderly. Currently, estimated that 5.8 million Americans age 65 and older are living with Alzheimer’s related dementia and this number is expected to rise to 13.8 million by 2050 [27]. AD was first observed by German clinical psychiatrist and neuroanatomist, Alois Alzheimer on November 26, 1901 while examining a patient Auguste Deter, 50-year-old woman who presented symptoms of sleep disorders, memory disturbance, and progressive confusion. After her death in 1906, post-mortem of the brain showed senile plaques and neurofibrillary tangles. Later, the disease was coined as “Alzheimer’s disease” [28].

Drug development for AD so far has mainly focused on cholinergic, beta amyloid hypothesis and tauopathy. Recently, the field has expanded to other pathologies including mitochondrial dysfunction and neuroinflammation [29]. Extensive research on drug discovery and development has led to FDA-approved drugs which include cholinesterase inhibitors such as donepezil (DPZ) [30–32], rivastigmine (RIV) [33–35], galantamine [36, 37], and a partial *N* -methyl-D-aspartate (NMDA) antagonist, Memantine[38] (Figure 3) [39]. Unfortunately,

these drugs can only manage the symptoms of AD for short-term and do not slow or stop the disease progression. Thus, a more effective therapeutic agents which can prevent progression or reverse the disease course is warranted. Chalcone has been studied as potential scaffold for the discovery of anti-AD agents.

Several chalcone analogs have been prepared as inhibitors of either one or more enzymes/proteins involved in the pathogenesis of AD such as cholinesterase (Bu/AChE), beta secretase (BACE), tau proteins etc. Moreover, chalcone has gained an attention as a potential molecular probe for *in vivo* imaging of Aβ deposits in AD. Use of several chalcone derivatives for single or multiple targets involved in AD pathogenesis or diagnostic purpose for AD will be described in the following sections.

## 3. Chalcone and its analogs as therapeutic agent(s) for AD

### 3.1. Cholinesterase inhibitors (ChEIs)

Development of cholinesterase inhibitors is based on the cholinergic hypothesis [40]. According to the cholinergic hypothesis, first proposed by Peter Davies and A.J.Maloney in 1976 [41], neuronal synapses in AD patient have low levels of neurotransmitter, acetylcholine (ACh) accompanied by a decreased activity of choline acetyltransferase (ChAT). ACh is synthesized in cytoplasm of presynaptic cholinergic neurons from choline and acetyl coenzyme A (Acetyl-CoA) catalyzed by ChAT [42]. Once formed, it is transferred into synaptic vesicles. Exocytosis from presynaptic neuron upon depolarization releases ACh into synapses, which can bind with nicotinic or muscarinic receptors in postsynaptic neurons causing neurotransmission [43]. In synapses, ACh is primarily hydrolyzed by the enzyme called acetylcholinesterase into choline and acetic acid which switches off the cholinergic neurotransmission [44]. Reuptake of choline by presynaptic neurons for re-synthesis of ACh completes the cycle [45].

Inhibition of AChE to prevent the reduction of ACh level in AD patients has been a popular strategy. Butyrylcholinesterase (BuChE, pseudocholinesterase) is another abundant cholinesterase and it differs from AChE with regards to substrate specificity. AChE is highly specific to ACh whereas BuChE favors butyrylcholine (BuCh) and several other cholinesters including ACh. Structurally, AChE and BuChE share 65% amino acid sequence homology and their active site contains the peripheral anionic site (PAS), a narrow gorge (~20 Aº deep, 5 Aº wide) which gives access to the catalytic anionic site (CAS) [46, 47]. Catalytic site of AChE is responsible for the hydrolysis and is located at the bottom. The three essential amino acids, Ser200, His440 and Glu327, a catalytic triad, in AChE are involved in the transfer of acetyl group to Ser200 [48]. In BuChE, Ser198, His438 and Glu325 forms the catalytic triad [49]. AChE anionic site which comprise Trp84, Tyr130, Phe330 and Phe331 facilitates the binding of quaternary ammonium group by cation-π interactions [50]. The three amino acid residues present in the PAS of AChE are not found in the PAS of BuChE. Moreover, BuChE has wider gorge compared to AChE [51]. Initially, due to higher expression of AChE in CNS, and cholinergic neurons, compared to BuChE, AChE was preferred target of interest for AD drug development. The significance of BuChE in AD has been historically underestimated with renewed interest in BuChE as one of the key targets for AD drug discovery and development [52, 53]. In healthy brain, ACh is predominantly

hydrolyzed by AChE and BuChE plays a supportive role. However, in AD, the AChE level remains unchanged or decline whereas BuChE levels increases with the disease progression [54, 55]. In concurrence, selective inhibition of BuChE increased the ACh levels, reduced Aβ levels and improved cognitive performance *in vivo* [56]. Furthermore, increased levels of BuChE positively correlate with the transformation of relatively inert Aβ plaques to pathogenic forms associated with neuritic tissue degeneration and dementia [57, 58]. The potential of BuChE inhibition for treatment of AD has resulted in several patent applications on BuChE inhibitors (selective or multi-targeting) [59] and discovery of several classes of compound that selectively inhibit BuChE [60].

In the quest to find novel cholinesterase inhibitors, many researchers including medicinal chemists have explored the role of chalcone and its analogs. The availability of crystal structure of AChE [61] and BuChE [62] has facilitated this process. Recently, Chandrika et al. [63] reported chalcone-donepezil hybrids with significant cholinesterase and Aβ fibril assembly inhibition. They developed a series of 1,3- (Compound **1a**-**f**) and 1,4- (Compound **2a**-**f**) chalcone donepezil hybrids (Figure 4). In comparison, 1,4-chalcone-donepezil hybrids (**2a**-**2f**) showed better AChE inhibition than 1,3-chalcone-donepezil hybrids. In the series, compound **2a** showed better AChE inhibition than donepezil ($IC_{50}$: **2a**; 0.07 vs **DPZ**; 0.12 μM). In 1,3-chalcone series, **1b** ($IC_{50}$ = 0.65 μM, AChE) was the most potent AChE inhibitor. Similarly, most compounds in the 1,4-series (**2a**-**f**) showed better BuChE inhibition. In 1,3-series (**1a**-**f**), compounds **1a** ($IC_{50}$ = 0.020 μM) and **1b** ($IC_{50}$ = 0.03 μM) showed significant BuChE inhibition. It was observed that smaller linker between chalcone and donepezil favors cholinesterase inhibitory effects.

Similar approach of hybridizing chalcone with clinically approved rivastigmine has been reported [64]. These investigators modified chalcone ring A and B using several functional groups including the carbamate groups present in rivastigmine and tested for AChE and BuChE inhibitory effects. Several compounds showed hBuChE inhibitory effects at micromolar to sub-micromolar concentrations. These compounds showed selectivity for BuChE. Compound **3** was the most potent with activity comparable to rivastigmine against hBuChE ($IC_{50}$; **3**: 0.36 μM vs **Riv**: 0.38 μM). In addition, this compound showed hAChE inhibition at sub-micromolar concentration ($IC_{50}$ = 0.87 μM, hAChE). Molecular modeling showed that compound **3** occupied the catalytic pocket of hAChE and hBuChE. The carbamate ester of compound **3** binds with the catalytic triad of hAChE (Ser203 and His447) and hBuChE (Ser198 and His438).

Xiao et al. [65] has investigated the 4'-Aminochalcone-rivastigmine hybrids. All prepared compounds (18 examples) were assayed for AChE and BuChE inhibitory effects. Compound **4** showed the most potent AChE inhibition with $IC_{50}$ = 4.91 μM. Incorporation of carbamates on both 2 and 4 positions resulted in weaker AChE inhibitory activity. Molecular modeling of compound **4** with TcAChE (PDB: 1EVE) showed that it occupied CAS, mid-gorge sites and PAS of the enzyme. It (ring B) forms π-π interactions with Phe288, Phe331 and Phe290 in the PAS site along with hydrophobic interactions with Ile287, Arg289, Leu282. In the gorge of enzyme, hydrophobic interaction of α, β-unsaturated ketone group with Tyr334, π-π interaction of ring A with Phe330 and hydrogen bond of hydroxyl group in ring A with Tyr121 were observed. The carbamate moiety of compound **4** forms the

hydrophobic interactions with Acn85, Asp72 and Gln69 in catalytic site. In addition, this compound showed good antioxidant property compared to Trolox (2.83 equivalent) and selective monoamine oxidase-B inhibitory effect ($IC_{50}$ = 0.29 μM). Artificial membrane permeation assay [66, 67] to determine blood brain barrier permeability showed that compound **4** could penetrate the blood-brain barrier making it a promising candidate for AD drug development.

The Liu group has investigated a series of non-halogenated [68] as well as halogenated (F and Cl) [69, 70] chalcone derivatives for cholinesterase inhibitory activity. First, they prepared a series of non-halogenated chalcones with alkyl amine substituents at the hydroxyl group with variable carbon spacer (Figure 5). It was observed that compound **5** with the two-carbon spacer was the most potent selective AChE inhibitor. The group later developed the two-carbon spacer alkyl amine derivatives with fluorine or chlorine group at 2-, 3-, or 4-position of the phenyl ring on the other side. Among fluorinated derivatives, compound **6** was the most potent compound against AChE with $IC_{50}$ of 0.21 μM. In series of 12 compounds, most of them showed selectivity to AChE compared to BuChE. Similarly, among chlorinated derivatives, compound **7** was the most potent compound. It showed higher selectivity to AChE over BuChE as compare to compound **6**. They prepared the pyrazoline derivatives at α, β carbon position. All these derivatives showed weaker AChE inhibition. Authors remarked that α, β carbon position possibly plays an important role in determining the AChE inhibition. To determine the reason for specificity to AChE, they performed the molecular modeling of compound **5** with both AChE and BuChE. Interestingly, they found that compound **5** retains the multipoint interaction with AChE (**π-π** stacking with Trp279 and Ph330 at PAS and cation-**π** interaction with Trp84 in the CAS) whereas it retains only cation-**π** interaction with Trp82 in BuChE. They also prepared a series of compounds with alkyl amine substituents at different position (meta) of phenyl ring (Figure 5) [71]. Compound **8** was the most potent selective AChE inhibitor. Molecular modeling showed similar binding pattern with compound **5**.

Burmaoglu et al. [72] has reported tris-chalcones with fluorine(s) group on different position of phenyl ring. Nine derivatives were prepared and evaluated for their cholinesterase inhibitory activity. All evaluated compounds showed both AChE and BuChE inhibition at nanomolar concentrations. Compound **9** was the most potent among the series with $IC_{50}$ of 1.09 nM (AChE) and 5.24 nM (BuChE).

Rampa et al. [73] incorporated both alkylamine and carbamate groups in their chalcone derivatives as shown in compounds **10a-f**. All derivatives showed the cholinesterase activity at nanomolar concentrations with specificity to AChE. The most potent compound for AChE inhibition was **10d** with $IC_{50}$ of 0.81 nM. For BuChE it showed $IC_{50}$ at 106 nM concentration. Compounds **10a-10f** showed the AChE inhibition in the range of 0.81 to 51.8 nM. Compound **10f** ($IC_{50}$ = 51.8 nM) with longest chain length showed weaker AChE inhibition in comparison to other compounds. Several derivatives with piperidine spacer were developed by Zhao et al. [74]. Among 8 examples, compound **11** showed the most potent AChE and BuChE inhibition ($IC_{50}$ at 1.12 and 3.23 μM, respectively). From structure activity relationship (SAR) study, authors observed that electron donating groups (e.g.

Methyl as in compound **11**, methoxy) showed better activity compared to electron withdrawing (e.g. nitro, halogens) substituents in this series of compounds (Figure 6).

Importance of alkylamine functional group for cholinesterase inhibition led researchers to incorporate various alkylamine groups such as benzyl piperidine, piperidine, pyrrole and diethylamine on two side of chalcones (Figure 7) [75]. Compound **12** showed the most potent eeAChE inhibitory effect. Compound **13** showed significant hAChE and hBuChE inhibition. Similarly, compound **14** has shown the most potent eqBuChE inhibitory activity. Molecular docking study of compound **13** showed that it occupied the entire CAS, mid-gorge and PAS of AChE (PDB: 1EVE). Chalcone benzene ring form the **π-π** interaction with Phe330, two s-p interactions with Trp84 and one hydrogen bond with Phe288. In BuChE (PDB: 4TPK), compound **13** showed **π-π** and sp interaction with key amino acid Tyr332. The hydroxyl and carbonyl group form the H-bond with Pro285. Similarly, pyrrole ring forms the H-bond with Thr120. Other hydrophobic interactions were observed between **13** and Thr120, Asp70, Gly116, Phe329, Ala328, Tyr332, Trp82, His438.

Studies on tetramethyl pyrazine derivatives of chalcone has yielded few compounds with potent AChE inhibitory activity [76]. Compound **15** ($IC_{50}$ = 0.025 μM) showed better AChE inhibition than standard donepezil ($IC_{50}$ = 0.055 μM). In comparison, it showed weaker BuChE inhibition with $IC_{50}$ of 2.7 μM. Similarly, compounds **16** and **17** showed significant AChE inhibitory effects with $IC_{50}$ of 0.062 and 0.10 μM, respectively (Figure 8).

Several quinoline and piperidyl derivatives of chalcone were reported as cholinesterase inhibitors by Shah et al. (Figure 9) [77, 78] In the quinoline series with methyl or methoxy group [77], most compounds showed better BuChE inhibition except compound **18**, which significantly showed both AChE and BuChE inhibitory effects at $IC_{50}$ of 0.32 μM and 0.90 μM, respectively. Similarly, compound **19** showed significant BuChE inhibition but weaker AChE inhibition. Among methoxy derivatives, compound **20** and **21** showed significant BuChE inhibitory effect. Docking study of compound **18** with AChE (PDB: 1EVE) showed that quinoline ring forms **π-π** T-shaped interaction with Trp84 and **π-π** stacking with His440. Compound **19** was docked with BuChE (PDB: 4BDS). The dioxo benzene ring forms the **π-π** stacking with Trp82, Phe329 and His438. Similarly, the quinoline ring form the **π-π** stacking Tyr332 and Asp70. It also forms the **π**-sigma interactions with Trp82 and Asp70. From SAR and molecular docking study, authors believed that presence of bulky groups in the compounds might be the reason for better BuChE inhibitory effect as BuChE has larger active site gorge and can better accommodate the larger compounds than AChE. Previously, same group reported piperidyl derivatives of chalcones as cholinesterase inhibitors [78]. Interestingly, these derivates were found to be selective AChE inhibitors. Compound **22** was the most potent among the piperidyl derivatives with $IC_{50}$ of 0.16 μM. Compound **23** in the same class also showed significant AChE inhibition in sub micromolar concentration. Molecular docking study of compound **22** with AChE showed that it occupies both PAS and CAS of enzyme. Piperidine ring in compound **22** form one **π-π** stacking with Phe330, and two **π-π** T-shaped interaction with Tyr121 and Phe331. Another **π-π** interaction was observed between thiophene ring and Trp29.

Several chalcone derivates containing imides (compound **24** and **25**) [79], coumarin (compound **26**) [80], and 2-acyl aniline (compound **27**) [81] were reported to inhibit AChE at sub micromolar concentrations (Figure 10). Most of the reported imide containing chalcones showed AChE inhibition in nanomolar range. Compound **24** and **25** showed the most significant activity. Similarly, among a series of coumarin containing compounds, **26** showed the most potent AChE inhibitory effect. In addition, compound **26** also inhibited BuChE at $IC_{50}$ = 4.11 μM. Molecular modeling of compound **26** with AChE showed that it forms multiple interactions occupying both PAS and CAS. In PAS, the coumarin ring form the **π-π** interaction with Trp279. Similarly, phenyl ring forms **π-π** interaction with Tyr334. In CAS, cation-**π** interaction was observed between protonated nitrogen of pyrrolidine ring and Trp84. Molecular docking of compound **26** with BuChE showed only cation-**π** interaction with Trp84.

Arylidene indanone, a rigid homolog of chalcone, has been investigated extensively for cholinesterase inhibitory effects due to its resemblance to clinically approved AChE inhibitor donepezil. Seng et al. [82] have reported the preparation of a series of indanone (16 examples) and aurone (16 examples) derivatives. All prepared compounds were tested for AChE and BuChE inhibitory effects. The arylidene derivative, compound **28** was the most potent AChE inhibitor ($IC_{50}$ = 0.035 μM). Almost all of the reported compounds showed selectivity towards AChE. From SAR, they deduced that double bond (CH=CH) was important for AChE inhibition. However, there was not much differences in activities while comparing indanone and aurone derivatives. Molecular docking study of compound **28** with AChE showed that it occupies both PAS and CAS. In CAS, the charged diethylamine forms cation-**π** interaction with Trp84 and a hydrophobic interaction with Asp72 and Phe331. In the gorge, **π-π** stacking between phenyl ring and Tyr334 and Phe330 was observed. In the PAS, the indanone ring forms **π-π** interaction with Trp279 and the carbonyl group interacts with Phe288 via H-bonding.

The Rampa group reported a series of indanone derivatives based upon hybrids of donepezil and their previously reported potent AChE inhibitor AP2238 [83]. They tested all prepared compounds against both human recombinant AChE and BuChE from human serum. Compound **29** was the most potent AChE ($IC_{50}$ = 0.19 μM) inhibitor in the indanone series with significant hBuChE ($IC_{50}$ = 2.70 μM) inhibitory effect. Previously, Belluti et al. [84] prepared several indanone derivatives that showed significant AChE inhibitory effect in nanomolar ranges. Among the arylidene indanone derivatives, compound **30** was the most potent AChE inhibitor with $IC_{50}$ = 1.80 nM. Similarly, Huang et al. [85] reported several arylidene derivatives with significant AChE and Aβ aggregation inhibitory effects. Compounds **31** and **32** showed both significant AChE (**31**; $IC_{50}$ = 14.8 nM and **32**; $IC_{50}$ = 18.6 nM) and Aβ aggregation inhibition (**31**; 85.5% and **32**; 83.8% at 20 μM). Importantly, compounds **31** and **32** exhibited good BBB permeability *in vitro*. Molecular docking study in AChE (PDB: 2CMF), showed that compounds **31** and **32** has similar interactions and occupied both CAS and PAS. In PAS, benzyl ring of docked compounds forms **π-π** stacking with Trp279. In the bottom of the gorge, cation-**π** interaction between protonated piperidine (**31** and **32**) and Phe330 and Trp84 was observed. Indanone ring of compounds **31** and **32**

forms hydrophobic and π-π interaction with Val71, Ser122, Phe331, Tyr121 and Tyr334 along the gorge.

Mishra et al. [86] also reported several arylidene derivatives that exhibit considerable inhibition of AChE and Aβ aggregation. Antioxidant and Aβ aggregation inhibitory properties of curcumin inspired authors to hybridize donepezil with α, β carbonyl group of curcumin to obtain several arylidene indanones. Most of the compounds showed potent AChE inhibition at sub-micromolar concentrations and greater inhibition of Aβ aggregation than curcumin. Particularly, compound **33**, **34** and **35** ($IC_{50}$ = 0.025 – 0.045 μM) showed AChE inhibition at similar or lower concentration than standard Donepezil ($IC_{50}$ = 0.039 μM).

Chierrito et al. [87] reported several hybrids of donepezil and tacrine with α, β unsaturated carbonyl group as arylidene indanones. They evaluated all prepared compounds for AChE and BuChE inhibition and observed that compound **36** with α, β unsaturated carbonyl group and quinoline amine moiety was the most effective at inhibiting AChE ($IC_{50}$ = 0.014 μM). It also possesses moderate BuChE inhibition ($IC_{50}$ = 3.69 μM). Besides AChE and Aβ aggregation inhibition, Meng et al. [88] reported several arylidene indanones with significant AChE and good metal chelating effects. These compounds were prepared by modifying the hydroxyl group at 6-position of indanone with several amine functional groups linked with different carbon chains. In this series, compound **37** with piperidine and 2 carbon linkers at 6-position of indanone and pyridine on β-carbon showed the most potent AChE inhibition ($IC_{50}$ = 0.0018 μM).

Rampa group [83] has also reported a series of tetralone derivatives. Among the series, compound **38** ($IC_{50}$ = 0.056 μM) and **39** ($IC_{50}$ = 0.052 μM) showed the strong AChE inhibition at nanomolar concentrations. Similarly, Belluti et al. [84], in addition to the indanones, has prepared a series of aurone derivatives and tested their cholinesterase activity. Aurone derivative, **40** showed potent AChE inhibition ($IC_{50}$ = 0.52 nM). Additionally, compound **41** possessed significant AChE inhibitory activity ($IC_{50}$ = 2.76 nM). Both compound **40** and **41** exhibited considerable BuChE inhibitory activity. Compound **41** was noted by investigators as it also showed a potential for inhibiting Aβ aggregation (67% at 100 μM) induced by AChE (2.3 μM).

The Shafiee group has extensively studied other conformationally constrained rigid groups such as indolinone [89], chromanone [90], and aurones [91, 92] for their cholinesterase inhibitory activities. They reported several potent AChE inhibitors with $IC_{50}$ in sub-micromolar range. Compounds **42** (indolinone), **43** (chromanone), and **44** (aurone) were found to be the most potent compounds in their classes reported by the group. Molecular modeling of **43** with AChE showed the cation-π interaction between the charged pyridinium moiety with Tyr334 in CAS. Other possible interactions observed at CAS were π-π stacking of benzyl and pyridinium ring with Trp84 and Phe330, respectively. In PAS, hydrophobic interaction between chromanone Trp279 was observed. In addition, there was formation of H-bonding between carbonyl group of chromanone and Tyr121.

Pourshojaei et al. [93] have reported a series of 18 chromanone derivatives that were tested for inhibitory effects on AChE and BuChE. Most derivatives with piperidinyl ethoxy residue showed the potency against AChE at sub-micromolar level. Compound **45** with $IC_{50}$ of 0.122 μM (AChE) was the most potent among the group. This compound also showed significant BuChE inhibition ($IC_{50}$ = 0.854 μM). Recently, Wang et al. [94] have investigated isochromanone containing compounds as a fused analog of chalcones for their cholinesterase activities. Most of the compounds showed significant AChE inhibition in sub micromolar range. Compound **46** with 1-(4-fluorobenzyl) substituent displayed the most potent AChE inhibition ($IC_{50}$ = 8.93 nM). Molecular modeling study of compound **46** with AChE showed that charged pyridinium moiety forms cation-π interaction and π-π stacking with Phe330 in CAS. Moreover, phenyl ring forms the π-π interaction with Trp84. In the PAS, isochromanone functional group forms the π-π stacking with Trp279 and H-bond with Tyr121. The Lee group [95] has also reported the AChE inhibitory effects of aurone derivatives. They carried out modification based upon the sulfuretin, an aurone flavonoid, and found compound **47** as the most potent AChE inhibitor with $IC_{50}$ of 0.45 μM (Figure 12).

### 3.2. Amyloid inhibition

The amyloid cascade hypothesis was proposed in the early 1990s [96, 97]. According to this hypothesis, deposition of Aβ due to imbalance in production and clearance results in Alzheimer's disease. Formation of insoluble amyloid plaques along with neurofibrillary tangles are believed to promote neuronal degeneration and cognitive decline. Aβ was produced from integral membrane protein amyloid precursor protein (APP) by the action of two proteases β- and γ- secretase [98]. APP follows two metabolic pathways, non-amyloidogenic or amyloidogenic, depending on its processing by α- or β- secretase, respectively.

In non-amyloidogenic pathway, APP undergoes α-secretase mediated proteolysis (step 1), which produces a soluble sAPPα and membrane bound COOH-terminus fragment (αCTF or C83). C83 is subsequently cleaved by γ- secretase (step 2) to produce non-amyloidogenic soluble peptides p3 and amyloid intracellular domain (AICD).

In amyloidogenic pathway, APP is first cleaved by β-secretase [99] near the N-terminus at extracellular β-site of the APP (step 1) to release sAPPβ, and membrane bound COOH-terminus fragment (βCTF or C99). C99 fragment is then subsequently cleaved by transmembrane γ-secretase at different γ-sites to produce Aβ of different lengths (step 2). The major species are Aβ40 and Aβ42, however, Aβ42 has shown to have the strongest aggregating property among the species [100, 101].

Inhibition of amyloid plaque formation has been one of the main strategies for developing the disease modifying AD therapies. Investigators have persistently tried to develop inhibitors of α-and β-secretase as these enzyme activities play key roles in Aβ production. However, due to involvement of α- secretase in Notch signaling and severe toxicity associated, β-secretase (beta-site amyloid precursor protein cleaving enzyme 1; BACE-1) has gained much attention as an optimum therapeutic target for AD.

**3.2.1. BACE-1 inhibitors—**BACE-1, primarily present in the neurons, is an aspartyl protease bound to the membrane which is responsible for cleavage of APP at the beta site and considered the rate limiting step in the generation of Aβ. Its predominant location in CNS, role in Aβ production, and proof of no significant phenotypic alterations in BACE-1 knockout mice [102] encouraged many researchers to develop its inhibitor as a disease modifying agents for AD. Development of crystal structure of BACE-1 with substrate inhibitor OM99–2 [103] further support the concept of exploiting BACE-1 as a potential therapeutic target. Initially, BACE-1 inhibitors were peptidomimetics based upon the transition analog of APP. However, these compounds lacked good pharmacokinetic (PK) profile including poor BBB permeability. Therefore, researchers searched for non-peptidomimetic(s) large enough to fit the larger cavity of BACE-1 active site and display favorable PK profile and BBB permeability. Moreover, compounds selectivity to BACE-1 as compared to other aspartyl protease such as its homolog BACE-2, cathepsin D was an important factor to consider while developing BACE-1 inhibitors to avoid adverse side effects. Several large companies were involved in the discovery and development of BACE-1 inhibitors. Thus several potent non-peptidomimetic BACE-1 inhibitors such as verubecestat (MK-8931), lanabecestat (AZD3293; LY3314814), elenbecestat (E2609), atabecestat (JNJ-54861911), Umibecestat (CNP-520) (Figure 13) were developed and tested in clinical trials for treatment of AD [104–108]. Unfortunately, most of these compounds were unsuccessful and the studies has been discontinued due to low efficacy and/or adverse side effects [109]. Failure of most BACE-1 inhibitors necessitates a reconsideration of understanding the target enzyme or development of multitargeting drugs.

Several natural and synthetic chalcone derivatives have also been explored as BACE-1 inhibitors. Youn et al. [110] reported the BACE-1 inhibitory activities of three flavonoids from *Boesenbergia Rotunda* including a chalcone, cardamonin (compound **48).** Among three flavonoids, compound **48** ($IC_{50}$ = 4.35 μM) showed the most potent noncompetitive BACE-1 inhibitory activity. Docking study revealed compound **48** having hydrophobic interaction rather than H-bonds with the enzyme. Another natural chalcone, 2, 2′,4′-Trihydroxychalcone acid (TDC) (compound **49**) from *Glycyrrhiza glabra L* (licorice) reportedly displayed specific non-competitive BACE-1 inhibitory activity with $IC_{50}$ of 2.45 μM [111]. After enzyme assay, *in vitro* (HEK293-APPswe cells) and *in vivo* (B6C3-Tg mice) studies showed that compound **49** effectively decreased the Aβ in cells without any toxicity. Furthermore, there was no effect on other secretases (α- and γ). In a mouse model, at a dose of 9 mg/kg per day, compound **49** significantly decreased the $Aβ_{40}$ and $Aβ_{42}$. Morris water maze (MWM) test, after 100 days of compound **49** administration, clearly indicated improved memory function.

Rampa et al. [112] designed several chalcone derivatives based on naturally inspired small molecules. After screening in house collection of small molecules, two hit compounds which includes a chalcone derivative (compound **50**) and a benzophenone derivative was identified (Figure 14). Computational modeling showed that N, N'-benzyl methylamine groups of benzophenone derivative interact with the catalytic dyad of the BACE-1. Thus, investigators fused compound **50** (along with other various aryl groups) with benzophenone derivative to give new chalcone derivatives including **51** and **52**. The most potent BACE-1

inhibitor in the series was compound **51** ($IC_{50}$ = 1.06 μM). In comparison, 3,4,5-trimethoxyphenyl ring was more favorable than naphthyl ring for enzyme inhibition. In addition, compound **51** showed good Cu (II) chelating activity and significantly reduce the formation of Cu (II) mediated ROS.

On the basis of natural chalcone isoliquiritigenin ($IC_{50}$ = 33.0 μM) with moderate BACE-1 inhibitory activity, Ma et al. [113] prepared a series of 21 hydroxyl substituted chalcone derivatives and tested for BACE-1 inhibitory activity. They observed several compounds with better BACE-1 inhibitory effects than isoliquiritigenin, compound **53** ($IC_{50}$ = 0.27 μM) being the most potent. Mphahlele et al. [114] studied several halogenated chalcone derivatives for BACE-1 inhibition along with cholinesterase inhibitory effects. They found compound **54** ($IC_{50}$ = 4.7 μM) was the most potent BACE-1 inhibitor in the series. It also possessed moderate BuChE inhibitory activity. In one study [115], donepezil was modified to yield several chalcone derivatives. Prepared compounds possessed the donepezil scaffold with α, β-unsaturated carbonyl functionality like chalcone. All the prepared compounds were tested for cholinesterase (AChE and BuChE) and BACE-1 inhibitory activity. Compound **55** and **56** displayed the potent dual functionality against AChE and BACE-1. Compound **56** showed the most potent BACE-1 and AChE inhibition in the series with $IC_{50}$ = 0.333 and 0.043 μM, respectively. Inspired with compound **56**, Gabr et al. [116] synthesized a new series of arylidene indanone (chalcones) as rigid analogs of donepezil. All prepared compounds showed better dual inhibitory effects on AChE and BACE-1 in nanomolar ranges. Compound **57** showed the most potent inhibition of BACE-1 ($IC_{50}$ = 13.1 nM) and AChE ($IC_{50}$ = 14.7 nM). From docking study, it was observed that 2-aminoquinoline moiety of **57** is oriented towards the catalytic Asp32 and Asp228 residues of S3 pocket of BACE-1. The hydrophobic phenyl ring occupied the S1 pocket and its **π-π** interaction with Tyr198 facilitates the favorable orientation of 2-aminoquinoline.

**3.2.2. Amyloid beta aggregation inhibitors—**Another approach in impeding the formation of amyloid plaque is to prevent the aggregation of Aβ into pathogenic oligomers and fibrils. This approach is believed to be more beneficial than inhibition of physiologically relevant Aβ production as it may avoid the mechanism-based toxicity. Therefore, development of disease modifying Aβ aggregation inhibitors has emerged as an attractive area of AD drug discovery [117, 118]. Development of small molecules as inhibitors of Aβ aggregation is challenging due to several reasons including larger size and geometry of protein-protein interaction surface, and absence of grooves or binding pockets for small molecules to fit [119]. However, discovery of specific amino acids responsible for Aβ fibril formation [120] has provided hope to the idea of developing small molecule inhibitors of Aβ aggregation. All subregions of Aβ such as N-terminus, hydrophobic core, hinge or turn regions and C-terminus contribute differently and are critical for Aβ aggregation. His13-Lys16 (HHQK), central hydrophobic core, and hydrophobic C-terminus are the key sites important for nucleation of β-sheet rich conformation [121, 122]. The formation of hinge or turn regions helps to bring two hydrophobic segments to initiate the β-strand formation and subsequently assembly of β-sheet. Electrostatic and hydrophobic interaction plays and important role in Aβ aggregation. Moreover, it has been identified that the C-terminus of Aβ has significant contribution in aggregation. Two additional hydrophobic residues at C-

terminus of $A\beta_{42}$ is responsible for its higher tendency for aggregation and neurotoxicity as compared to $A\beta_{40}$ [123]. Development of Aβ aggregation inhibitors has focused on targeting these subsections. Several compounds such as Tramiprosate, RS-0406, and Scyllo-inositol (Figure 15) which binds specifically to HHQK region (N-terminus), central hydrophobic region and C-terminus, respectively, have entered the clinical trials [124–126]. However, none of the inhibitors have made it to clinic yet. Another strategy to inhibit the Aβ aggregation is by disruption of interaction between metal and Aβ. It is evident that excess metals such as zinc, copper worsened the Aβ mediated oxidative stress and act as a catalyst for Aβ aggregation [127, 128]. PBT2 (Figure 15) is an example of copper/zinc ionophore and metal mediated Aβ aggregation inhibitor [129].

Natural product curcumin which is closely related to chalcone has been reported to prevent oligomerization of Aβ and disaggregate preformed Aβ fibrils [130]. Hirohata et al.[131] have studied the mechanism for anti-amyloidogenic effects of five flavonoids. It was observed that Myricetin bound reversibly to the Aβ fibrils rather than the monomers.

Liew et al. [132] reported a synthesis of several aurone derivatives with amine and carbamate functional groups. They evaluated these compounds for their Aβ aggregation activity along with cholinesterase and monoamine oxidase inhibitory effects. Compound **58** with piperidine side chain was the most potent to inhibit Aβ aggregation (36.1% at 25 μM) as compared to curcumin (30.5% at 25 μM). Compound **58** demonstrated neuroprotective effect in *Caenorhabditis elegans* neurodegeneration model against Aβ and 6-hydroxydopamine induced toxicities.

Cong et al. [133] prepared a series of hydroxylated chalcones (10 examples) and tested for their dual inhibitory effects on Aβ aggregation and ferroptosis. They observed that trihydroxy compounds **59a-c** showed better Aβ aggregation inhibition (76.3% to 70.3% at 25 μM) than other compounds. *In vitro* study showed that trihydroxy substituted chalcones showed better neuroprotection against $A\beta_{1–42}$ induced neurotoxicity as compared to EGCG and curcumin. In addition, these compounds were evaluated for inhibition of ferroptotic cell death induced by RSL3 and erastin *in vitro*. Compound **59a** was the most potent inhibitor of ferroptosis with $IC_{50}$ = 0.45 μM (RSL3 induced) via inhibition of lipid peroxidation.

A series of indanone derivatives were reported by Wang et al. [134] and evaluated for their Aβ aggregation and monoamine oxidase B inhibitory effects. Among twelve evaluated derivatives, compound **60** showed the most potent inhibition of Aβ aggregation ($IC_{50}$ = 1.8 μM). It disaggregated the preformed Aβ fibrils with $IC_{50}$ = 7.9 μM. Compound **60** exhibited the selective MAO-B inhibition ($IC_{50}$ = 0.031 μM) as well as neuroprotective effects against $A\beta_{1–42}$ induced toxicity in SH-SY5Y cells.

### 3.3. Tau-based therapeutics

Neurofibrillary tangles (NFTs), aggregates of hyperphosphorylated tau protein are one of the hallmarks of several neurodegenerative diseases (tauopathies) including AD. Tau, a microtubule-associated protein, is thought to be responsible for stabilization of neuronal microtubules and help in intracellular transport [135]. Hyperphosphorylation of tau is believed to be one of the earliest events in pathogenesis of AD [136]. Tau has multiple

phosphorylation sites with the process of phosphorylation and dephosphorylation being tightly regulated by protein kinases and phosphatases, respectively. Examples of such kinases are cyclin-dependent-like kinase 5 (CDK5), [137–139] glycogen synthase kinase-3β (GSK3β), [140–142] tyrosine kinase Fyn [143, 144] and c-JUN N-terminal kinase (JNK) [145, 146]. Besides hyperphosphorylation, other post-translational modifications such as acetylation, [147, 148] and N-glycosylation [149] are thought to be associated with abnormal tau proteins. In AD, these underlying mechanisms lead to tau protein conformational changes and misfolding resulting in loss of tau binding to microtubules, subsequently dissociation, and aggregation to form fibrillary tangles inside neurons [150].

There has been an increased focus on tau-based agents subsequent to failure of drug development based on Aβ related targets in clinical trials. Inhibitors of kinases responsible for tau hyper phosphorylation, modification of other post translational events, microtubule stabilizers, tau-aggregation inhibitors and anti-tau immunotherapy are the major current strategies for developing tau-based therapeutics [151, 152]. This has led to several molecules such as tideglusib [153, 154], BMS-986168 (BIIB092) [155] methylene blue, Salsalate [148], curcumin and other drug candidates that has entered clinical trials (Figure 16).

Several researchers have reported the chalcone-based compounds that could prevent the formation of neurofibrillary tangles. These reported compounds exert their activity by either directly inhibiting the a) tau protein oligomerization or b) kinases involved in the hyperphosphorylation of tau proteins responsible for conformational changes, dissociation from microtubule, and subsequently aggregation to form tangles.

**3.3.1. Tau aggregation inhibition—**It is noteworthy that covalent inhibitors of tau aggregation contain α, β unsaturated carbonyl group which act as an electrophilic Michael acceptor similar to chalcones (Figure 17). For example, Cinnamaldehyde has been reported to inhibit the tau aggregation *in vitro* [156]. From the study, it was observed that the compound interacted with two cysteine residues in tau protein undergoing nucleophilic attack at Michael acceptor by cysteine. To confirm that α, β unsaturated carbonyl group was involved in interaction, investigators tested the 2-Phenylpropionaldehyde (2-PA), a reduced form of cinnamaldehyde (without α, β unsaturated carbonyl group). It did not show inhibitory effects on tau aggregation confirming β-carbon in cinnamaldehyde is essential for its activity. Another well-known natural compound that shares this electrophilic pharmacophore is curcumin. Presence of Michael acceptor, with similar mechanism, makes chalcone (and its analogs) a potential scaffold to develop as tau aggregation inhibitors. Xanthohumol, a natural chalcone based compound has been reported to inhibit tau protein aggregation and even disaggregate tau fibrils by directly interacting with tau proteins [157]. *In vitro* study showed that it reduces the apoptosis induced by tau oligomers. Similarly, Sonawane et al. [158] reported the anti-tau aggregation activity of another chalcone based natural product Baicalein ($IC_{50}$ = 35.8 μM). It was able to disaggregate the preformed tau fibrils as well as oligomers. Authors demonstrated that the Baicalein inhibit the tau aggregation by covalent modification as adduct of tau and baicalein was observed in mass analysis.

Lin et al. [159] studied licochalcone A and five derivatives for their ability to prevent tau misfolding, ROS scavenging and neuroprotection in human cells expressing proaggregant ΔK280 TauRD-DsRed. Among tested compounds, licochalcone A and compound **61** showed reduced tau misfolding and associated ROS. Increase in expression of protein HSPB1 (heat shock protein B1), involved in prevention of tau misfolding [160], by these compounds was attributed for their tau misfolding inhibitory activity. In streptozocin-induced hyperglycemic 3 × Tg-AD mice, compound **61** reduced the Aβ and tau levels and ameliorated cognitive dysfunction.

**3.3.2. Kinase inhibition—**The Bellluti group [161] developed a series of β-keto-enol curcumin analogs and tested their dual inhibitory effects in BACE-1 and GSK-3β. Compound **62** and **63** were the most potent BACE-1 and GSK-3β inhibitors, respectively. Compound **64** showed balanced inhibitory activity against BACE-1 and GSK-3β. Docking simulation showed that Cys199 of GSK-3β interact with α, β unsaturated carbonyl of compound **63**. Experimentally, they performed the thiol trapping assay using $^{1}$H NMR. It yields thia-Michael adduct in a very short time as evident by the disappearance of olefin proton signals.

Jeon et al. [162] reported chalcone derivatives that reduce tau phosphorylation and insoluble Aβ. They prepared 11 analogs and tested for the μ-calpain and cathepsin B inhibitory effects. In AD, hyperactivated μ-calpain are observed that cleaves p35 to p25 [163]. This causes hyperactivation of CDK5 which is associated with hyperphosphorylation of tau leading to formation of NFT. Among the tested compounds, investigators selected compound **65** ($IC_{50}$ = 18.83 μM for μ-Calpain and 6.34 μM for Cathepsin B) and **66** ($IC_{50}$ = 16.81 μM for μ-Calpain and 11.05 μM for Cathepsin B) for further studies based upon their potency against cathepsin B as well as μ-calpain. Compound **65** and **66** reduced the phosphorylated tau protein via inhibition of MAPK phosphorylation and cleavage of p35 to p25 associated with μ-calpain inhibition.

## 3.4. Neuroinflammation Inhibition

Several hypotheses exist to explain the causes and progression of AD, including those based on the cholinergic system, Aβ aggregate, NFTs, glucose hypometabolism and mitochondrial dysfunction, deficiency of autophagy, calcium homeostasis, neurovascular dysfunction, inflammatory hypothesis, metal ion hypothesis, and the lymphatic system hypothesis [164]. Neuroinflammation has emerged as a common feature of AD and a central link that corroborates how innate immune system mediate many of the pro-inflammatory processes. The significance of inflammation in AD was initially noted due to accumulation of immune-related proteins and cells within close proximity to amyloid plaques, protection against AD by anti-inflammatory drugs (e.g. NSAIDs), and reduction in AD pathology by NSAIDs in transgenic animals [165]. Acute inflammation is considered to be neuroprotective while chronic inflammation can be injurious. Sustained activation of immune cells in the brain is now considered to be the third core pathology in AD besides amyloid plaques and phosphorylated tau protein [166, 167]. Thus, acute-phase activation of immune cells to protect neurons may start contributing to injury through persistent generation of pro-inflammatory molecules.

#### 3.4.1. Microglial activation and production of inflammatory mediators—

Activation of glial cells (astrocytes, microglia) results in accumulation of proinflammatory molecules exacerbating Aβ and tau pathology among other factors and causes progressive neuronal damage [165]. Microglia are also considered as resident immune cells of central nervous system. They have been recognized for their diverse role in surveying the microenvironment in CNS, phagocytosis of plaques, cellular debris or molecules. Microglia can initiate the immune response with the help of pattern recognitions receptors (PRRs) including TLRs that are present on their surface. TLRs 1 to 9 are expressed in microglia [168]. TLRs can recognize both pathogen-associated molecular patterns (PAMP) and endogenous danger signals known as damage associated molecular patterns (DAMP). In AD, DAMPs such as Aβ or tau aggregates can activate microglia by binding with TLRs, receptors for advanced glycation end products (RAGE), TREM2 and scavenger receptors [169, 170]. This results in production of proinflammatory cytokines such as IL-1β, IL-18, IL-10, IL-6, and TNF. Expression of these cytokines in acutely activated microglia drive enhanced phagocytosis, uptake and clearance of Aβ. However, if the activation persists, the phagocytic nature of microglia is compromised and lead to continuous generation of cytokines that causes neuroinflammation and ultimately neurotoxicity and neuronal cell death. Ion channels involved in potassium (THIK-1, $K_v$), chloride and purinergic signaling aid in microglial function through regulation of mobility and surveillance [165, 171–173].

Inflammasome plays a key role in inflammatory pathway. These are the protein complexes of sensor molecules (NLRs), apoptosis associated spike like protein (ASC) and pro-caspase that are formed in the cytosol in response to damage or pathogen- associated molecular patterns. NLRP1, NLRP3, NLRC4, AIM2 and PYRIN are the major cytoplasmic sensors that have been reported to form the inflammasome. NLRP3 inflammasome is one of the best studied among all the inflammasomes [174]. Assembly of these protein complex facilitates the conversion pro-caspase-1 to mature caspase-1 via proximity-induced autocatalysis. Caspase-1 is then involved in processing of precursor of inflammatory cytokines pro-1β and pro-IL8 into mature IL-1β and IL-18. Once secreted extracellularly, these matured cytokines can exhibit proinflammatory role. Moreover, casaspe-1 can trigger the cleavage of pore-forming Gasdermin D (GSDMD) which in turn induces the pro-inflammatory cell death called pyroptosis [175, 176].

Endogenous Aβ plaques can initiate the NLRP3 inflammasome mediated inflammatory responses which produces several proinflammatory and neurotoxic cytokines and chemokines [177]. Direct association of NLRP3 inflammasome in the development of AD has been demonstrated *in vivo* [178]. The transgenic mice (APP/PS1) with NLRP3 and caspase-1 deficiency have reduced AD-related pathogenesis. These mice have reduced neuroinflammation, and cognitive impairment as well as reduced Aβ secretion [178]. Recently, work by Ising et al. [179] demonstrated that microglia and NLRP3 inflammasome plays an important role in promoting Aβ and tau pathology. Their work supports the hypothesis that NFTs are the downstream product of amyloid-beta-induced microglial activation. Association of NLRP3 inflammasome in AD pathogenesis and demonstration that pharmacological intervention of NLRP3 inflammasome improves cognitive impairment in AD mouse model has attracted many researchers on developing NLRP3 inflammasome inhibitors for AD [180, 181].

With increasing evidence supporting a central role of inflammatory processes in AD and other neurodegenerative disease, it is imperative to develop drugs to modulate targets involved in neuroinflammation. Currently used drugs mostly act as cholinesterase inhibitors [182]. A recent report showed 121 total drugs in clinical trials including drugs for cognitive function enhancement (12 agents) and for treating behavioral and neuropsychiatric symptoms (12 agents). In addition, they include several disease-modifying agents (97 agent) that target Aβ, tau, inflammation, oxidative stress and mitochondrial function. This report indicates an increasing number of disease-modifying agents that targets pathways other than amyloid or tau in 2020 compared to 2019 [183, 184]. There is an unmet need for developing new drugs that target pro-inflammatory molecules/pathways.

Chalcones and several flavonoids have been studied for their anti-inflammatory properties. Presence of Michael acceptors in chalcones makes it easier to target many proteins involved in immune responses and inflammation. They can undergo Michael addition with the cysteine present in these proteins. Inhibitory kappa B kinases (IKKs) are one such group whose inhibition causes the suppression of nuclear translocation of NF-ƙB [185] which is a key mediator of inflammatory immune response [186, 187]. Some examples of chalcones that inhibit the IKKβ and NF-ƙB mediated inflammatory responses include butein [188], isoliquiritigenin, and licochalcone A [189, 190]. Isoliquiritigenin, a natural flavonoid from licorice root has been demonstrated to reverse LPS induced cognitive impairment due to its antioxidant and anti-inflammatory properties [191].Moreover, Isoliquiritigenin was found to inhibit NLRP3 inflammasome independent of its inhibitory potency on TLR4 [192]. Prenylated chalcones, Bavachalcone and isobavachalcone were demonstrated to have anti-inflammatory activity in BV-2 microglial cells [193]. Similarly, plant derived 2,2’,5’-trihydroxychalcone (225THC), a potent antioxidant, exerts neuroprotective activity against the TLR4 mediated inflammation in microglia. It inhibited the LPS stimulated TNF-α and IL-6 secretion [194].

Lee et al. [195] reported a synthetic chalcone derivative (compound **67**) and its anti-inflammatory effects in microglial cells (BV2) by blocking (TLR4)-mediated inflammatory responses. Inhibition of Akt by compound **67** decreases the IkB phosphorylation which ultimately downregulate the NF-ƙB. Downregulation of NF-kB signaling pathway alleviates the expression of iNOS, COX-2, as well as the production of pro-inflammatory cytokines IL-1β and IL-6. Mateeva et al. [196] synthesized a series of 24 chalcone and flavone derivatives and tested their anti-inflammatory activity on LPS stimulated microglial cells (BV2). Compound **68** and **69** caused a potent inhibition of NO production and iNOS protein expression. Compound **68** reduced the production and release of pro-inflammatory cytokines IL-1α, IL-6 and IL-10.

However, an unsuccessful clinical trial using the anti-inflammatory properties of tetracycline antibiotic minocycline to treat the progression of AD in individuals with mild disease [197] points to explore drugs with ability to reach more than one target.

### 3.5. Multi-target directed ligands (MTDLs)

Drug discovery and development has mainly focused on selectively targeting a single protein to avoid side effects involving off-targets. However, polypharmacology [198], single agent

targeting two or more proteins, is emerging as a new approach for treating many complex and chronic diseases including neurodegenerative diseases such as AD [199–201]. Extensive studies on this multi-targeting approach have already provided several drugs with dual and/or multiple target effects. Data from 2015–2017 show that 21% of drugs approved were multi-targeting drugs [199]. Some of the examples are brexpiprazole, a partial agonist of dopamine (D2) and serotonin (5-HT1A) receptors, cariprazine, partial agonist of D2 and D3 receptors, and midostaurin, a multi-kinase inhibitor. Partial inhibition of multiple targets, instead of complete inhibition of one target, is considered advantageous as it would maintain the balance between the normal physiological functions of proteins targets and prevention of the disease progression [202]. Moreover, it has an advantage of easier prediction and control of pharmacokinetic profile (PK) of single drug compare to combination therapy along with lower or no risk of drug interactions as in combination therapy [203, 204].

In multifactorial diseases such as AD, multiple-target directed ligands (MTDLs) have gained attention for drug development [205, 206] as approaches targeting single mechanism (proteins) or pathology has not led to a successful disease modifying drugs. Several chalcone derivatives targeting multiple pathologies of AD are being investigated due to flexibility of chalcone for modifications (Figure 19). Sun et al. [207] reported the multitargeted tacrine-homoisoflavonoid (rigid chalcone analogs) as an inhibitors of cholinesterases and monoamine oxidase B (MAO-B). They connected tacrine and homoisoflavonoid with different chain length carbon spacer. Among the tested compounds, compound **70** showed the most promising results with $IC_{50}$ at sub-micromolar range for all three targets ($IC_{50}$ = 67.9 nM, eeAChE; 33.0 nM, eqBuChE; and 0.401 μM, hMAO-B). Li et al. [208] have also prepared a series of homoisoflavonoid as a multitargeting agents. They tested the prepared compound for cholinesterases, MAO, $A\beta_{1–42}$ aggregation and antioxidant properties. Compound **71** showed the most potent AChE inhibition at nanomolar concentration ($IC_{50}$ = 2.49 nM). In addition, it showed MAO-B inhibitory activity with $IC_{50}$ of 1.74 μM. The compound showed good self or $Cu^{2+}$ induced $A\beta_{1–42}$ aggregation inhibitory and metal chelating activity. Molecular modeling showed that compound **71** occupied the CAS, and PAS of AChE.

Li et al. [209] also used the aurone functional group and prepared several aurone Mannich bases as rigid analogs of chalcones. Compound **72,** along with good metal chelating ability, Aβ-aggregation inhibition, and antioxidant activity, showed the most potent inhibitory effect on AChE from different species ($IC_{50}$ = 8.78 nM, ratAChE; 21.2 nM, eeAChE and 37.1 nM, hAChE). This compound displayed the significant neuroprotective effect against $H_2O_2$ induced injury in PC-12 cell. Previously, they reported a series of 4-hydroxyl aurone derivatives and evaluated their effects on MAOs, Aβ-aggregation, metal chelation and antioxidant properties [210]. Based upon balanced activities, they selected **73** as a candidate compound for further investigations.

Other chalcone derivatives reported by the Deng group as multifunctional ligands for AD include the chalcone-flurbiprofen hybrids **74–76** [211, 212]. Cao et al. [211] prepared a series of 18 4’-OH flurbiprofen-chalcone hybrids and evaluated for MAO inhibitory effects, Aβ-aggregation inhibition, metal chelating effects and antioxidant activity. Compound **74** and **75** displayed a significant inhibition of Aβ aggregation and antioxidant activity. Anti-

inflammatory activity of **74** and **75** were performed in BV-2 cells by analyzing inhibition of LPS-induced NO and TNF-α production. Both compounds showed better TNF-α and NO inhibitory activity as compared to flurbiprofen. Both compounds exhibited 3-fold higher antioxidant effect compared to efficient antioxidant Trolox as determined by *in vitro* oxygen radical absorbance capacity-fluorescein (ORAC-FL) assay.

In a latter study, Tian et al. [212] prepared 7 flurbiprofen-chalcone hybrids. They tested all prepared compounds for inhibition of cholinesterase, MAO, Aβ-aggregation inhibition as well as for metal chelation and antioxidant properties. Compound **76** showed the most potent inhibitory effect on MAO-B ($IC_{50}$ = 0.43 μM) and Aβ-aggregation (70.6%, self-induced and 54.9, $Cu^{2+}$ induced, at 25 μM). TNF-α and nitric oxide (NO) inhibitory activity was measured to assess its anti-inflammatory properties. It inhibits NO (52.5% and 77.5% at 2.5 and 10 μM, respectively) and TNF-α (56.5% and 77.1% at 2.5 and 10.0 μM, respectively) expression better than flurbiprofen (23.0%; NO and 30.3%; TNF-α, at 10 μM).

## 4. Chalcone as molecular imaging agent in AD

Aβ plaques and neurofibrillary tangles (NFTs) in the brain are the pathological hallmarks of AD [213]. *In vivo* detection of these pathological markers using molecular probes facilitates the diagnosis as well as monitoring of the disease progression and treatment [214]. Molecular imaging methods such as positron emission tomography (PET) and single-photon emission computed tomography (SPECT) are noninvasive, sensitive and powerful diagnostic techniques that use radiolabeled molecular probe to visualize, characterize and quantify the physiological alterations *in vivo and in situ* [215, 216]. Several radiolabeled PET imaging agents to image Aβ or tau proteins (NFTs) have been investigated. The ideal PET imaging agent needs to be a) easily BBB permeable b) selectively bind with the target of interest e.g amyloid plaque or NFTs with high affinity and c) easily cleared from non-target brain regions. Physicochemical requirements of the probe include low molecular weight (<600), neutral species with logP value in the range of 1.0 to 3.5 for easy BBB permeation through passive diffusion [217, 218].

Several fluorinated Aβ PET tracers (florbetapir [219], florbetaben, and flutemetamol) for *in vivo* imaging of Aβ plaques have been approved. However, use of these probes is limited to support other clinical assessment for AD diagnosis and cannot be used to measure the extent of cognitive impairment or diagnose AD on its own as amyloid burden does not necessarily correlate with AD severity. Recently, first tau PET imaging agent, flortaucipir F18 (Tauvid) [220] has been approved by FDA as intravenous injection to determine tau pathology, precise distribution and density of tau tangles, in AD.

For imaging Aβ by PET/SPECT in vivo, the most commonly used radiolabels are [$^{11}$C] ($t1_{/2}$ = 20 min) and [$^{18}$F] ($t1_{/2}$ = 110 min) [221]. [$^{99m}$Tc] and [$^{125}$I] are other radiolabels used for imaging Aβ. [$^{99m}$Tc], due to easy production using the $^{99}$Mo/$^{99m}$Tc generator is favored than the latter.

Small molecular size, and feasible optimization of lipophilicity (LogP) to enhance BBB permeability makes chalcone a good candidate scaffold for the development of chemical

probes or imaging agents in AD. Ono and Nakayama group have reported the use of chalcones as a template for development of several radiolabeled molecular probes e.g radio iodinated chalcones, fluoro-pegylated chalcones, 99mTc labeled chalcones [222–226]. Compound **77**, iodinated chalcone with N, N-dimethyl [225], showed significant $A\beta_{1–42}$ binding affinity (*Ki* = 3.9 nM). Authors suggest that the binding site of compound **77** is different than known Aβ imaging probes Congo red and thioflavin T. In mouse model brain sections, **77** showed strong staining of Aβ plaque. In vivo biodistribution of [$^{125}$I]-**77** displayed good uptake (2.56% ID/g, 2 min post injection) and rapid clearance from brain (0.21%ID/g, 60 min post injection). Similarly, another iodinated chalcone **78** [222] also showed high binding affinity with $A\beta_{1–42}$ (*Ki* = 2.9 nM) and like **77** has non-competitive binding with congo red and thiovalvin T. Radioiodinated [$^{125}$I-**78**] was evaluated for the biodistribution study in normal mice. It was observed to have good brain uptake (2.04% ID/g, 2 min post injection) and rapid clearance from brain (0.49% ID/g, 30 min post injection). O-Substituted derivatives **79** and **80** with iodinated radio label [226], also displayed good binding affinity with $A\beta_{1–42}$. Compound **79** showed better affinity than **80**, however **80** has better pharmacokinetic profile as observed in *in vivo* biodistribution study. Uptake and clearance percentage for **80** was 4.82% ID/g at 2 min and 0.45% ID/g at 60 min, post injection, respectively). Cui et al. [227] prepared a series of indole moiety containing chalcones and evaluated them for Aβ imaging. Most of the compounds showed good binding affinity to $A\beta_{1–42}$. In particular, compound **81** with 4-iodophenyl substituents, showed the most significant binding affinity ($IC_{50}$ = 8.22 nM) with specific binding to Aβ plaque *in vivo*. However, biodistribution study in normal mice showed poor uptake into the brain (0.41% ID/g at 2 min). Therefore, authors concluded that more modifications of the indole containing chalcone derivatives is warranted. Several fluoro-pegylated chalcones were developed [223] as molecular probes for PET imaging of Aβ plaques. In this series, compound **82** exhibited significant affinity to $A\beta_{1–42}$ (*Ki* = 38.9 nM). From SAR, it was found that dimethylamino group was important for binding activity as derivatives with this group have higher *Ki* values than monosubstituted or free amine group. Recently, Kaide et al. [228] has shown that substitution of iodinated chalcone with fluorine-18, compound **83** and **84**, has improved its binding affinity to Aβ. Both compounds showed high binding affinity to $A\beta_{1–42}$ with *Kd* values in nM range (4.47 and 6.50 nM for **83** and **84**, respectively). Biodistribution study in normal mice showed a higher uptake in brain (4.43 and 5.47% ID/g at 2 min post injection for compound **83** and **84**, respectively). It was rapidly cleared from the brain (0.52 and 0.66% ID/g at 30 min post injection for **83** and **84**, respectively.

The Ono group [224] has also prepared the (99m) Tc-labeled chalcone derivatives and their corresponding rhenium analogs as probes for Aβ aggregates. Compound **85** displayed the desirable characteristics with the potential for being developed as Aβ imaging probe. In normal mice, it showed high uptake in brain (1.48% ID/g) and rapid clearance from brain (0.17% ID/g) at 2 min and 60 min post injection, respectively. These developments have inspired other group to develop chalcone based $^{11}$C PET imaging agents [229]. Authors reported the preparation of homodimeric chalcone as a ligand for Aβ. They used the ligand to image the Aβ plaques after labeling it with $^{11}$C (compound **86**) and performed the comparison with monomeric $^{11}$C radiolabeled ligand (compound **87**). The bivalent

compound, **86**, showed ~1.6-fold higher binding affinity to $A\beta_{1–42}$ as compare to its monomeric congener, **87**. PET images after administration of these probes indicated that the uptake of **86** [standard uptake value (SUV) ~3.6] is higher than **87** (SUV ~2.1). Studies on its molecular modeling to show the binding mode with Aβ fibril (PDB: 2BEG) and other basic chemical properties beneficial for the CNS drugs such as molecular weight, BBB permeability were also considered while preparing the core chalcone ligand.

Conformationally constrained analogs of chalcone such as aurone and indanone have been explored for Aβ plaque imaging. Ono et al. [230] reported iodinated aurones with primary (**88**), secondary (**89**) and tertiary amine (**90**) groups in the phenyl ring. All compounds were tested for the $A\beta_{1–42}$ binding affinity and showed the binding affinity in nanomolar range (*Ki* = 1.24–6.82 nM). The radio iodinated **88** also showed good binding affinity with *Kd* = 7.9 nM. The aurone derivative clearly stained Aβ plaques in AD mouse model. From biodistribution study in normal mouse, they showed good uptake to brain and clearance from the brain as well. For e.g. $^{125}$I-**88** showed uptake of 4.57% ID/g at 2 min post injection and clearance of 0.49% ID/g at 30 min post injection. Later the amine moiety was replaced with ethylene oxide to give compound **91** [231]. It showed significant $A\beta_{1–42}$ binding affinity with *Ki* of 1.05 nM. Biodistribution study clearly indicated significant brain uptake (4.5% ID/g at 2 min post injection) of **91** and its clearance from brain (0.09% ID/g at 60 min post injection).

Later, Watanabe et al. [232] introduced dual fluorinated and iodinated chalcone derivatives as a radio labeled probe for PET and SPECT imaging of Aβ. The fluorinated and iodinated chalcone (Figure 22) was evaluated for $A\beta_{1–42}$ binding affinity which gives *Ki* value at 6.81 nM. In AD mouse model, it showed intense staining of Aβ plaques. The radio labeled derivatives **92** ($^{125}$I) and **93** ($^{18}$F) were prepared and tested for their biodistribution in normal mice. Both showed good brain uptake and clearance. Compound **92** showed initial uptake of 2.34% of ID/g at 2 min post injection. It was rapidly eliminated in 60 min post-injection (0.19% of ID/g). For compound **93**, the radioactivity reading was 3.66% of ID/g and 1.75% of ID/g at 2 min and 60 min post injection, respectively. Iodinated indanone derivatives with methyl substituted amines were reported as potential Aβ plaques imaging probes [233]. Particularly, compound **94** and **95** with methyl amine or dimethyl amine showed significant $A\beta_{1–40}$ binding affinity with *Ki* = 5.8 and 11.8 nM, respectively. Both compounds showed great affinity in AD patient brain homogenates with *Ki* values in nanomolar range. Compound **95** was radio labeled with $^{125}$I and further tested for biodistribution in mice, partition coefficient measurement, in vitro stability test etc. It was observed that compound **95** exhibited significant brain uptake of 5.29% ID/g at 2 min post-injection. Also, it showed fast clearance from brain (0.84% ID/g at 60 min post injection).

In addition to radiolabeled imaging agent, chalcone derivatives have been investigated as fluorescent probes to image the Aβ aggregates. *In vivo* use of these agents in humans is limited because of a lack of deep penetration. However, they are good candidates for pre-clinical investigations because they are easy to synthesize, handle and less expensive compared to radiolabeled agents. In contrast to PET/SPECT, where expensive and specialized instrument is required to generate short lived radionuclides, fluorescent probes are nonradioactive and gives real-time high-resolution imaging [234]. Chalcones conjugated

system (**Figure 1)** with proper electron withdrawing or electron donating functional groups on the benzene ring(s) can pertain fluorescence. Jung et al. [235] have reported chalcone based fluorescent probes, **96 a**nd **97** (Figure 23). Both probes showed increased fluorescence when bound with Aβ aggregates. The apparent binding constants (*Kd*) for **96** and **97** was observed at 1.59 and 2.30 μM, respectively. Probe **96** was chosen for the ex-vivo imaging because of its better LogP value. Its emission wavelength of 532 nm after binding to Aβ aggregates limits the use for *in vivo* experimentation. Later they developed compound **98** [236] boronic acid-based chalcones as fluorescent probes that exhibit a significant increase in binding affinity (*Kd* = 0.79 μM) for Aβ aggregates. The Ono group, in addition to their work on radio labeled chalcone derivatives, reported the fluoresence probes to stain β-amyloid *in vitro* [237]. All four probes showed moderate binding affinity for Aβ (1–42) aggregates ($K_i$ = 72–114nM). However, only molecules **99** and **100** showed stronger fluroescence (6.7 and 14.2 fold, respectively) in the presence of Aβ (1–42) aggregates. In Tg2576 mouse brain sections, these two probes clearly visualized Aβ plaques in contrast to two other probes they developed in the study. Thus author concluded that these two probes are suitable for *in vitro* staining of Aβ plaques.

Recently, some investigators are focused on developing several near infrared (NIR, 650–900 nm) fluorescence probes for Alzheimer's disease as it has advantages of deep tissue penetration and high sensitivity. Several probes such as NIAD-4 (bisthiophene derivatives), benzophenoxazine dyes, curcumin derivatives, BODIPY based probes have been explored as NIR fluorescence probes for AD [238].

## 5. Future perspectives: Potential theranostic agent for AD

Theranostics defines the approach of using a single molecule or agent that possess both therapeutic and diagnostic properties [239]. In contrast to conventional strategy of using two different agents, this approach provides the advantage of avoiding differences in the biodistribution and selectivity of multiple ligands. This idea has been explored in the drug discovery and development for treating several diseases such as cancers, HIV infection, multiple sclerosis and atherosclerosis [240] and found to be beneficial. Undeniably, most of such work has been done in the field of oncology [241–243]. This approach is attainable in Alzheimer's disease as well, however, the field of developing theranostic for AD is in its infancy.

Evidently, chalcone and its analogs have been widely investigated for their therapeutic application as cholinesterase inhibitor, Aβ aggregation inhibitor, tau protein related kinase inhibitors, anti-inflammatory agents to prevent neuroinflammation and several others. On the other hand, several radiolabeled chalcone derivatives have been studied for their possibility as PET/SPECT imaging agents to detect amyloid plaques *in vitro* and *in vivo.* Similarly, several chalcone based fluorescent probes with significant binding affinity for Aβ are currently being investigated. These studies justify an idea of incorporating both therapeutic and imaging capability in one chalcone molecule to obtain theranostic chalcone derivatives. For instance, developing a chalcone compound that can give intense fluorescence upon binding to Aβ aggregates or NFTs and inhibit the aggregation can be a plausible approach to yield theranostic chalcones as supported by a few studies on other classes of compounds.

Such examples include NIR fluorescence probe phenothiazine [244–246], curcumin derivatives ($^{18}$F labeled curcumin, NIR fluorescent probes such as CRANAD derivatives [244]. Phenothiazine derivative **101** [244], showed significant binding affinity to Aβ aggregates (*Kd* = 7.5 nM) and effectively inhibited the formation of Aβ fibrils. It also showed ability to disaggregate already formed Aβ fibrils. This compound showed maximum emission in PBS at >650 nm. Taken together, it has displayed a potential to evolve as theranostic agent for AD. Later same group developed another phenothiazine based NIR probe, **102** [245], that has protective effects on human neuroblastoma cells. It has high binding affinity to Aβ aggregates (*Kd* = 24.5 nM) and metal-chelating property. This probe has the ability to image Aβ plaques in AD mouse model. It prevents the Aβ aggregation and protect human neuroblastoma SH-SY5Y cells from Aβ induced toxicity and oxidative stress. One of the best examples of compounds with theranostic potential in AD is curcumin which is structurally related to chalcone. Several studies suggest that it has very high binding affinity to Aβ [248, 249]. Several curcumin derivatives have been developed to evaluate Aβ plaques *in vivo* e.g $^{18}$F curcumin derivatives, CRANAD derivatives etc [250–252]. In addition, it has been demonstrated to possess Aβ aggregation inhibitory activity,[130, 253, 254] metal chelating effect [255], antioxidant, and anti-inflammatory [256, 257]. The Ran group has developed several curcumin based NIR fluorescence probes (CRANAD derivatives) for Aβ plaque imaging. **CRANAD-17** was designed to possess both imaging and therapeutic potential [251]. Imidazole moiety was incorporated into **CRANAD-17** to compete Aβ peptide (Histidine-H13 and H14) for copper binding, thereby preventing crosslinking of Aβ. Collectively, curcumin and its derivatives show great potential to develop a theranostic agent for AD.

On the foundation of the above examples and the fact that chalcone shares structural similarity with curcumin, chalcone has a potential to be explored as theranostic agents in AD. Currently, there are no clinically approved disease modifying agents for AD. Several chalcone derivatives have been reported to have high binding affinity to Aβ, increased fluorescent after binding to Aβ, and inhibitory effects on Aβ aggregation as well as other therapeutic targets of AD. Therefore, vigorous and extensive studies are warranted to develop chalcone as MTDL which possess higher binding affinity to Aβ or NFTs and fluorescence properties, particularly at NIR range to enable molecular imaging of AD *in vivo*.

## 6. Conclusion

Limited efficacy of currently available FDA approved drugs for AD treatment and lack of any disease modifying agents has attracted many researchers including medicinal chemists to explore different chemical scaffolds in search of a potential therapeutics for AD. Chalcone is one of the privileged scaffolds with diverse biological functions that is being extensively studied for Alzheimer's disease, both as therapeutics and molecular probe. For the development of CNS drugs, BBB permeability is one of the key factors to be considered in addition to potency of the drugs. As mentioned earlier, chalcone has low molecular weight, and easy to optimize its lipophilicity (logP) with appropriate substituents which makes chalcone scaffold interesting with a potential CNS therapeutic agent. Currently, several amyloid and tau-based agents for AD in clinical trials have failed. Thus, researchers

have extended their focus on development of novel agents targeting other measures such as neuroinflammation, mitochondrial dysfunctions for the AD treatment. As evident, several natural chalcone and its analogs (e.g. butein, licochalcone, Isoliquiritigenin) has shown considerable anti-neuroinflammatory activities *in vitro* and *in vivo*. Moreover, AD is a complex multifactorial disease. Inhibition of single protein target/mechanism involved in the pathogenesis of AD, would not be sufficient to treat AD. Therefore, development of multi-target directed ligands would be an essential approach to succeed in finding novel therapeutic agents for AD. In this quest, chalcone and its analogs has shown a great potential as many derivatives has been reported to show multi-targeted functions. Furthermore, early diagnosis of disease is a critical step in determining the efficacy of treatment. In AD, several biomarkers such as $A\beta_{42}$, $A\beta_{42/40}$ ratio, phosphorylated tau proteins (pTau181) are specified as core neurochemical biomarkers [258]. Several Aβ and NFTs molecular probes were discovered. However, they are radiolabeled agents associated with high cost, and toxicities. Researchers are in search of developing NIR fluorescence probes to image Aβ and NFTs. One of the most studied compounds for developing molecular probe that is closely related to chalcone is a natural product curcumin. Some of the NIR fluorescence probes (related to curcumin) has theranostic potential in AD as they have ability to inhibit the protein (Aβ) aggregation as well. Chalcone share structural similarity with curcumin, and studies showed that several chalcone analogs have significant binding affinity to Aβ and inhibition of Aβ aggregation. Exploration and optimization of chalcone and its analogs is applicable for the development of NIR fluorescence theranostic agents (for AD). In summary, this review highlights different pathological mechanisms of AD and current development of chalcone and its analogs in drug discovery and molecular imaging for AD treatment and diagnosis, respectively. We hope the information provided in this review will be adequate and encourage medicinal chemists and many other researchers to consider exploration of chalcone as therapeutic or diagnostic or even beyond as a theranostic agent in their future AD drug discovery endeavors.

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## Highlights

- Comprehensive overview of current developments related to chalcone and its analogs as therapeutic or diagnostic agents in Alzheimer's disease (AD).
- Chalcones as multi-target directed ligands (MTDL) in AD.
- Potential use of chalcones as theranostic agents for AD.

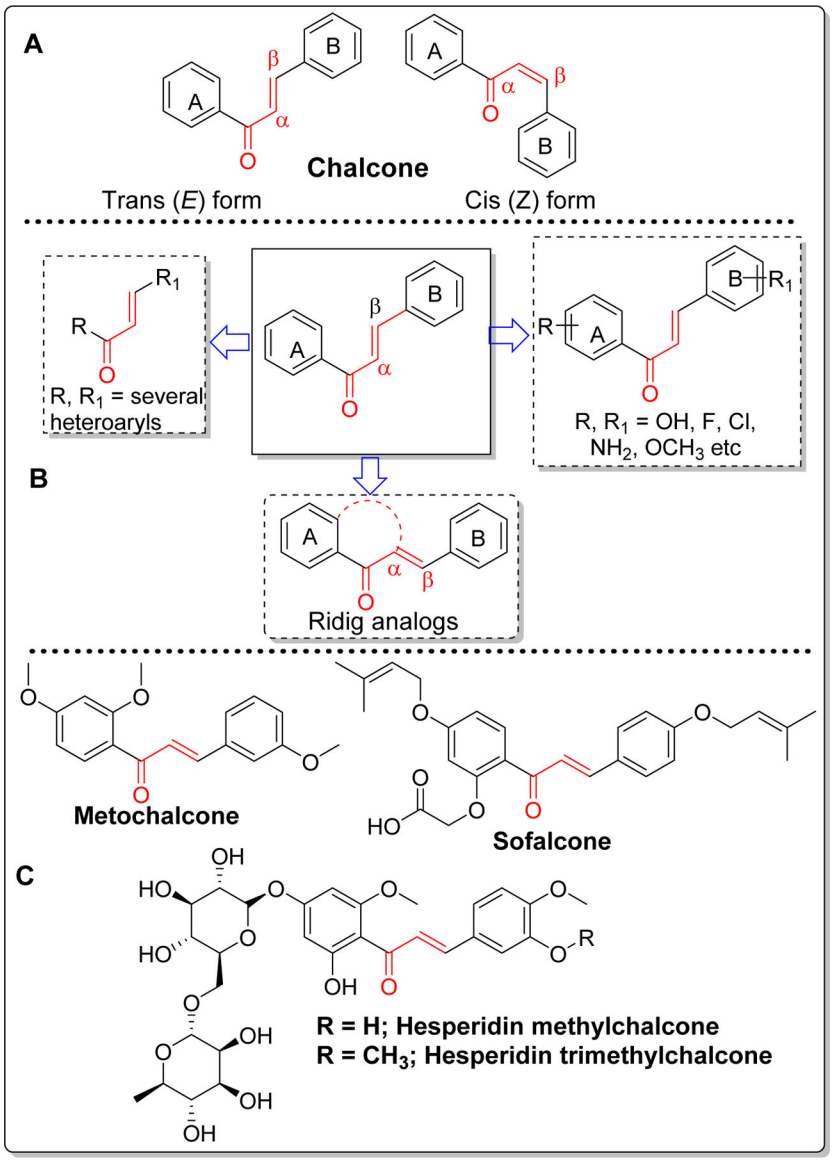



**Figure 1.**

Structure of chalcone and its form (A), major possible modifications (B) and clinically used and/or tested chalcone-based drugs (C).

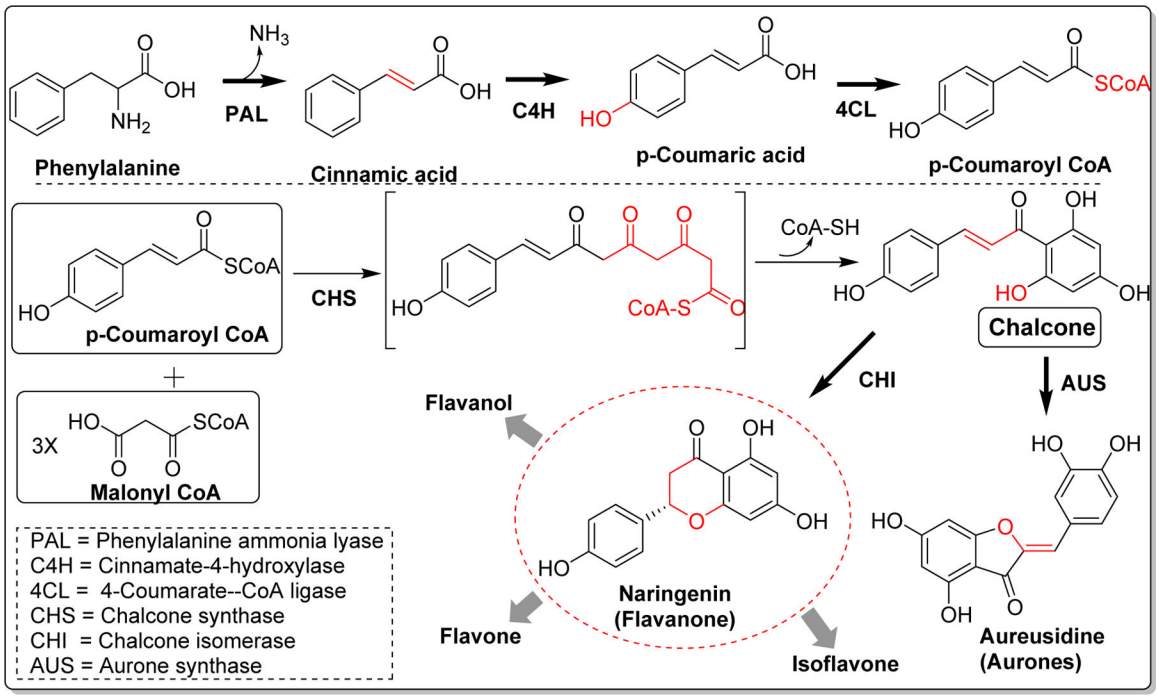



**Figure 2.**
Biosynthesis of chalcone and its subsequent conversion to natural flavonoids.

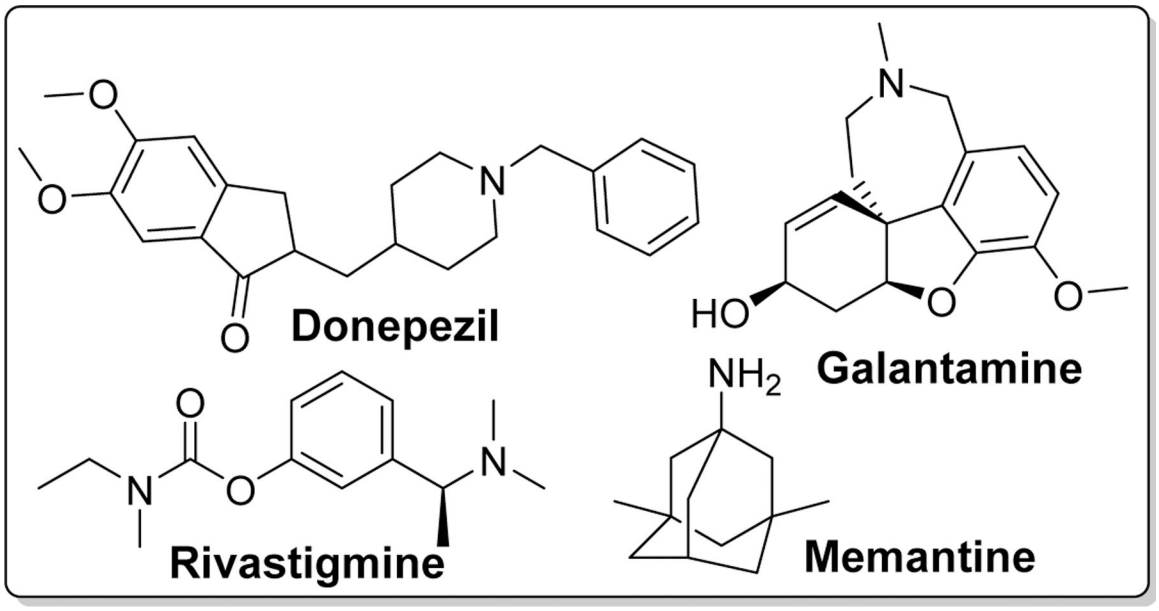



**Figure 3.**
Structures of clinically approved drugs for the treatment of AD.

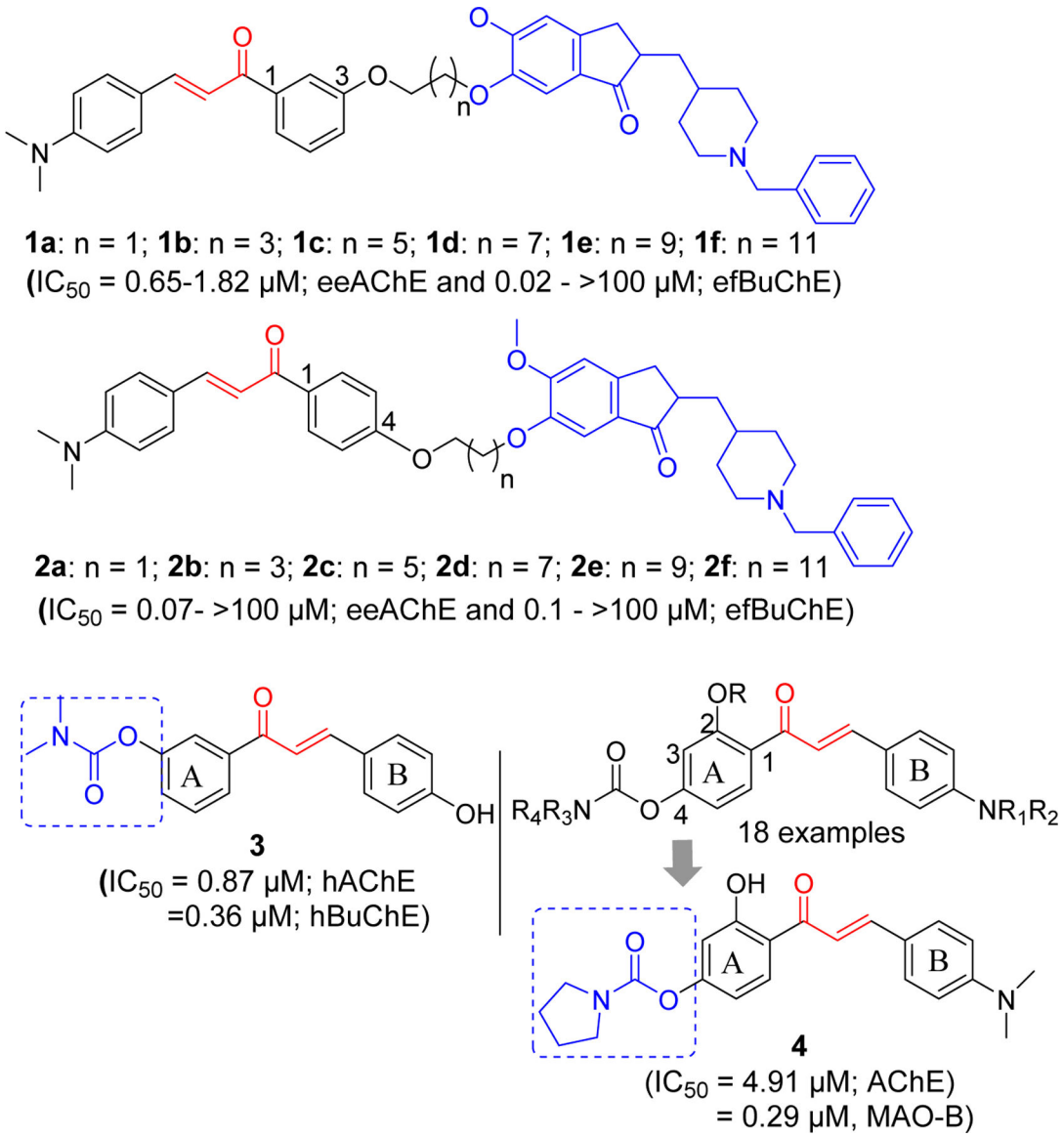



**Figure 4.**
Chalcone-Rivastigmine/Donepezil hybrids.

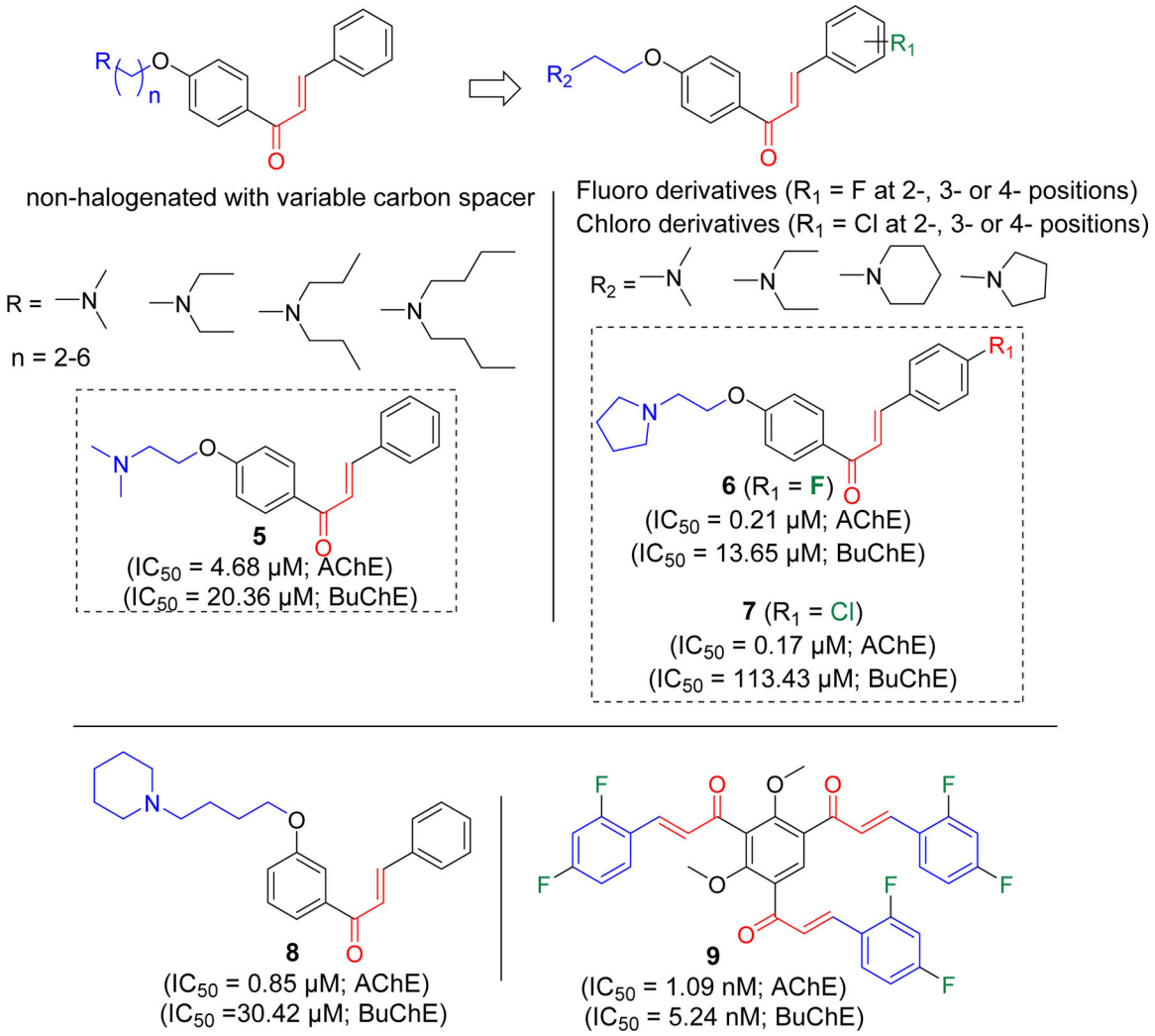



**Figure 5.**
Halogenated and non-halogenated alkyl amine derivatives of chalcones.

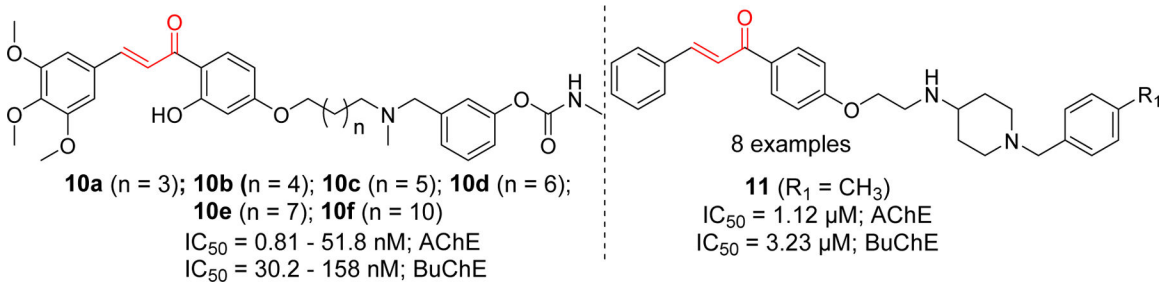
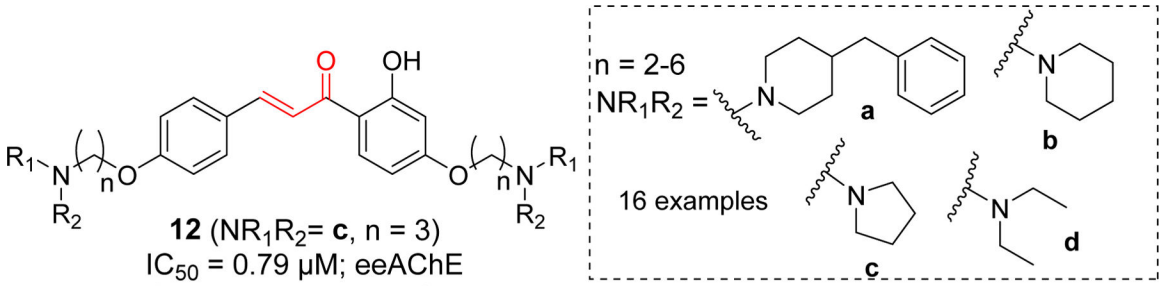



**Figure 6.**
Chalcone derivative with alkylamine functional groups.




**12** ($NR_1R_2$= **c**, n = 3)
$IC_{50}$ = 0.79 μM; eeAChE
$IC_{50}$ = 3.80 μM; eqBuChE
$IC_{50}$ = 8.30 μM; MAO-B

**14** ($NR_1R_2$= **a**, n = 6)
$IC_{50}$ = 1.30 μM; eeAChE
$IC_{50}$ = 0.80 μM; eqBuChE
$IC_{50}$ = 1.10 μM; MAO-B

**13** ($NR_1R_2$= **c**, n = 6)
$IC_{50}$ = 1.30 μM; eeAChE and 0.78 μM; hAChE
$IC_{50}$ = 1.20 μM; eqBuChE and 0.91 μM; hBuChE
$IC_{50}$ = 0.57μM; MAO-B

**Figure 7.**
Chalcone derivative with di O-alkylamine substituents.

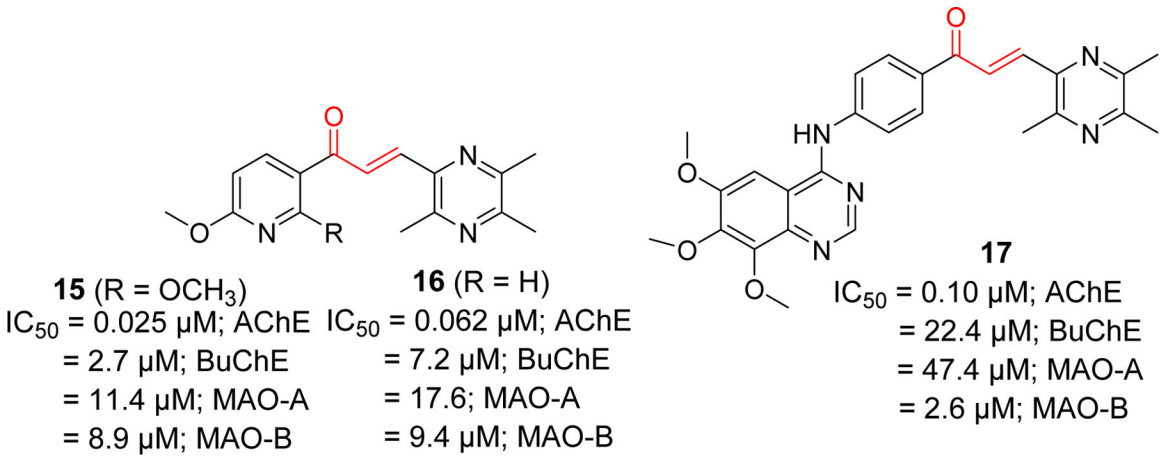



**Figure 8.**
Tetramethyl pyrazine derivatives of chalcone.

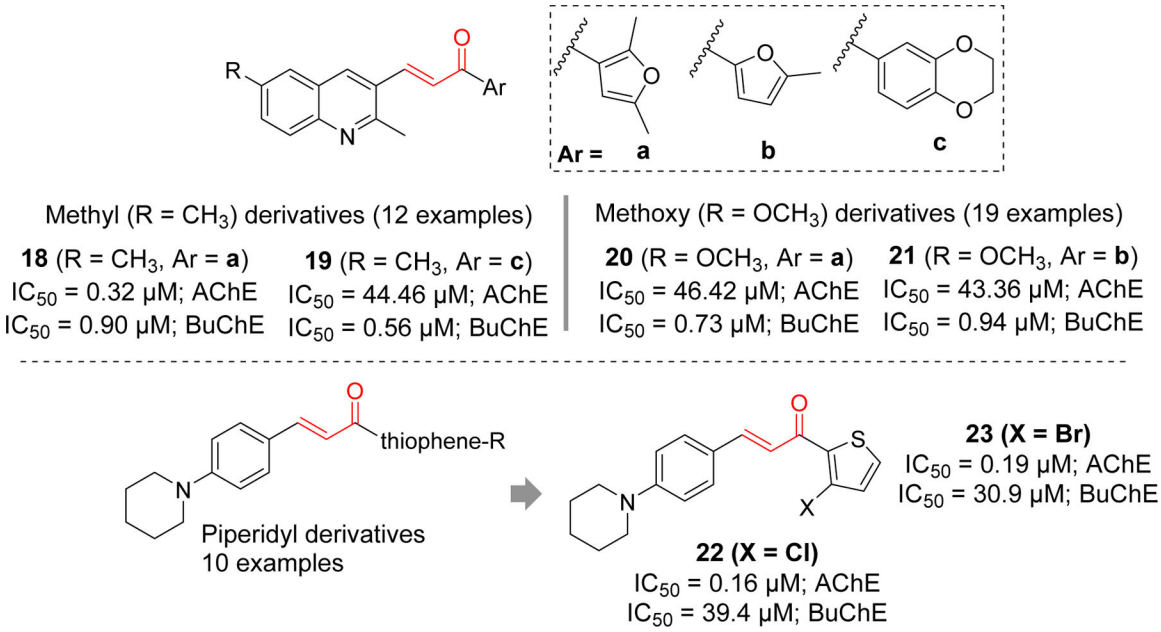



**Figure 9.**
Quinoline and piperidyl derivatives as cholinesterase inhibitors.

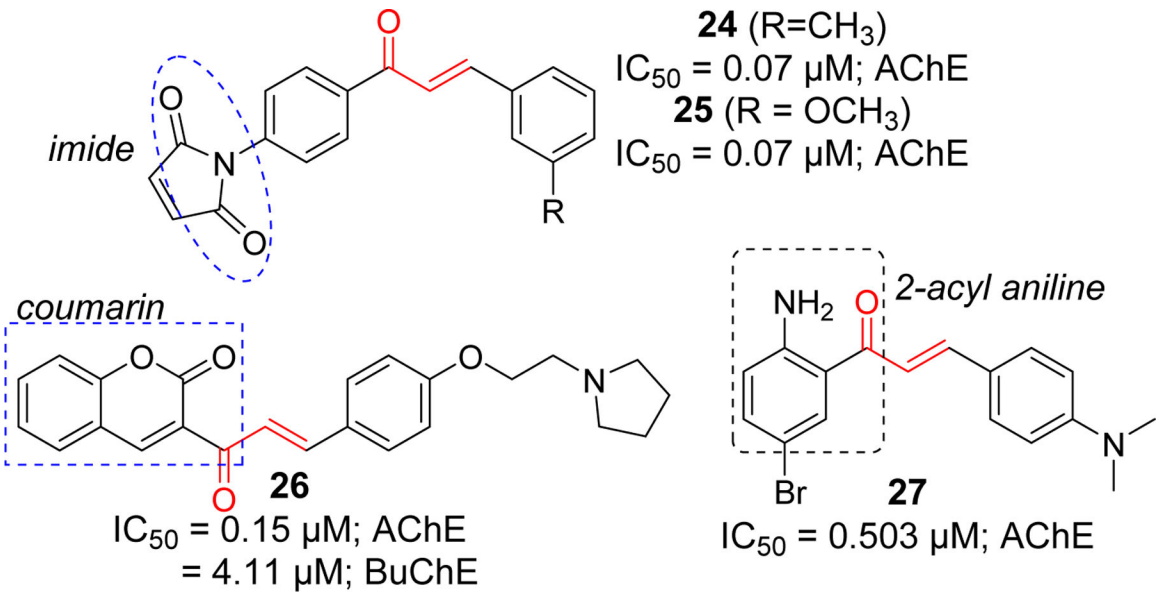



**Figure 10.**
Chalcones derivatives with imide, coumarin and aniline functional groups as cholinesterase inhibitors.

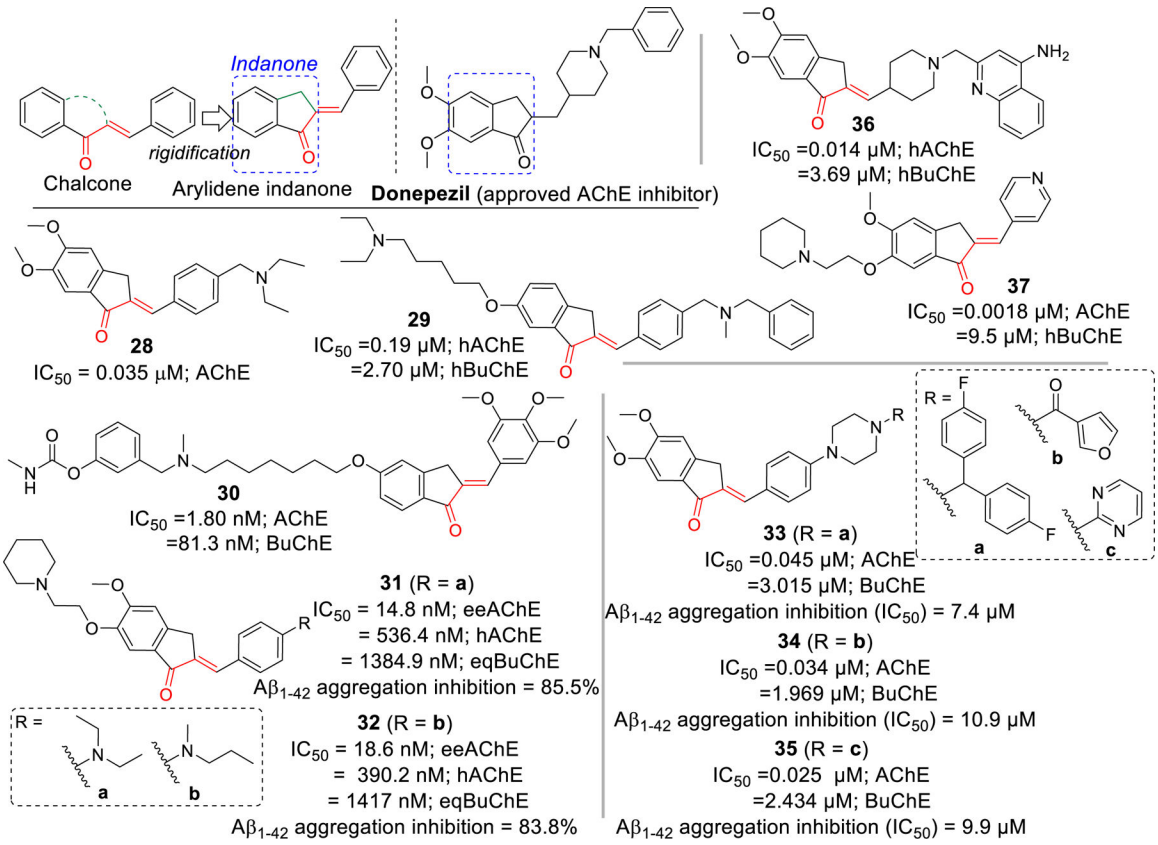



**Figure 11.**

Arylidene indanones (rigid analogs of chalcones) as cholinesterase inhibitors.

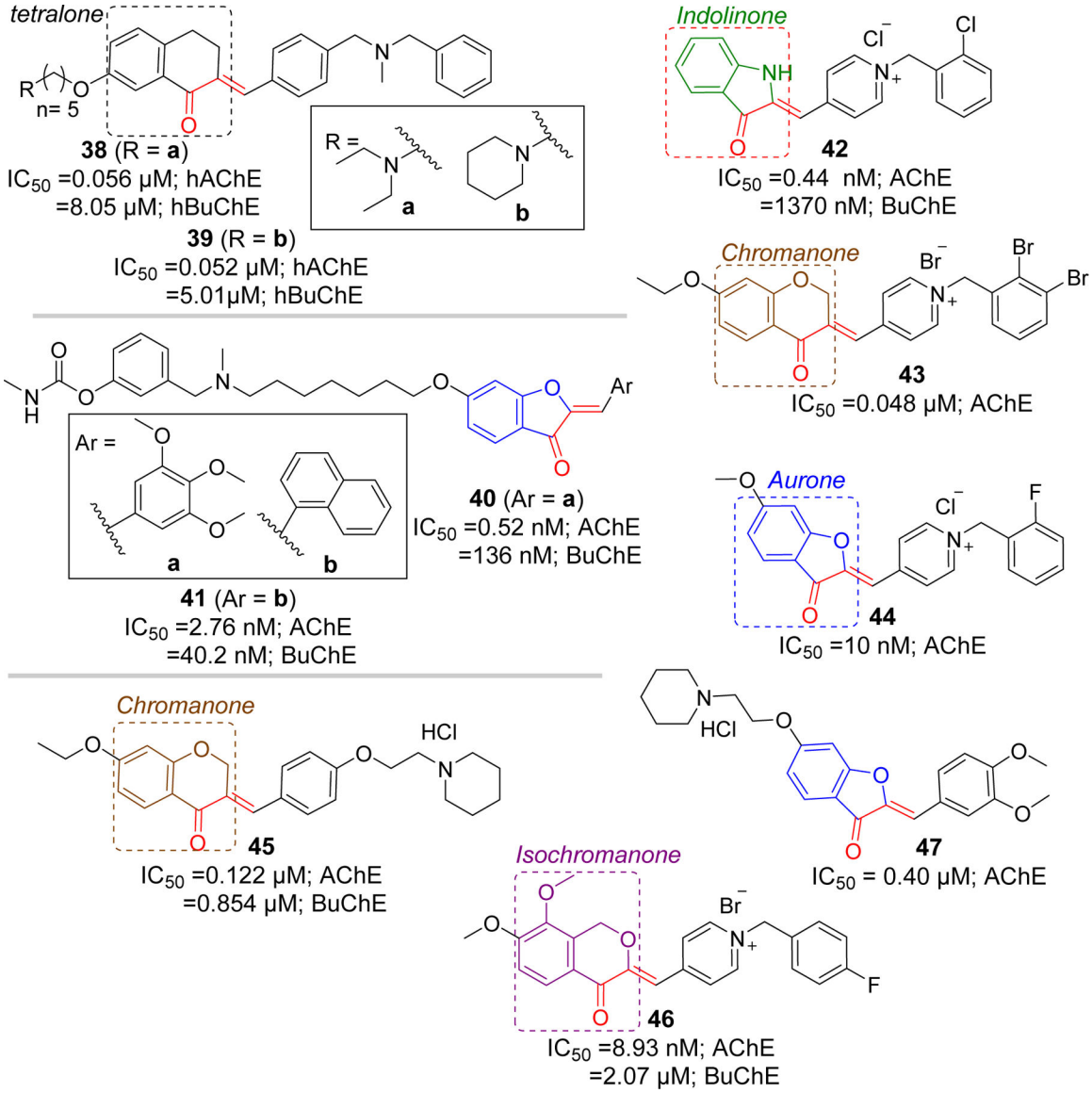



**Figure 12.**

Other rigid analogs of chalcones as cholinesterase inhibitors.

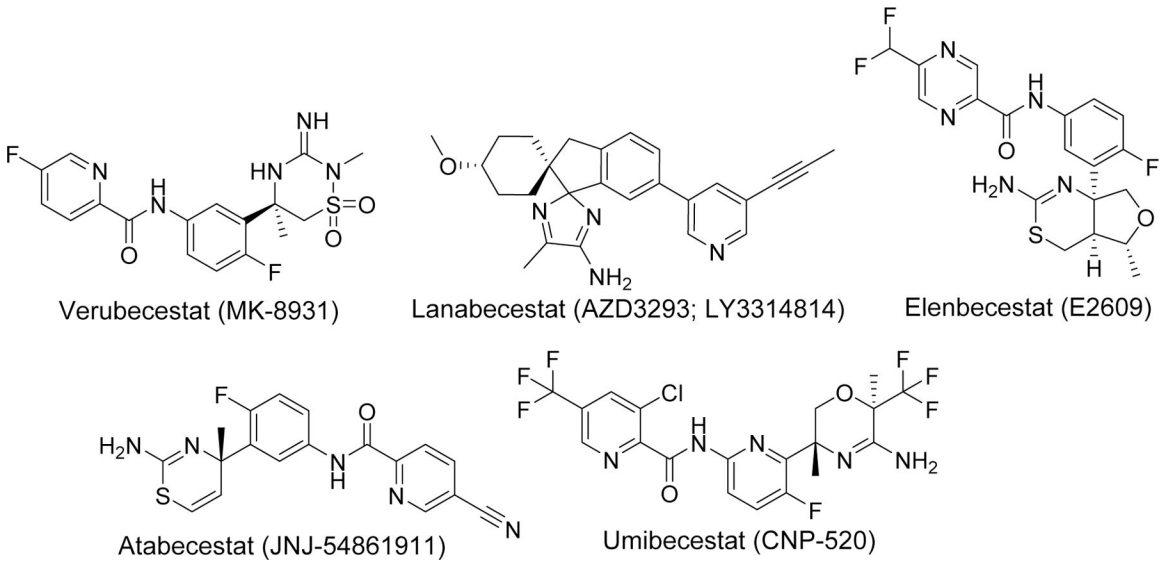



**Figure 13.**
Examples of potent BACE-1 inhibitors that enter clinical trials.

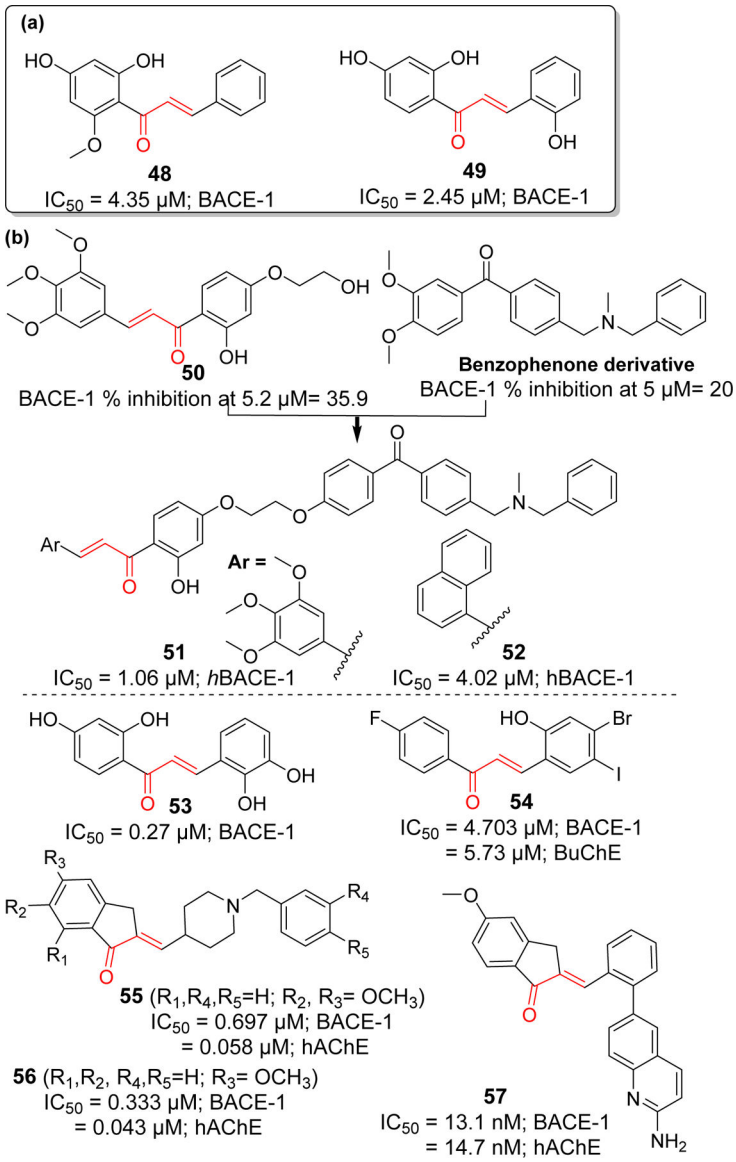



**Figure 14.**

BACE-1 inhibitors: (a) natural chalcone and (b) synthetic derivatives.

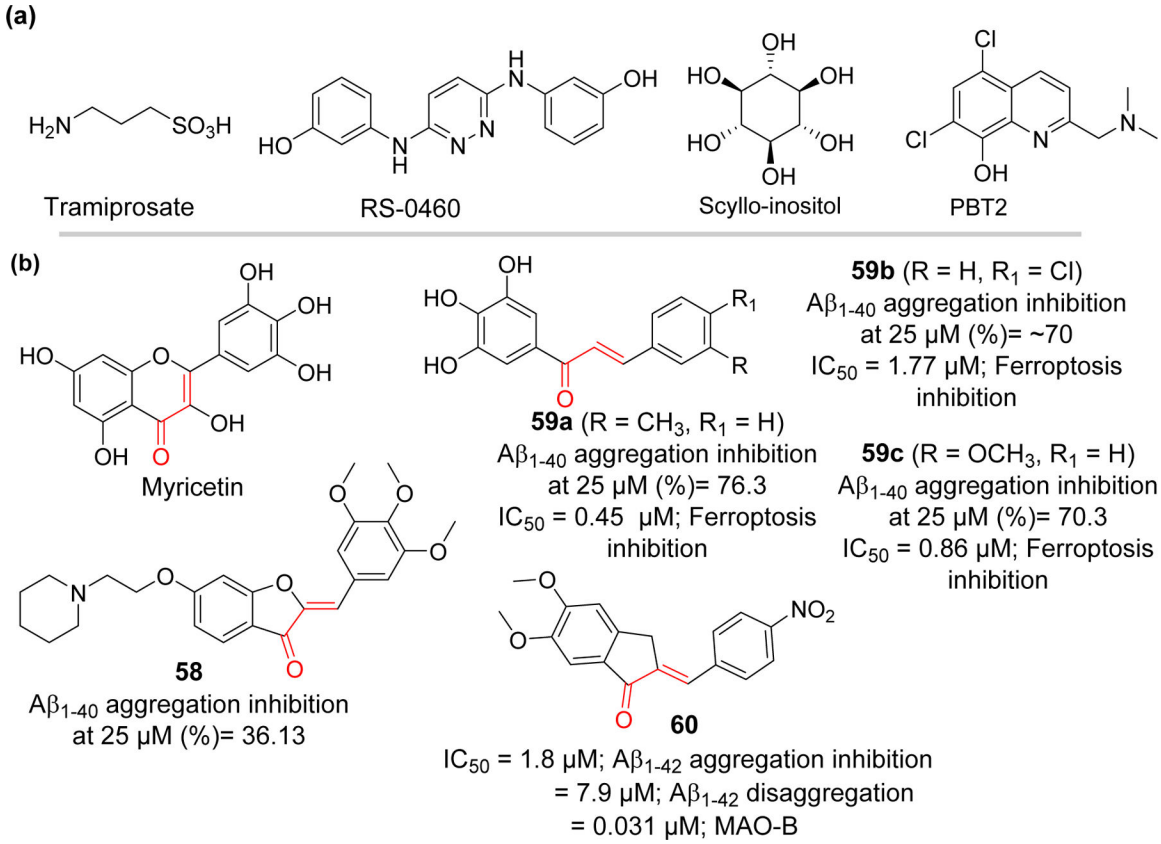



**Figure 15.**

Aβ aggregation inhibitors: (a) compounds that entered clinical trials and (b) natural and synthetic chalcone-based compounds.

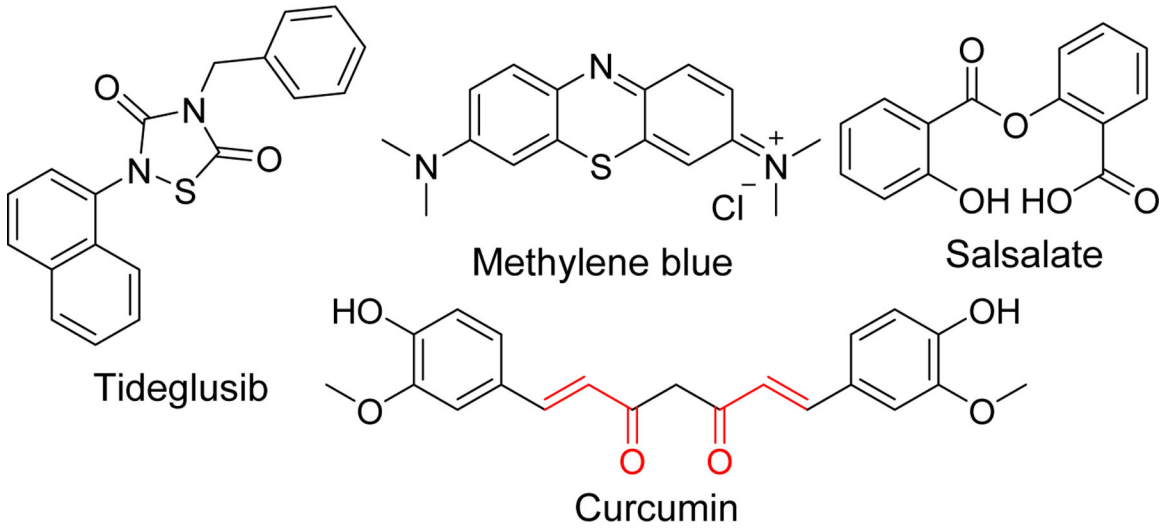



**Figure 16.**
Structure of tau-based inhibitors in clinical trials

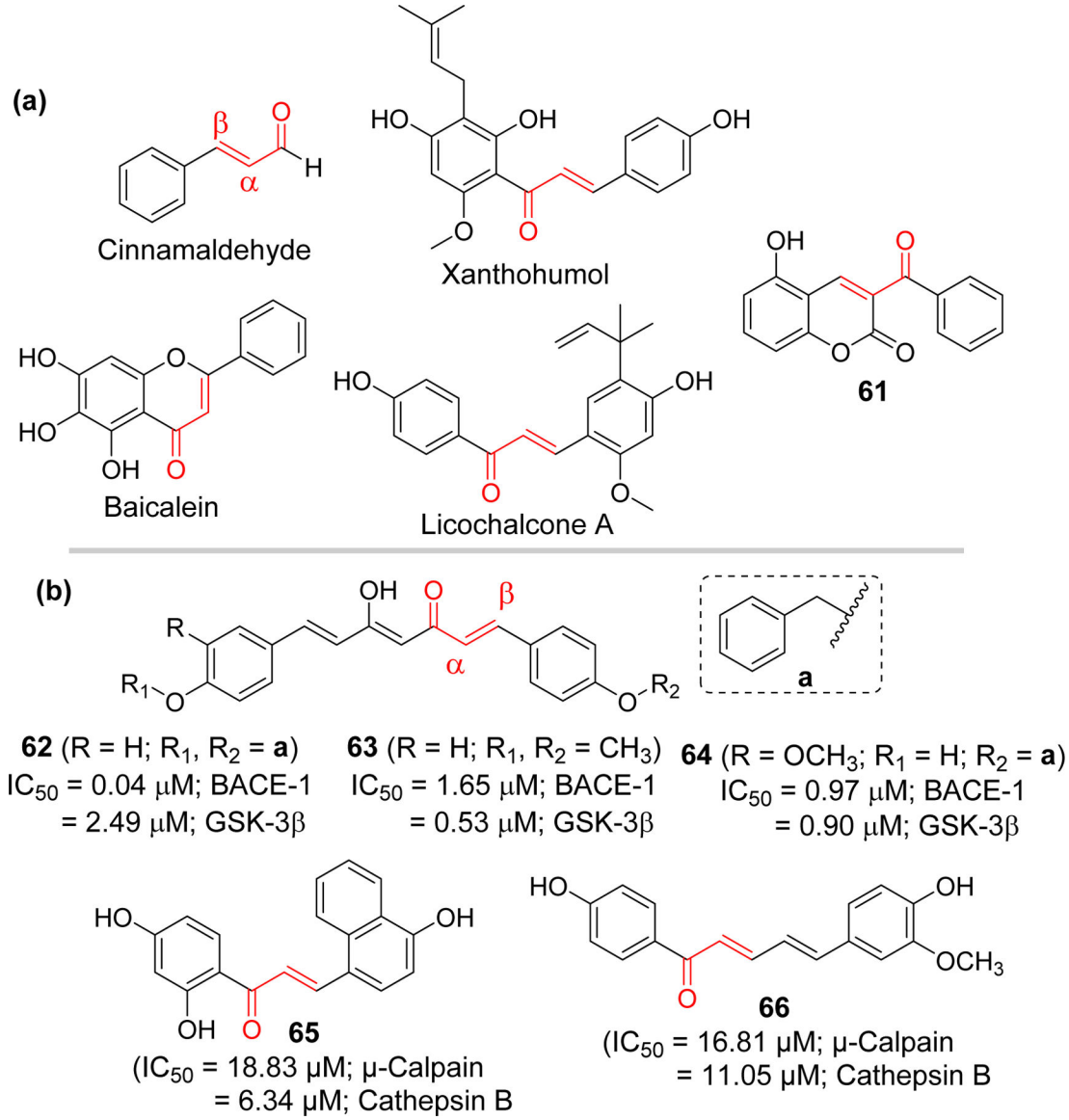



**Figure 17.**
Structures of (a) tau aggregation and (b) kinase inhibitors containing α,-β unsaturated carbonyl group

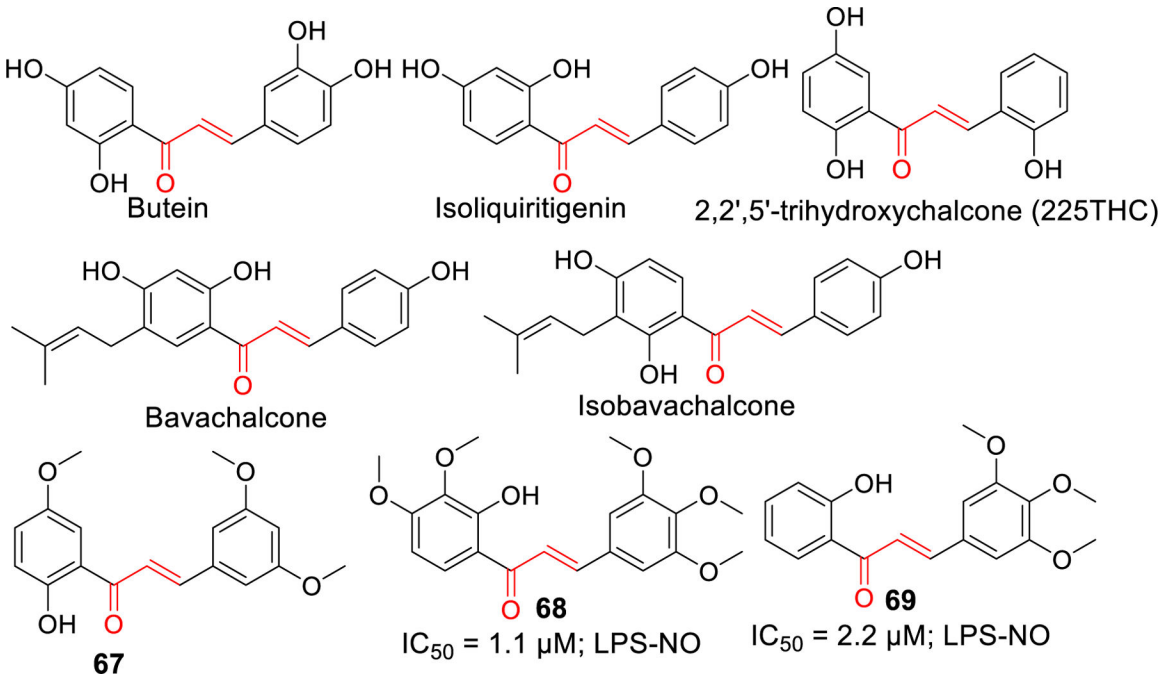



**Figure 18.**
Natural and synthetic chalcone derivatives as anti-neuroinflammation agents

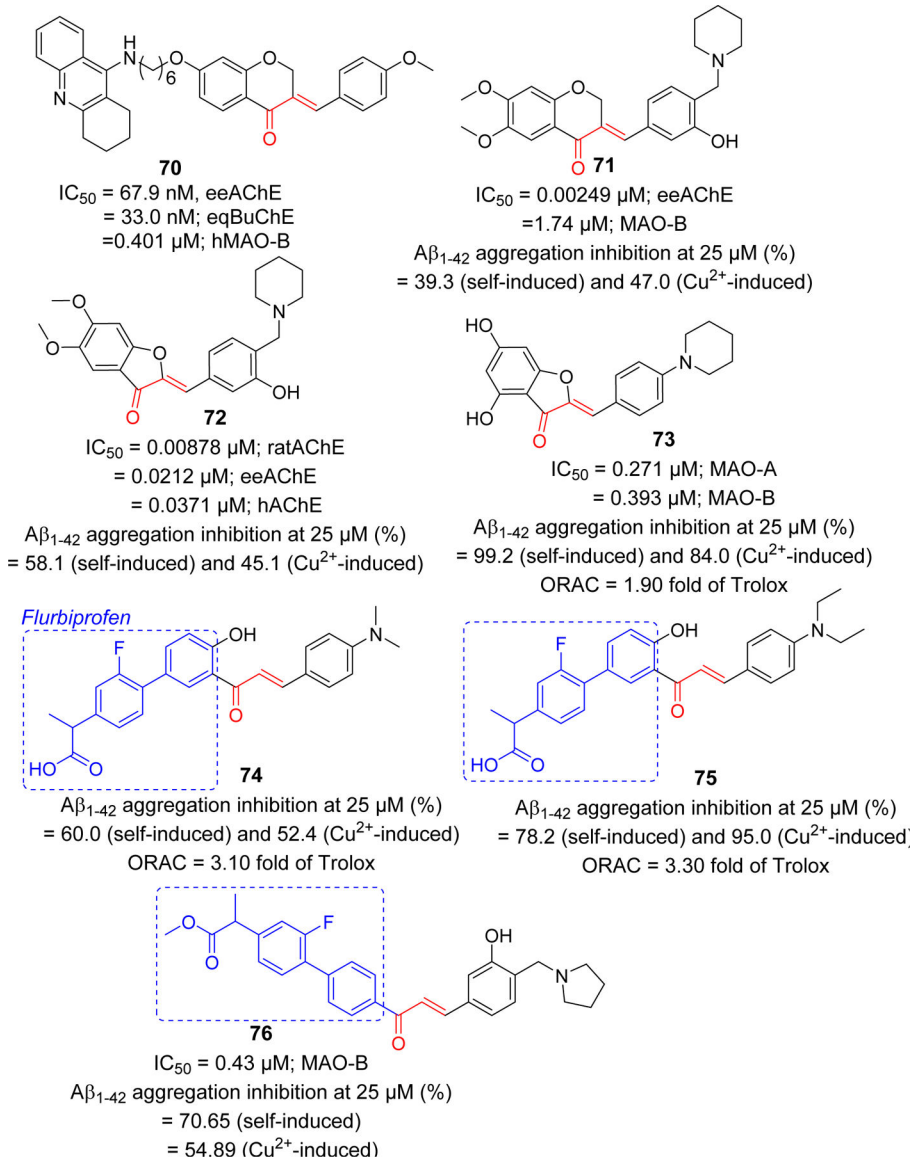



**Figure 19.**

Rigid analogs (chromanone, aurone) of chalcone and flurbiprofen-chalcone hybrids as multifunctional agents in AD.

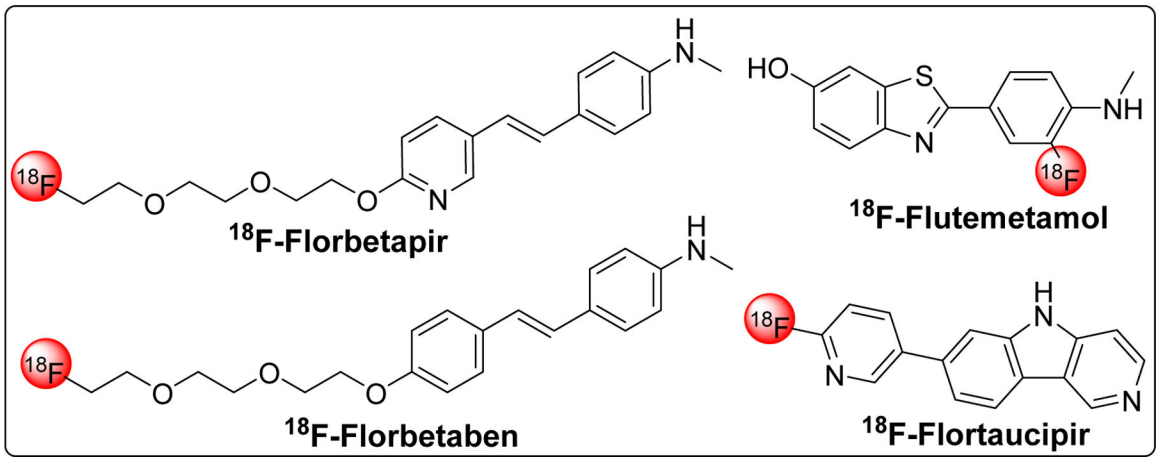



**Figure 20.**
FDA approved PET imaging probe for amyloid (Aβ) and tau proteins (NFTs)

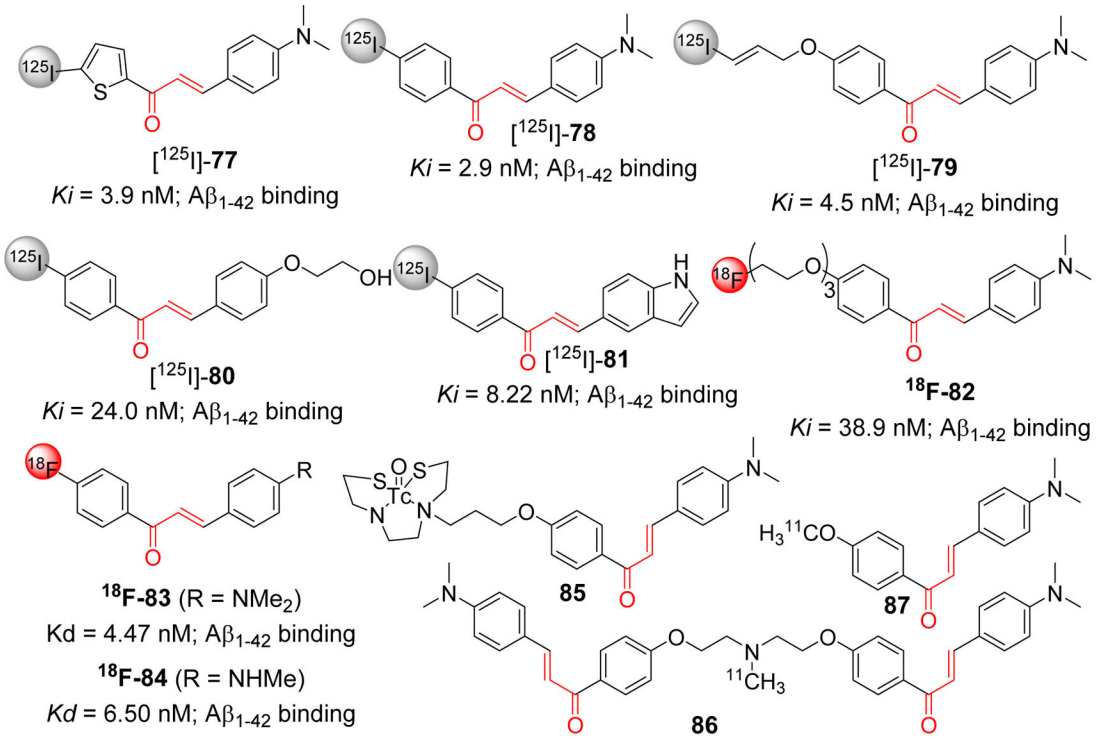



**Figure 21.**

Radiolabeled chalcone derivatives ($^{125}$I, $^{18}$F, $^{11}$C and $^{99m}$Tc) as a molecular probe for detection of amyloid beta plaques.

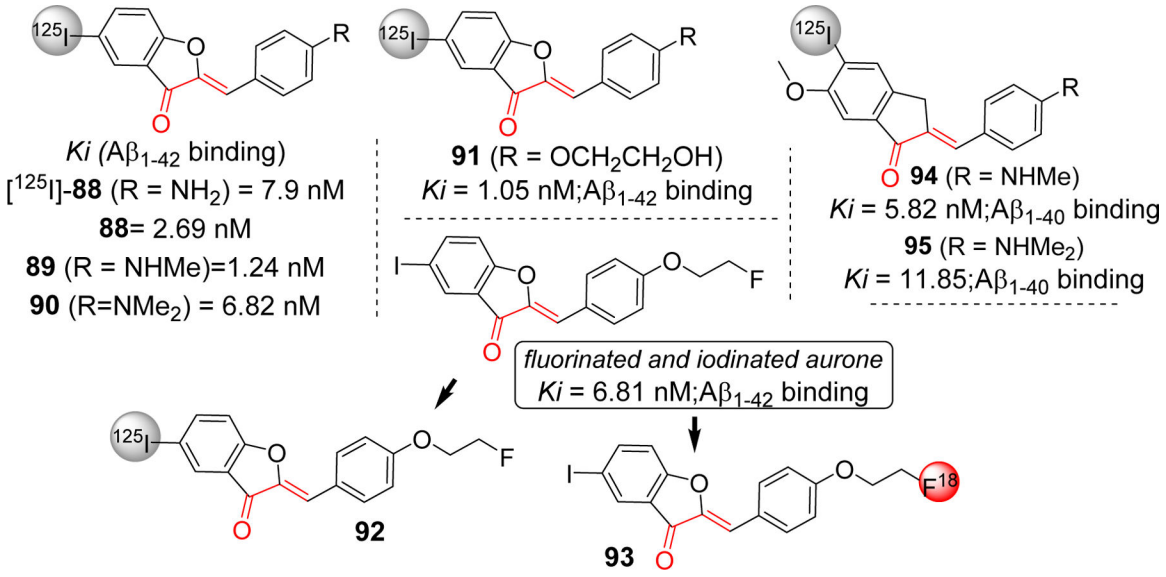



**Figure 22.**

Radiolabeled conformationally constrained chalcone derivatives (aurone and indanone) as a molecular probe for detection of amyloid beta plaques

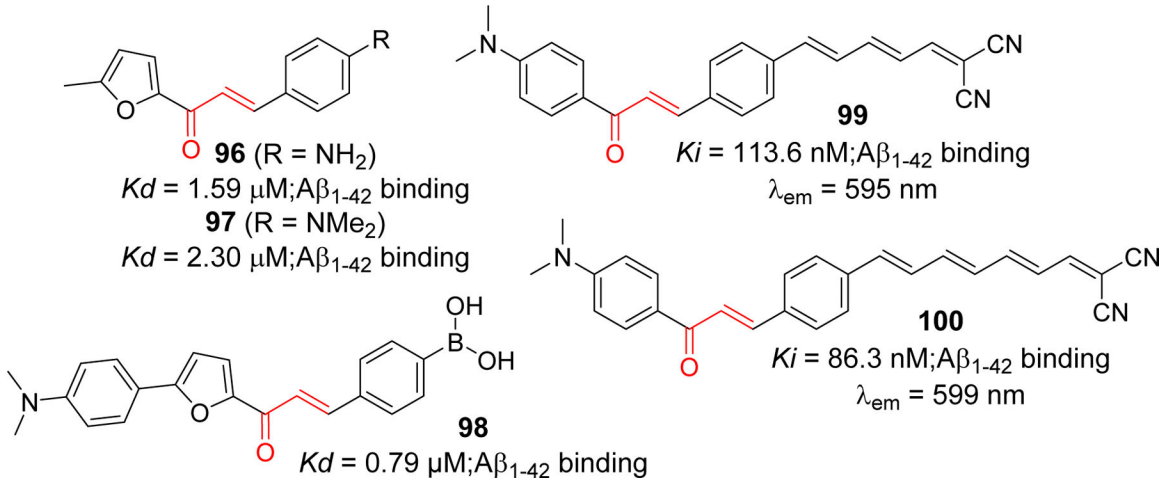



**Figure 23.**
Chalcone based fluorescent probe for imaging Aβ aggregates

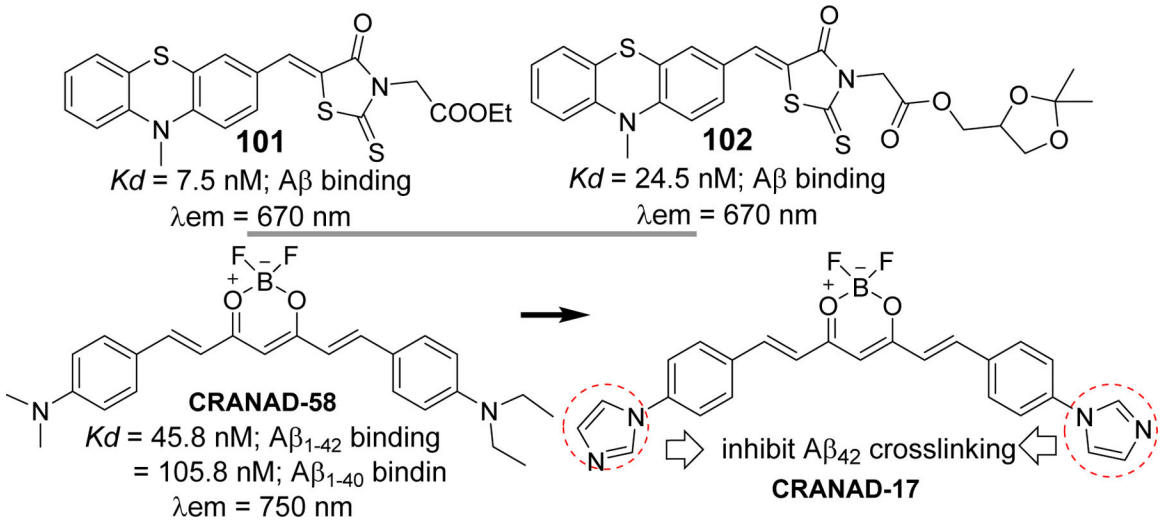



**Figure 24.**

Representative phenothiazine based (**101** and **102**), and curcumin based (**CRANAD-58** and **17**) NIR fluorescence probe with theranostic potential.