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REVIEW ARTICLE

From Hybrids to New Scaffolds: The Latest Medicinal Chemistry Goals in Multi-target Directed Ligands for Alzheimer's Disease

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Abstract: Alzheimer's disease (AD) is a chronic, progressive, and fatal neurodegenerative disorder affecting cognition, behavior, and function, being one of the most common causes of mental deterioration in elderly people. Once thought as being just developed because of β amyloid depositions or neurofibrillary Tau tangles, during the last decades, numerous AD-related targets have been established, the multifactorial nature of AD became evident. In this context, the one drug-one target paradigm has resulted in being inefficient in facing AD and other disorders with complex etiology, opening the field for the emergence of the multitarget approach. In this review, we highlight the recent advances within this area, emphasizing in hybridization tools of well-known chemical scaffolds endowed with pharmacological properties concerning AD, such as curcumin-, resveratrol-, chromone- and indole-. We focus mainly on well established and incipient AD therapeutic targets, AChE, BuChE, MAOs, *β*-amyloid deposition, 5-HT_4 and Serotonin transporter, with the aim to shed light about new insights in the AD multitarget therapy.

Keywords: Alzheimer disease, multi-target directed ligands, cholinesterase inhibitors, serotonin transporter, 5-HT receptors , β – amyloid aggregation, tau protein, monoamine oxidase.

1. INTRODUCTION

According to the World Alzheimer Report (2019), around 50-60% of the overall dementias correspond to Alzheimer's disease (AD). Although it has been for years a major health concern in developed economies, it is increasing in the developing countries as life expectancy increases. Even though WHO estimates that around 47 million people currently suffer from AD, this number is expected to double every 20 years; thus, the AD population could reach 75 million by 2030 [1]. Despite multiple efforts carried out within the last decades by universities, foundations, research centers and pharmaceutical companies, the detailed pathogenesis of AD is still unclear, and the underlying mechanism leading to this disease is not yet fully understood. Unfortunately, given the continuous failures in clinical trials, pharmaceutical companies are pulling out AD research, and it has been 17 years since the last drug, memantine, reached the market in 2003 [2].

AD is a progressive neurodegenerative disease resulting in the irreversible loss of neurons, particularly in the cortex and hippocampus [3]. Symptoms may include progressive loss of memory, cognition, motor, and functional capacity, often accompanied by behavioral disturbance such as aggression, depression and wandering [4], being the most common cause of dementia among elderly people [5].

Many authors defined AD as a heterogeneous disease caused by a combination of environmental and genetic factors, being the age one of the most important risk factors for the development of the disease [6, 7]. Some of the predisposing factors of this pathology include vascular disease [8], diabetes [9], depression [10], and hypertension [11]. On the other hand, many lifestyle modifications such as physical activity, sleep, feeding, smoking, alcohol, and intellectual stimulation are thought to have an impact cognitive impairment [12] even though more evidence is still needed. So far, AD has been related to several altered brain functions, including extracellular plaques containing abnormal deposits of beta-amyloid peptides [13-16], the hyperphosphorylated form of the microtubular Tau protein involving twisted fibers [17-20], inflammation [21-24], oxidative stress [25-28], cholinergic neuron damage (cholinergic hypothesis) [29-31], serotonin misregulation (serotoninergic hypothesis) [32-34], and many others [35-39].

Despite many years of evidence suggesting a connection between amyloid plaques or neurofibrillary tangles as the earliest lesions in AD, the role of such processes remains controversial [40] even though there is no doubt that those aggregates promote inflammation responses and activate neurotoxic pathways, leading to dysfunction and death of brain cells. In this line, the inflammatory process significantly contributes to AD pathogenesis [41]. In a recent review [42], the importance of understanding the inflammation process was explained, suggesting that the control of interactions between the immune and nervous system could be a key to the prevention or delaying of most late-onset central nervous system (CNS) diseases, including AD. Authors con-

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cluded that the brain can no longer be viewed as an immune-privileged organ.

At present, only 4 drugs have been approved for AD treatment, acetylcholinesterase inhibitors donepezil, rivastigmine, galantamine and the *N*-methyl-D-aspartate (NMDA) receptor antagonist memantine (Fig. **1**), and they only address associated symptomatology without halting or reversing the disease progression [43]. To this day, AD has also been related to additional targets/functions, whose misregulation has been proposed to lead to AD onset. These include ApoE [44], dopamine D_2 receptor [45], γ-aminobutyric acid receptor [46], acetylcholinesterase and butyrylcholinesterase [4], β- and γ-secretases [47, 48], serotonin 5-HT_6 and 5-HT_4 receptors [49, 50], serotonin transporter [51], or SRFP1 [52]. After providing this big picture, the only clear issue is that we are facing a multifactorial disorder, which cannot be managed by drugs acting at just a single level.

The "one drug-one target" paradigm has not succeeded and does not provide a solution in the treatment of complex and multifactorial diseases like AD [7, 53]. In this context, the multitarget approach has recently emerged as a potential solution by using multi-target directed ligands (MTDLs) [54, 55]. Thus, the aims of this proposal are based on the design of new drug candidates simultaneously modulating different biological targets involved in the neurodegenerative AD cascade. Due to the complex etiology and multifactorial nature of this disease, various hypotheses have been proposed in an attempt to address it, although none of them is able to explain the onset and progression of the disease on its own [56].

1.1. Cholinergic Hypothesis

The cholinergic hypothesis is based on the association between low levels of acetylcholine (ACh) and a decline in learning, cognitive function and memory in AD patients [57-60]. It has been demonstrated that the dysfunction and neuronal loss in basal forebrain regions are directly related to the expression and activity of choline acetyltransferase (ChAT) and acetylcholinesterase (AChE), specific enzymes related to CNS functions. Their activities play an essential role in cholinergic transmission, showing variations in the cerebral cortex and the hippocampus in AD-suffering subjects [61]. The presynaptic cholinergic deficit is associated with a marked loss of cholinergic cells from the nucleus basalis of Meynert, decrease of ACh releasing and reuptaking [62]. The cholinergic hypothesis has not had widespread support because the AChE inhibitor-based AD treatment only brings a slight symptomatic improvement, failing in curing or preventing the disease progression [57, 60].

1.2. Amyloid Hypothesis

Another plausible and widely studied cause of AD is based on the amyloid cascade hypothesis. The accumulation of the hydrophobic amyloid-beta (Aβ, Aβ_{40} and Aβ_{42}) peptides resulting in self-aggregation and insoluble plaques formation is still considered to be the main feature of AD etiology [63-65]. It is originated from the proteolytic cleavages of the transmembrane amyloid precursor protein (APP) by specific secretases (β-, and γ-secretase) [66, 67]. Aβ fibrils accumulation is thus considered an early toxic event that activates neurotoxic pathways. Some studies suggest that these oligomers can destroy the integrity of the cell membrane and disrupt the steady-state of brain cells [68-70], leading to brain cell dysfunction and death [71]. Some authors indicate that Aβ aggregates can also induce oxidative stress [72, 73], initiate an inflammatory response [41, 74, 75], and alter calcium homeostasis [70, 76]. Furthermore, Selkoe [77] emphasizes that the word "cause" of AD pathology cannot necessarily be directly applied to the Aβ accumulation, due to the existence of some genetic mutations or polymorphisms that can produce an increase in other peptide accumulation (presenilin or apolipoprotein E) [78, 79]. Despite what was previously indicated, the self-aggregation of Aβ itself is insufficient to explain the accumulation of the peptide in specific brain regions of AD patients. The "metal hypothesis of AD" is based on the effects of Aβ accumulations (as senile plaques) promoted by Aβ-metal interactions. The metal ion content of the brain are essential trace elements that are stringently regulated with virtual no passive flux of metals from the circulation to the brain, but interestingly, elevated concentration of copper, zinc, and iron have been detected in amyloid plaques, which induces the protein to precipitate into metal-enriched masses [80]. However, the mechanism of how these metals bind to and promote its aggregation is still unknown [80-82]. A plausible approach may be modulating these interactions by metal chelators, and indeed, this is considered another promising strategy for AD treatment.

1.3. Tau Hypothesis

The Tau protein is an important component of the neuronal cytoskeleton, being its principal activities related to stabilizing microtubules [83], cell shape maintaining and axonal transport [84]. In the normal brain, the balance between Tau phosphorylation and dephosphorylation is a dynamic process that causes conformational and structural changes, regulating the stability of the cytoskeleton and axonal morphology [85-88]. The imbalance in the action of different kinases and phosphatases is one of the possible proposals of Tau hyperphosphorylation [89, 90]. During the development of AD, Tau begins to phosphorylate in a massive way, which triggers its collapse and intracellular aggregation to form neurofibrillary tangles (NFTs) [91]. A progressive neuronal degeneration is the start of alteration leading to degradation of the cytoskeletons. In other words, these fibrils create a physical barrier within the neuron that generates a toxic medium with a high concentration of NFTs. Some authors [92-94] exposed that NFTs are inert and do not have influence in microtubules assembly, but they choke the affected neurons and facilitate cell death by acting as a space-occupying lesion. In a review [90], the authors summarize the evidences and therapeutic approaches that linked Tau misregulation to AD pathogenesis. One approach is the use of kinase inhibitors and phosphatase activators [95, 96], however, these enzymes are present in nearly every cell in the body and the problem would be finding molecules that alter the activi-

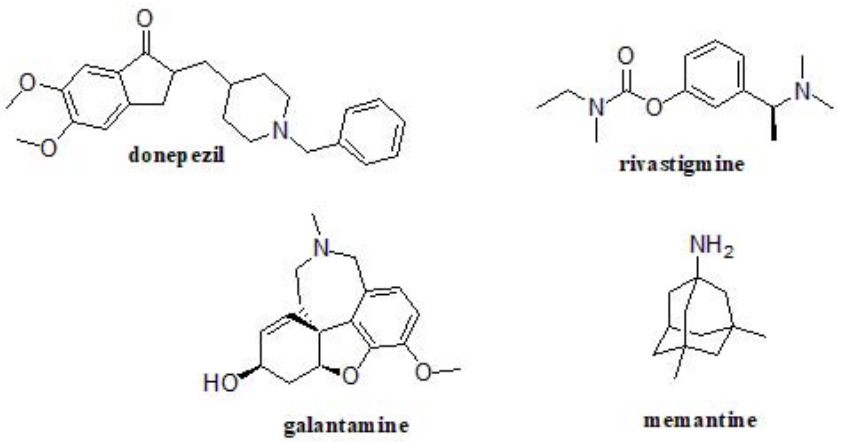


Fig. (1). Approved drugs for AD treatment.

ty specifically of the target enzyme without affecting the others. Identifying key sites of Tau in order to develop small molecule anti-aggregators is still a hopeful field of research [97].

Certainly, another proposed approach involving Tau and Amyloid hypotheses is immunotherapy, which is the use of immunity-enhancing techniques as a medical treatment. Huge advances in immunotherapy AD research have been achieved within the last decade [98, 99], supported by several Clinical Trials and the recent FDA approval of Aducanumab. However, in order to stick to the script, such an interesting approach will not be considered here as it falls far beyond the scope of this review.

Indeed, it is worth mentioning that the Tau hypothesis alone is inadequate to explain all the symptomatic conditions observed in AD, so it is not surprising that drugs targeting Tau protein itself have not achieved any relevant progress.

1.4. Serotonergic Hypothesis

Depression may be one of the initial symptoms of neurodegenerative disorders, and it is regarded as a risk factor for later development of dementias, being depressed mood in elders associated with an increased risk of AD [100]. Nowadays, our concept of the nature of the relationship between cognitive impairment and the serotonin system is evolving, thus the serotonergic hypothesis of AD is slowly emerging [101], as long as more and more researchers worldwide are suggesting AD modulators based on monoamine oxidase (MAO) inhibitors, serotonin reuptake inhibitors (SSRIs) [102-104], and 5-HT_4 and 5-HT_6 modulators [49, 105]. According to many authors, the accumulation of Aβ-amyloid could be a secondary effect of reduced monoamine neurotransmitters [101].

The MAO enzyme exists as two isoforms, MAO-A and MAO-B, and their principal activities are related to catalyzing the oxidation of monoamines and are thus responsible for the metabolism of neurotransmitters such as serotonin, noradrenaline, and dopamine [106]. They are located in the CNS and in peripheral tissues. Some studies revealed that MAOs are associated with psychiatric and neurological disorders, including AD [107-110]. MAO-A inhibitors are used as antidepressants and anti-anxiety agents, while MAO-B inhibitors have been revealed to be useful in neurodegenerative disorders such as Parkinson´s disease and AD, also inhibiting their associate oxidative damage [111, 112]. In summary, simultaneous inhibition of both MAOs, have been suggested to provide additional benefits in AD therapy. Along with MAO, 5-HT_4 receptor (5-HT_4R) ligands have also been proposed in AD research since many studies have shown the involvement of 5-HT_4R in cognitive processes. Moreover, many authors provided important findings suggesting that 5HT_4R agonists may also affect the amyloid β-peptide pathway, supporting the serotonergic approach in AD [113].

The scope of this review is to describe some widely studied bioactive structures: *curcumin*-, *resveratrol*-, *chromone*-, and *indole*-derivatives as MTDLs for Alzheimer's Disease, mainly oriented to interact with the aforementioned targets, included or not in the previously described hypotheses. This literature review is focused in identifying small molecular fragments as promising starting points for biological target modulation [7], 114] with the aim of shifting the current paradigm towards a disease-modifying strategy.

In this review, we summarize the latest medicinal chemistry goals in AD-related MTDLs development: small molecule fragment with known biological activities combined through hybridization or fine chemical tuning, in order to develop true MTDLs to face such devastating disease from a multifactorial point of view.

2. CURCUMIN AND CURCUMINOIDS HYBRIDS

The major curcuminoids present in turmeric (*curcuma longa*) are curcumin, demethoxycurcumin and bisdemethoxycurcumin [115] (Fig. **2**), being curcumin the most bioactive component [116]. Curcuminoids from turmeric

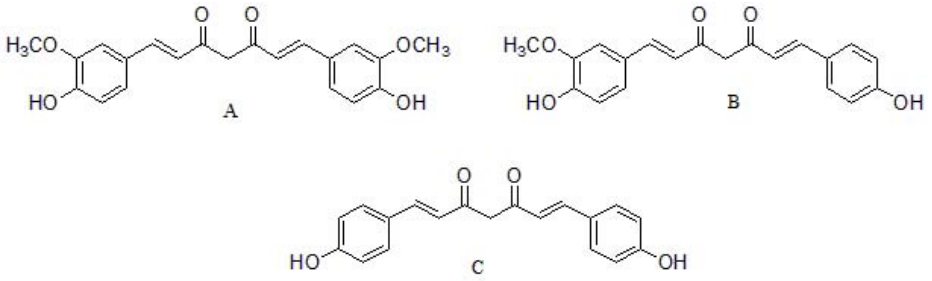


Fig. (2). Chemical structures of (A) curcumin, (B) demethoxycurcumin and (C) bisdemethoxycurcumin.

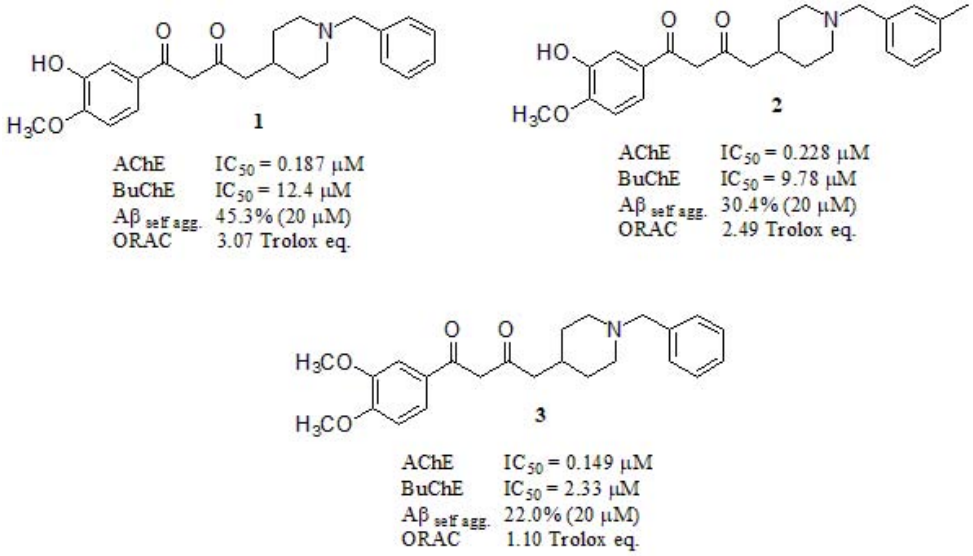


Fig. (3). Multi-target directed ligands based on donepezil and curcumin scaffolds reported by Yan *et al*.

have shown anti-inflammatory, antioxidant, anticancer, antimicrobial, and neuroprotective effects, among others [117]. These compounds display different chemical functions: a methoxy phenolic group; α, β-unsaturated β-diketo linker, and keto-enol tautomerism having a predominant keto form in acidic and neutral solutions, and stable enol form in alkaline medium. The aromatic groups confer hydrophobicity, the linker brings flexibility and tautomeric structures also influence the hydrophobicity and polarity [118]. However, curcumin exhibits several limitations, such as chemical instability, poor solubility in water, low bioavailability, and fast metabolism under physiological conditions, thereby resulting in a rapid systematic elimination and limiting its application as a drug candidate [119]. In this sense, it is reasonable to design curcumin analogs able to enhance the aforementioned drawbacks. Several groups tested curcumin derivatives using cells and mouse models of AD and reported that curcumin derivatives have strong anti-amyloid beta aggregation property, are able to cross the blood-brain barrier (BBB), ameliorates cognitive decline, and improve synaptic functions in a mouse model [120-124]. Besides, curcumin itself also exert MAO-B inhibitory capabilities, in addition to the ability to degrade Tau neurofibrillary tangles [125], although the mechanism of action of such processes are not fully understood.

Yan *et al*. [126] reported the synthesis and biological activities of MTDLs based on chimerical structures consistent in donepezil-curcumin fused scaffolds. The most active studied compounds **1**, **2**, and **3** were evaluated in AChE and butyrylcholinesterase (BuChE) inhibition, BuChE /AChE selectivity, A$\beta_{1\text{-}42}$ self-aggregation inhibition and antioxidant effects (Fig. **3**). Compound **1** was revealed as potent AChEi (IC_{50} = 187 nM) compared to the rest of the series (donepezil (DPZ) AChE IC_{50} = 37 nM as reference), and the highest selectivity ratio (BuChE /AChE: 66.3) which was significantly better than Tacrine and Galantamine (selectivity: 0.15 and 25.3, respectively) although still far away from DPZ (selectivity: 85.4). Inhibitory activity against A$\beta_{1\text{-}42}$ self-aggregation was evaluated employing curcumin as reference (54.9% at 20μM). Compounds **1**, **2** and **3** displayed 45.3%, 30.4% and 22.0%, respectively, evidencing the importance of the hydroxy group in the A$\beta_{1\text{-}42}$ self-aggregation inhibitory activity. They also conducted an oxygen radical absorbance capac-

ity assay (ORAC), evaluating their antioxidant activity *in vitro* with Trolox as standard. All compounds exhibited good ORAC values of 1.01 – 3.07 Trolox equivalent (expressed as μM of Trolox eq/ μM tested compounds). It is known that curcumin (2.52 Trolox eq.) displays potent antioxidant activity, but compound **1**, featuring a hydroxyl group at the meta position, displayed a stronger one.

Due to the poor solubility and oral bioavailability of curcumin, scientists have seen the need to modify its structure to improve these deficiencies. In this way, Wang *et al*. [127] designed and synthesized L-lysine-functionalized curcumin derivatives to improve their water-solubility and inhibition of amyloid fibrillation *in vitro*, using Hen egg-white lysozyme (HEWL) as a model protein (Fig. **4**). They used N^{α}-Fmoc-N^{ε}-Boc-L-lysine as a novel water-soluble amino acid derivative. Compounds **4** and **5** exhibited enhanced solubility (3.32×10^{-2} g/mL and 4.66×10^{-2} g/mL, respectively) in water compared to curcumin (1-10 μg/mL) [128]. Moreover, these compounds showed amyloid fibrillation inhibition of HEWL when the concentration of **4** and **5** reach to 20.14 mM and 49.62 mM, respectively. In addition, the lag phase duration of **4** (*e.g.*, 7.3 days) is longer than **5** (*e.g.*, 6.2 days), the authors attributed it to the phenolic hydroxyl group and the charged amino acid, concluding that it is an effective way to improve its solubility.

In a recent work, Cui *et al*. [129] studied and synthesized water-soluble curcumin derivatives based on Boc-L-isoleucine (Fig. **5**). The inhibitory potency of the monosubstituted derivative **6** on the formation of HEWL amyloid fibrils was superior to the disubstituted counterpart **7** at low concentration, suggesting the importance of the free hydroxyl group in the aromatic ring (20% and 3.5% at 0.1 mM; both reached to 70-80% at 0.5 mM). Regarding the solubility profile, both derivatives exhibited enhanced solubility 3.05 mg/mL and 2.12 mg/mL in water respect to curcumin [128]. It is worth mentioning that both derivatives displayed low cytotoxicity in HeLa cell line, above 70% viability at 10-50 μM.

Many authors proposed that the intractable nature of the A*β* plaques and tangles stimulates a chronic inflammatory reaction to clear this debris [22, 130-139]. These plaques depositions in the brain stimulate an inflammatory response generating the overexpression of proinflammatory mediators, such as the neuroinflammatory interleukin [140], playing a key role in inflammatory and anti-inflammatory processes in AD. Interleukin-6 (IL-6) is a soluble mediator with a pleiotropic effect on inflammation, immune response, and hematopoiesis [141-144]. Inhibition of IL-6 secretion is frequently used as a readout of anti-inflammatory activity. In this line, Lakey-Beitia *et al*. [140] reported new curcumin derivatives synthesized by etherification, and esterification of curcumin and benzyl bromide, acetyl chloride, 4-(benzyloxy)-4-oxobutanoic acid, and 4-(cyclopentyloxy)-4-oxobutanoic acid, displaying anti-aggregation capabilities and anti-inflammatory activity (Fig. **6**). In order to evaluate the IL-

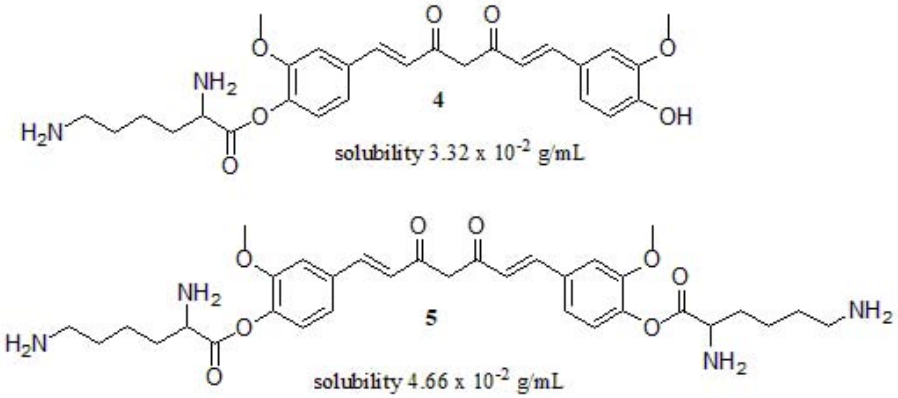


Fig. (4). Water-soluble functionalized curcumin derivatives reported by Wang *et al*.

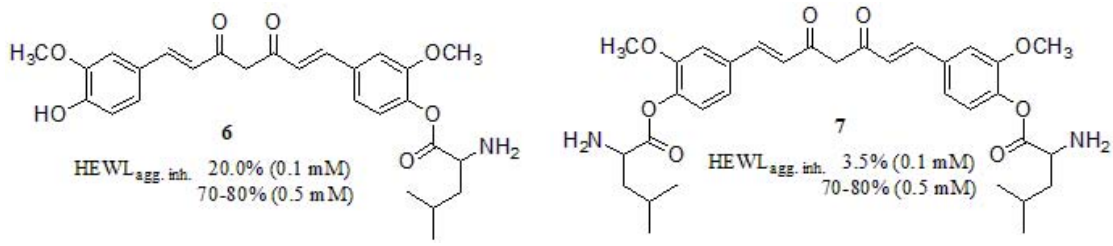


Fig. (5). Functionalized curcumin derivatives described by Cui and coworkers.

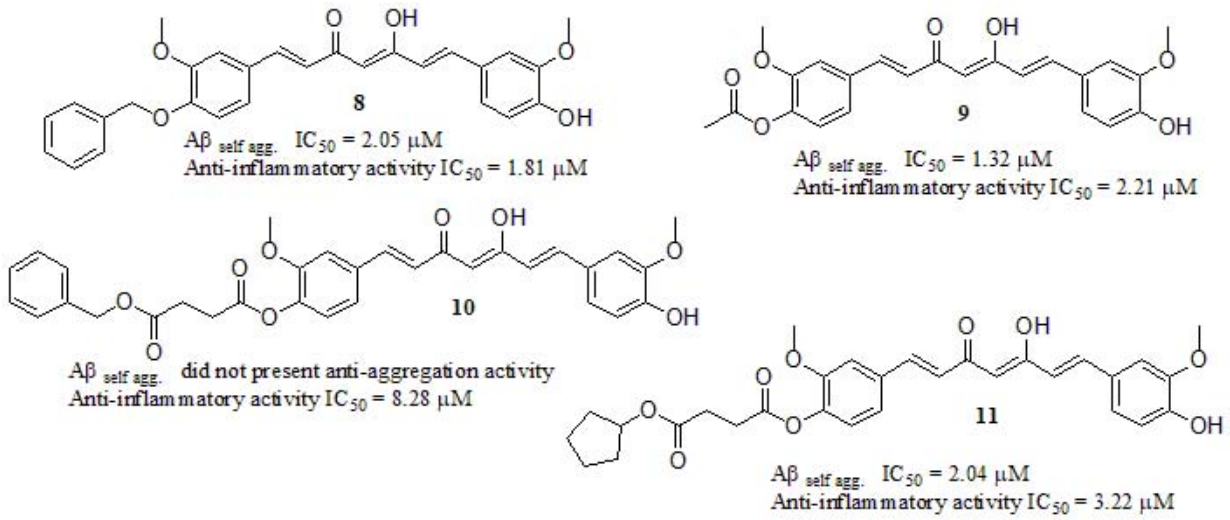


Fig. (6). Curcumin derivatives reported by Lakey-Beitia *et al*.

6 production, lipopolysaccharide-stimulated macrophages were used. Compounds **8**, **9**, and **11** exhibited more potent anti-inflammatory activity compared to curcumin (IC_{50} = 8.25 μM), while compound **10** displayed a similar effect. The introduction of a benzyl moiety liked through an ether bond in one of the curcumin rings (**8**) led to the most potent anti-inflammatory derivative, but the presence of a bulky diester group was conducted to less active derivatives **10** and **11**. They concluded that hydroxyl groups on the aromatic rings of the curcumin were the pharmacophore required to diminish the IL-6 production. Regarding the anti-aggregation profile *in vitro*, compounds **8**, **9**, and **11** inhibited the A*β* aggregation in a concentration-dependent manner, with IC_{50} values ranging from 1.32 to 2.05 μM, showing an amyloid anti-aggregation effect in the same magnitude as the standard curcumin (IC_{50} = 1.4 μM) but, surprisingly compound **10** did not present anti-aggregation activity.

To delve into this concept, Okuda *et al*. [145] designed a series of asymmetric curcumin derivatives by different strategies, and the most active compounds are summarized in (Fig. **7**). Firstly, a compound series were synthesized by changing the hydroxyl and methoxyl substitution pattern on one of the aromatic moieties (**12**), showing that the inhibitory activity on A*β* aggregation increased when these substituents were located in meta position to each other, displaying higher inhibitory activity compared to curcumin (IC_{50} = 5.4 μM). Next, by only exchanging one aromatic ring for other cyclic structures, curcumin derivative **13** was achieved with interesting results, suggesting that a bicyclic structure may increase the inhibitory activity, especially in Tau aggregation. Combining the aforementioned results, compound **14** was designed and synthesized. Taking into account that in animal models [146-150], curcumin undergoes rapid metabolic reduction and conjugation, resulting in poor systematic bioavailability after oral administration [151], they introduced various residues in order to protect the residual phenolic hydroxyl group (**14**) from being metabolized, although just one compound (**15**) exerted comparable inhibitory activity to **14**. Additional performed experiments were related to obtaining the pharmacokinetic profile. Each compound was orally administered to rats at 50 mg/kg. The C_{max} of **15** was found to be 20-fold lower than that of curcumin (5.7 ± 3.3 ng/mL at 30 min and 125 ± 65 ng/mL at 15 min), but the concentration in the brain was 13-fold lower compared to curcumin itself. In order to achieve a more convenient pharmacokinetic profile, many structural changes were necessary. They modified the central diketone skeleton in **15** by introducing a pyrazole ring (**16**). Although the IC_{50} = 1.2 μM for A*β* aggregation and IC_{50} = 0.66 μM for Tau aggregation cannot be denoted as a stunning result, the concentration of **16** in the brain was 300-fold higher than that of **15** and 20-fold higher than that of curcumin.

Li *et al*. [82] synthesized and evaluated MTDLs based on rivastigmine and curcumin hybrids. Rivastigmine demonstrated unique central selective towards AChE and BuChE inhibitory activity free of hepatic metabolism, while curcumin represents a neuro-protective agent, with a variety of functions (Fig. **8**). Compound **18** was the most potent AChE inhibitor by 20-fold compared to the reference compound (rivastigmine, IC_{50} = 2.07 μM). Regarding the AChE inhibitory profile, the position of the aminoalkyl group in the benzene ring resulted crucial for the inhibition potency. While the derivate **17** displayed only moderate micromolar activity, shifting this group to the 4-position conducted to nanomolar IC_{50} values, as shown in (Fig. **8**) (compounds **18** and **19**). On the other hand, all compounds exerted good inhibitory activity regarding BuChE with compounds **17** and **19** showing 40-50-fold improvement respect to rivastigmine (BuChE IC_{50} = 0.37 μM). A*β* aggregation inhibitory profile of compounds **17**, **18**, and **19** were qualitatively evaluated by Transmission Electron Microscopy (TEM). As depicted in this work, after incubating $A\beta_{1\text{-}40}$ along with the selected

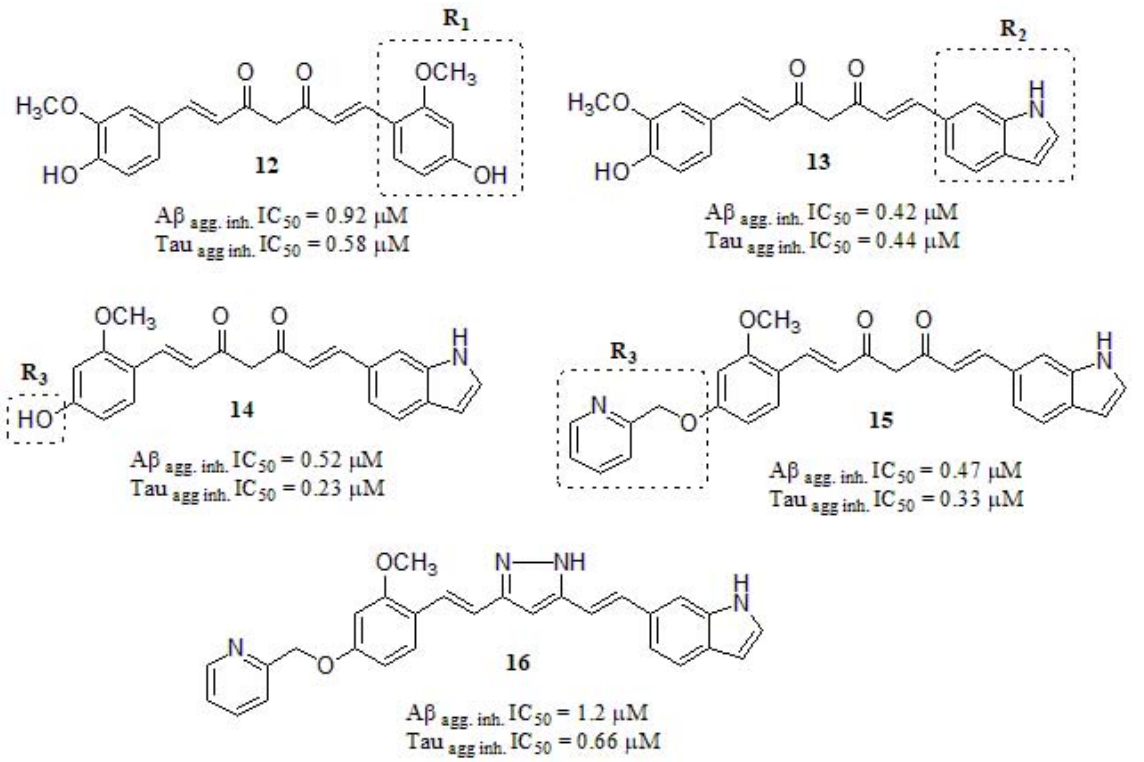


Fig. (7). Curcumin asymmetric derivatives as amyloid β and tau aggregation inhibitors.

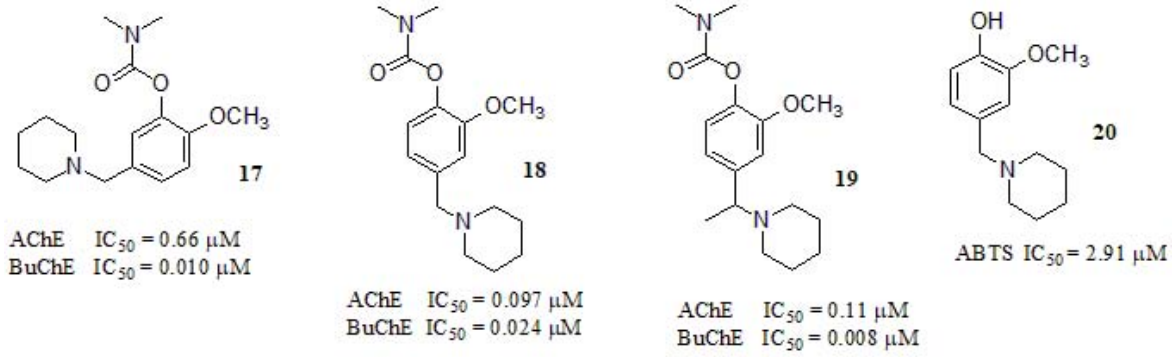


Fig. (8). Multi-target direct ligands based on rivastigmine and curcumin hybrids investigated by Li *et al*.

molecules, the reduction in A$\beta_{1\text{-}40}$ deposition was evident, as only a few fibbers could be observed, which was similar to curcumin and indicated that all compounds were also endowed with potent Aβ anti-aggregation capabilities. Interestingly, the addition of rivastigmine had little effect on its aggregation. In a further assay designed to shed light on initial metabolism, compound **18** was incubated with rat cortex homogenate (AChE) and the extract was analyzed by HPLC-PS after 24 h, in which the prodrug activation process was confirmed by obtaining compound **20**. This compound showed potent ABTS [2,20-azinobis-(3-ethylbenzothiazoline-6-sulfonic acid)] radical cation scavenging capacity (IC_{50} = 2.91 μM) respect to melatonin control (IC_{50} = 1.92 μM), and moderate copper ion chelating activity *in vitro*.

In 2017, Liu *et al*. [152] reported the synthesis and biological evaluation of tacrine-curcumin derivatives as MTDLs (Fig. **9**) along with a deep molecular modeling study in order to rationalize their results. They evaluated *in vitro* the AChE and BuChE inhibition and the most active compounds were selected for further investigation. The AChE inhibitory activity of **21** and **23** was higher than the tacrine (IC_{50} = 0.10 μM). Compound **21** showed higher inhibitory activity against both enzymes compared to the other compounds. The authors attributed this result to the absence of

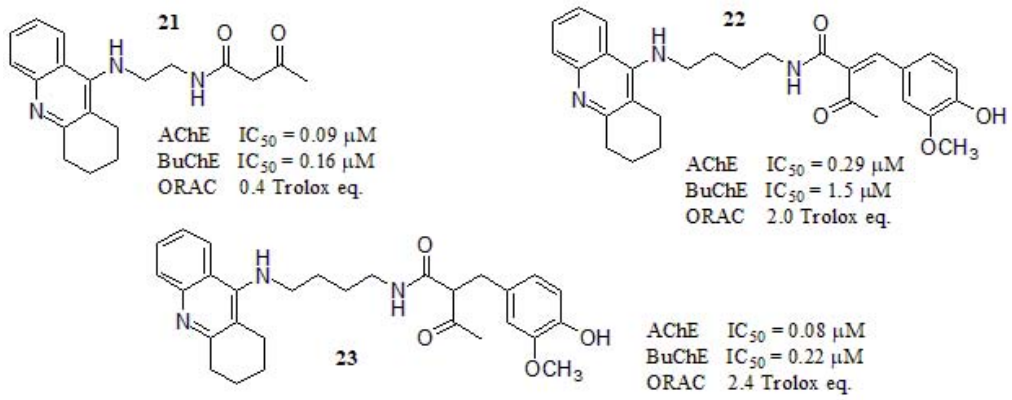


Fig. (9). Fusion of tacrine and curcumin as actives hybrids.

the aromatic ring at the end of the side chain and the smaller structure, making it suitable for the accommodation into the catalytic gorge of AChE, since this is relatively narrow and with large steric hindrance. Regarding the composition of AChE and BuChE, they mainly differ in their amino acid composition at the mid gorge level. While AChE has several aromatic residues, those in BuChE are replaced by smaller aliphatic counterparts resulting in a larger pocket in the latter. The molecular modeling study of compound **21** showed interactions with Trp84 and Phe330 through a π- π staking due to the relatively small side chain on the tacrine derivative and could smoothly enter the catalytic active site (CAS) pocket. On the other hand, compound **23** has an aromatic ring at the end of the side chain, resulting in a stabilized interaction by hydrogen bonding between the carbonyl group and Tyr121 residue, so that the ligand can be perfectly located in the gorge of AChE with the benzene ring binding to CAS, and the tacrine moiety binding to the peripheral anionic site (PAS). It is, therefore, understandable why **23** presented the most potent activity in the AChE enzymatic assay. The antioxidant capabilities of **21**, **22**, and **23** were determined by ORAC, using curcumin and tacrine as positive and negative controls, respectively. Curcumin was a potent scavenger of peroxyl radical (3.1 trolox eq.). Compounds **22** and **23** showed potent ability to scavenge reactive oxygen species (2.0 and 2.4, respectively) while compound **21** exhibited a weak ROS scavenger profile (0.4) in the same order to tacrine (0.3).

By taking advantage of the aforementioned properties of curcumin derivatives as MTDLs, Dias *et al*. [153] designed a series of compounds based on the combination of feruloyl subunit present in curcumin, and *N*-benzylpiperidine (a pharmacophoric subunit from DPZ) with the aim to obtain MTDLs as promising leads prototypes for AD (Fig. **10**). Compounds were evaluated as *EeAChE* inhibitors, resulting in two active compounds (**24**, **25**) in relation to curcumin as reference (*Ee*AChE IC_{50} = 132.12 μM), even though still far from DPZ (*Ee*AChE IC_{50} = 0.026 μM). On the other hand, compound **24** was also active in equine serum butyrylcholinesterase (*eq*BuChE), exhibiting a discrete value compared to standard DPZ (*eq*BuChE IC_{50} = 4.69 μM for DPZ) but more active than curcumin (*eq*BuChE IC_{50} > 300 μM for curcumin). The authors found in a substrate competition assay that compound **24** followed a non-competitive inhibition mechanism (complemented by molecular docking studies), and interestingly, they conclude that the substitutions on the aromatic ring of the *N*-benzylpiperidine lead to a decrease in the AChE activity independent of its ability to donating or withdrawing electrons, or its size. The antioxidant activity of compounds was evaluated *in vitro* by using the radical scavenging DPPH assay; compounds **24**, **25**, and **26** displayed antioxidant profile and were effective in scavenging free radicals compared to Ferulic acid, *iso*-ferulic acid, and trolox as standards (DPPH EC_{50} = 35.54 μM, > 100 μM, and 40.86 μM, respectively). It is worth mentioning that compounds bearing a ferulic acid moiety displayed 100-fold more potency in radical scavenging compared to its *iso*-ferulic acid counterparts, settling the evidence about the importance of curcuminoid framework as an antioxidant. The neurotoxic effects of compounds **24** and **25** were evaluated in SH-SY5Y cells and they showed the absence of cytotoxic and pro-oxidant effects, and authors suggest that the ferulic acid subunit contributes to counteract the ROS formation. The ability of compounds **24-26** to chelate biometals was studied by UV-Vis spectroscopy: all compounds were able to chelate only Cu^{+2} and Fe^{+2}, but no Fe^{+3} and Zn^{+2}. Taking these results into consideration, selected compounds were evaluated *in vivo*, and they showed that compound **24** displayed significant anti-inflammatory activity in different animal models, highlighting this compound as a potential multifunctional lead for AD treatment.

3. RESVERATROL HYBRIDS

Resveratrol is a stilbene which contains two aromatic rings linked by an ethylene bridge. This compound exists in two geometric isomers, cis-(*Z*) and trans-(*E*), as shown in (Fig. **11**). This compound is found in many vegetables such as peanuts, pistachios, grapes, red and white wine, blueberries, cranberries, and even cocoa and dark chocolate. Some of its studied biological properties include anti-cancer, anti-inflammatory, anti-aging, cardioprotective, antioxidant, chelating, and scavenging capability towards reactive ox-

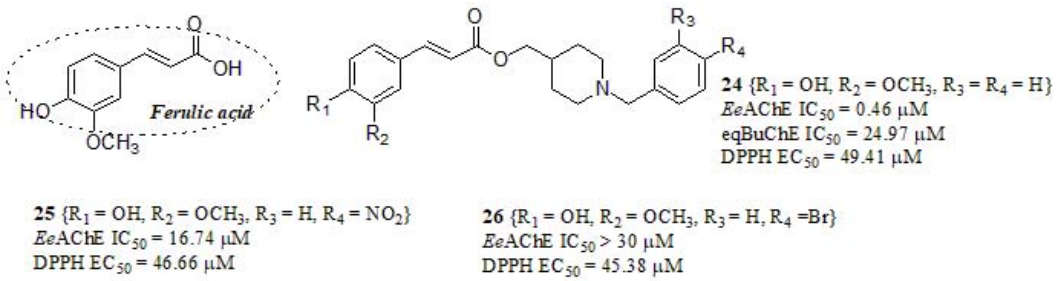


Fig. (10). Feruloyl-donepezil hybrids as MTDLs synthesized by Dias *et al*.

ygen species. Multiple studies detail the ability of resveratrol and its derivatives to inhibit amyloid β aggregation, although their underlying mechanism of action is not well understood [154]. The versatile function of these compounds in plant defense mechanisms as phytoalexins to fight fungal infection, ultraviolet radiation, stress, and injury confers them promising potential as pharmaceutical agents. This framework has attracted lots of interest in order to understand their biosynthetic pathways and their biological properties. One major limitation in the use of resveratrol as a therapeutic agent is associated with their inherent poor aqueous solubility and low bioavailability [155]. The studies of resveratrol and several other stilbenes in AD models suggest that stilbenes may be very effective modulators of AD development and progression, depending on their bioavailability and activity *in vivo* [156]. To solve the bioavailability and solubility concerns of resveratrol, several drug delivery systems have recently been developed, such as encapsulation in liposomal formulations [157-160], use of cyclodextrin complex as a drug carrier for enhanced binding to the protein [161-164], and solid lipid nanoparticles to enhance matrix-based delivery [165-168], among others [169].

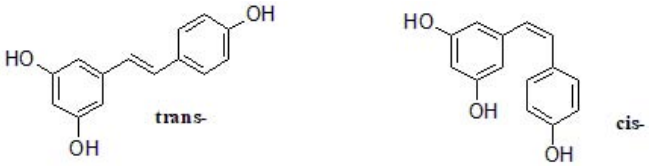


Fig. (11). Isomers of resveratrol.

Resveratrol is also associated with the activation of silent information regulator-1 (SIRT1), and it plays a critical role in neuronal protection as it regulates reactive oxygen species (ROS), nitric oxide (NO), proinflammatory cytokine production, and Aβ expression in AD patients brains [170]. SIRT1 was found to be essential for synaptic plasticity, cognitive functions [171-173], modulation of learning and memory function [174-176]. In a recent review, the importance of the neuroprotective role of resveratrol towards the activation of SIRT1 was discussed, even though the mechanisms of action are still unclear and the anti-inflammatory and antioxidant action of this molecule may be independent of SIRT1 [170]. The challenge of devising resveratrol derivatives is mainly focused on obtaining compounds with improved efficiency, low toxicity, better bioavailability, and solubility for developing more active drugs for clinical application [177].

In a recent paper, Pan *et al*. [178] described the synthesis and evaluation of resveratrol-based compounds as MTDLs. Inhibitory activities against AChE and BuChE were tested along to tacrine and galantamine as reference standards (Fig. **12**). Compounds **27**, **28**, and **29** displayed higher inhibitory activity against cholinesterases than resveratrol (AChE IC_{50} = 165.24 μM, BuChE IC_{50} = 752.46 μM), indicating that the introduction of amino group side chains may result in increasing the inhibitory capability of the target compounds. In their original contribution, the authors evaluated different chain lengths and found that a six-carbon linker between the trans-stilbene moiety and the amino group was the optimal length for biological activity. Besides, they explored different terminal amines resulting in compound **28** as the most potent (almost 8-fold more potent than **27**), concluding that the methylene group could increase the lipophilicity leading to a rise in AChE inhibitory potency [179, 180]. Compound **28** was selected for kinetic measurements using Lineweaver-Burk plots, the authors found in the graphical representation of the steady-state for the inhibition of AChE that both slopes and intercepts were increased at increasing concentration of the inhibitor, concluding that compound **28** was a mixed-type inhibitor, which could bind to the CAS and the PAS sites of AChE. Besides, the inhibition of Aβ_{42} self-induced aggregation was compared with resveratrol (68.51% at 20 μM) and curcumin (52.21% at 20 μM) as reference compounds, while **28** and **29** displayed a similar inhibition profile. Compound **29** endowed with the terminal cyclic amine displayed stronger inhibitory activity compared to the open-chain amino derivative **28**. Authors also pointed out that MAO-A inhibitory ability of compounds was not relevant and apparently lacked a structure-activity relationship, while their MAO-B inhibitory activity was relatively potent and could be related to the length of the alkyl chain, resulting in a n = 3 carbon spacer compound (data not shown) exerting the best MAO-B inhibition (IC_{50} = 5.01 μM). While compounds **27** and **28** did not display relevant activity against MAOs compared to iproniazid as reference (MAO-A IC_{50} = 6.58 μM; MAO-B IC_{50} = 7.82 μM). Eventually, compound **29** displayed significant inhibition towards both MAO-A and MAO-B at the same time, it showed no toxicity in the SH-SY5Y neuroblastoma cell line at 1-50 μM.

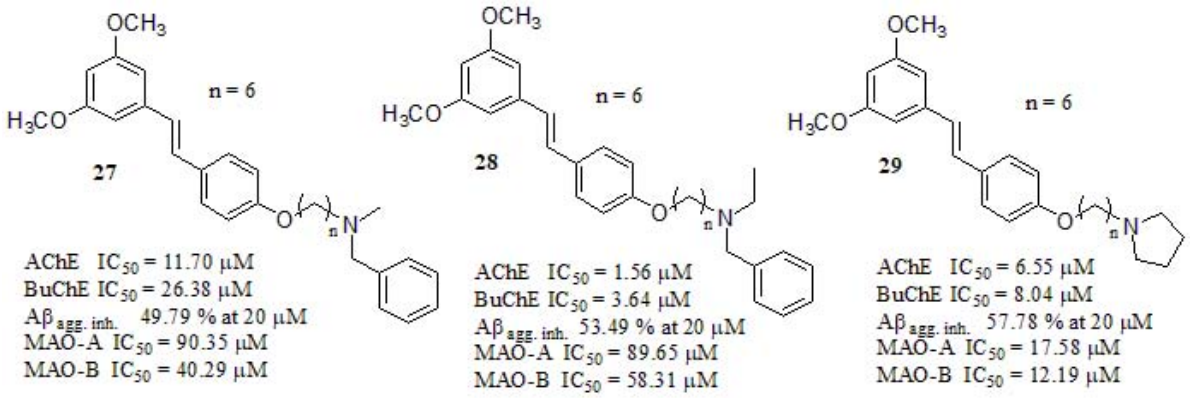


Fig. (12). Resveratrol derivatives as MTDLs against AD.

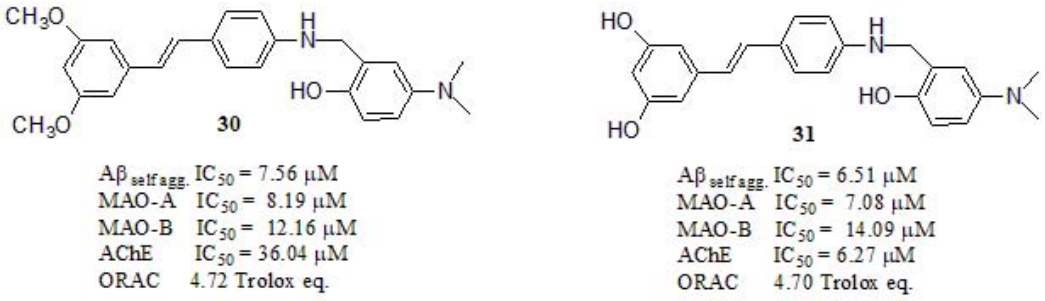


Fig. (13). Fusion of resveratrol and clioquinol as MTDLs.

Considering that biometal (Fe, Cu, and Zn) ions may be crucial participants in pathological processes of AD, Lu *et al*. [181] combined resveratrol and clioquinol, a well-known metal chelator, to obtain a novel series of derivatives expected to behave as biometal chelators, antioxidants, and inhibitors of A*β* aggregation (Fig. **13**). Compounds **30** (79.50% at 20 μM) and **31** (78.06% at 20 μM) exhibited stronger A*β* aggregation inhibition than curcumin (52.77% at 20 μM, IC_{50} = 12.35 μM) and resveratrol (69.73% at 20 μM, IC_{50} = 15.11 μM). Regarding the antioxidant activity, compounds **30** and **31** exhibited strong but lower antioxidant capacity compared to resveratrol (5.92 trolox eq.) as a reference compound. Metal-Chelating properties of compounds were studied by UV−vis spectroscopy and the ability of **30** and **31** to complex biometals such as Cu (II), Fe (II), Fe (III) and Zn (II) was measured. Their results indicated the formation of **30**-Cu (II) and **31**-Cu (II) complexes, with 3:1 and 1:1 stoichiometry, respectively. Moreover, the ability of these compounds to inhibit Cu (II)-induced A*β* aggregation was investigated by ThT fluorescence and TEM. In the presence of Cu (II) well-defined A*β* fibrils were observed, while fewer fibrils were present when compounds **30** and **31** were added to the samples, demonstrating its capabilities in disassembling the highly structured fibrils induced by Cu (II). The MAO inhibitory ability of compounds was evaluated using ladostigil as reference (MAO-B inhibitor, IC_{50} = 37.1 μM) and clorgyline (MAO-A irreversible and selective inhibitor, IC_{50} = 4.1 nM), and both displayed a strong balance in MAO inhibitory activity. Furthermore, compounds **30** and **31** exhibited moderate AChE inhibitory activity. Intracellular antioxidant activity was evaluated in the SH-SY5Y cell line, resulting in **30** and **31** activity more potent than Trolox, indicating that resveratrol derivatives have the potential to be efficient multifunctional agents. Finally, compound **30** was able to cross the blood-brain barrier *in vitro* and did not exhibit any acute toxicity in mice at doses of up to 2000 mg/kg.

Jeřábek *et al*. [182] fused the cholinesterase inhibitor drug tacrine with resveratrol, designing a series of new MTDLs. All compounds carried a 6-chlorotacrine fragment connected to a resveratrol derivative moiety. Among other selected compounds (Fig. **14**) only **32** and **33** showed significant AChE inhibitory activity compared to tacrine as reference (tacrine AChE IC_{50} = 0.5 μM; 6-chlorotacrine AChE IC_{50} = 0.07 μM; data taken from ref [183].). Compound **34,** with a double bond, has a higher degree of structural rigidity in contrast with the other derivatives, displaying a weak AChE inhibition. Additionally, docking investigation revealed that chlorine in 6-position allows compounds to establish Van der Waals interactions in with AChE hydrophobic residues of the active site. Since chlorine can decrease the electron density on the aromatic ring in tacrine moiety, it favors π electron interaction with nearby residues [183, 184].

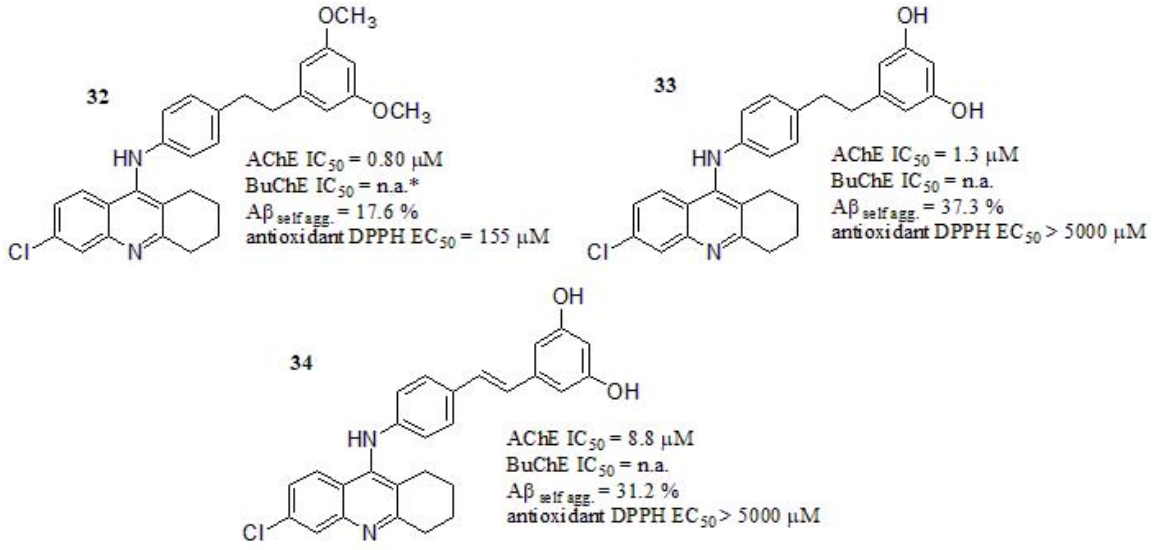


Fig. (14). Resveratrol-Tacrine hybrids reported by Jeřábek *et al*.

All compounds evaluated in BuChE displayed no enzyme inhibition when tested at 10 μM. In this sense, compounds **33** and **34** were the most active inhibitors even though it was not possible to establish a correlation between the rigid fragment and the anti-amyloid properties, however, the presence of resorcinol ring (1,3-dihydroxybenzene) seems to be important for the possibility of establishing hydrogen-bond interactions. This is clearly seen in compound **32**, endowed with a 2,4-dimethoxy substituent on the phenyl ring, exhibiting lower inhibitory activity on Aβ self-aggregation. However, compounds **33** and **34** with a resorcinol moiety displayed a similar Aβ_{42} inhibitory profile than resveratrol as reference (Aβ_{42} self-aggregation % inhibition = 30.0%). The antioxidant activity of compounds **32**, **33**, and **34** was assessed using 2,2-diphenyl-1-picrylhydrazyl (DPPH) in an antioxidant assay, expressed as the concentration that causes a 50% decrease in the DPPH activity (EC_{50} values) with Trolox as a reference compound. Compounds **33** and **34** carrying free hydroxyl groups on the phenyl ring were detrimental to the free radical scavenging efficacy, nevertheless, derivative **32** with two methoxyl groups, showed reasonable antioxidant activity although lower than that of resveratrol (EC_{50} = 25.6 μM). A clear cytotoxic effect was evident for compound **32** when assessing cerebellar granule neurons of rat at 5 μM concentration, compound **33** showed neurotoxic only at the highest tested concentrations (25 and 50 μM). Compound **34** showed no clear neurotoxicity at all tested concentrations. Finally, the authors found general hepatotoxicity for all derivatives, attributing it to the presence of hepatotoxic tacrine fragment.

In 2018, a significant advance was conducted by Cheng *et al*. [185] reporting the synthesis and *in vitro* evaluation of hybrids merging maltol and resveratrol as MTDLs (Fig. **15**) [186-188]. The ABTS radical scavenging method was used to determine the antioxidant capacity. Compounds **35** and **36** exhibited excellent antioxidant activity even higher than trolox (IC_{50} = 3.89 μM), showing that a modification in the substitution pattern of the benzene ring by fluoro, ethoxy, or methoxy resulted in a decrease of the antioxidant activity (compounds not included in this discussion). The A$\beta_{1\text{-}42}$ self-aggregation inhibition profile of **35** and **36** resulted to be more potent than resveratrol and curcumin, used as positive controls (IC_{50}=11.89 and 18.73 μM, respectively). Biometals (copper, iron, and zinc) were able to facilitate Aβ aggregation thought binding to three histidines (H_6, H_{13}, and H_{14}) of the A$\beta_{1\text{-}42}$ peptide [189]. The TEM experiment demonstrated a disaggregation of Aβ fibrils, indicating that compounds **35** and **36** can efficiently chelate Fe^{+3}, Cu^{+2}, and inhibit Fe^{+3}/Cu^{+2} –induced Aβ aggregation.

Synthesis and evaluation of prenylated resveratrol derivatives were recently discussed by Puksasook *et al*. [190] (Fig. **16**). Prenylation consists of the addition of a hydrophobic prenyl chain, as a natural active moiety of a β-secretase (BACE1) inhibitor [191, 192]. The A$\beta_{1\text{-}42}$ aggregation inhibition was evaluated using curcumin as a positive control (IC_{50} = 0.77 μM, Anti A$\beta_{agg.}$ 87.98% at 100 μM). The best result was obtained from derivative **39**, bearing a geranyl group at the C-4 position on the resorcinol ring, showing a similar effect than curcumin, followed by **37** bearing a prenyl group at the same position. Authors confirmed by molecular docking study that prenyl group at C-4 was less effective than a geranyl group at the same position, this may be due to the shorted alkyl side chain leading to less hydrophobic interactions. The inhibition of BACE1 was carried out using β-secretase inhibitor IV (Calbiochem®) as a reference compound (IC_{50} = 0.015 μM, β secretase inhibition 96.51% at 50 μM). Compound **40** was the most potent BACE1 inhibitor. The free

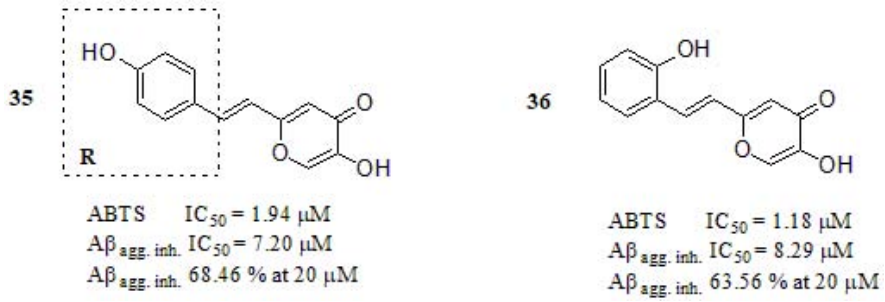


Fig. (15). Novel maltol-resveratrol hybrids as MTDLs reported by Cheng *et al*.

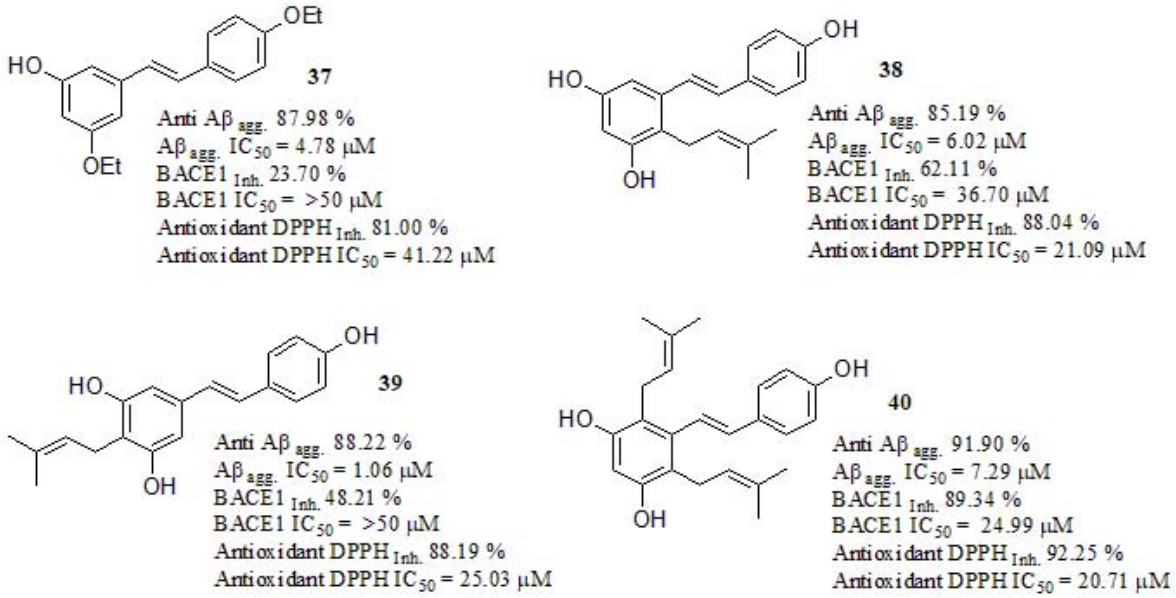


Fig. (16). Prenylated and geranylated resveratrol derivatives.

radical scavenging activity was evaluated using DPPH according to a modified version of the Brand-Williams method [193]. Compounds **38**, **39**, and **40** showed stronger activity than **37**. Authors attributed this result to the free -OH groups that were essential for the antioxidant activity because these can donate hydrogen atoms and stabilize electrons by conjugation [194]. The IC_{50} values were compared to vitamin C (IC_{50} = 21.63 μM, antioxidant DPPH inhibition 95.78% at 100 μM) used as a positive control resulting in compound **40** as the most potent antioxidant. Neuronal viability assay was carried out using the P-19-derived neuron cell line. Compound **37** (>100% neuron viability at 1 nM to 10μM concentrations), promoted high viability of the cultured neurons, while compounds **38**, **39**, and **40** geranylated resveratrol derivatives showed stronger neurotoxicity at 1 nM (% viability 51.25 ± 13.12, 70.07 ± 36.33 and 34.17 ± 29.98, respectively). The prenyl substituent at the C-4 position in compound **37** might play an important role in neuronal viability. The neuroprotective ability of compound **37** was evaluated in a serum deprivation model using P-19 derived neurons cultured in a concentration of 1 nM and 10 μM. Compound **37** significantly protected the cultured neurons against serum deprivation at 50.59 ± 3.98 and 53.19 ± 12.48% viability, respectively (assumed ROS toxicity from serum-depravation induced oxidative stress), and it was more effective than resveratrol (37.41 ± 4.40% viability), and comparable to that of the quercetin positive control (58.04 ± 9.20% viability). Finally, the neuritogenic activity of compound **37** caused more branching numbers (9.33) than the control (2.12), and longer neurites (109.74 μM) than the positive control quercetin (104.33 μM).

Tang *et al*. [195] designed and studied isoprenylated resveratrol dimers (Fig. **17**). The inhibitory activities against MAOs were evaluated *in vitro* using *p*-tyramine as a nonselective substrate of MAO-A and MAO-B. Compounds **41** and **42** displayed enhanced inhibition towards MAO-B respect to the A isoform. In addition, in order to evaluate the antioxidant activities of those, three independent approaches were used: DPPH and ABTS radical scavenging methods

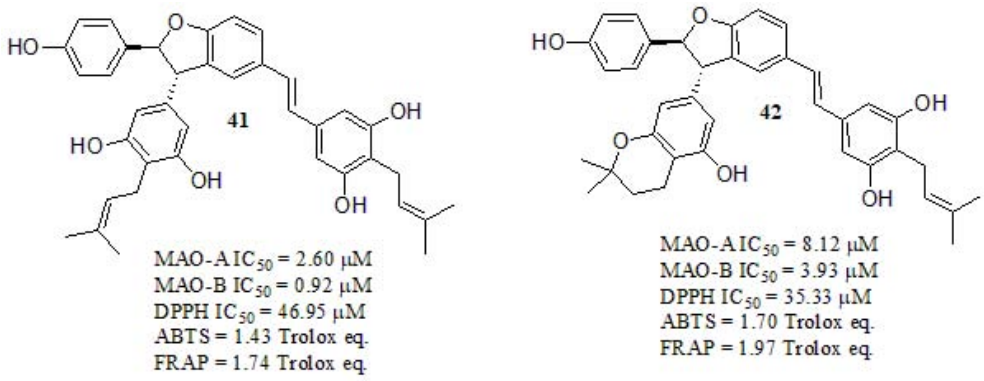


Fig. (17). Isoprenylation-Resveratrol dimer derivatives described by Tang *et al*.

and Ferric ion reducing antioxidant power (FRAP) assay. DPPH radical scavenging revealed that compounds **41** and **42** are endowed with significant antioxidant activity in relation to Trolox (IC_{50} = 49.77μM). ABTS and FRAP antioxidant analysis showed a similar trend of free radical scavenging activity. Potential toxicity effects were evaluated in PC12 and BV2 cells. Compounds **41** and **42** were tested in their capacities of protecting PC12 cells against oxidative stress associated death by H_2O_2. The results showed that these compounds could significantly inhibit cell death at concentrations ranging from 6.25 to 25 μM. Both compounds exhibited very low toxicity in PC12 and BV2 cell lines. The neuroprotective effect was evaluated against oxidative injuries in PC12 cells by using oligomycin-A and rotenone as toxic lesions simulation [196-198]. Both compounds exerted relatively poor neuroprotective activity against rotenone-induced cell damage, while they showed moderate to high neuroprotective activity against oligomycin-A. As depicted in (Fig. **17**), compound **41** displayed improved biological activities while its BBB crossing capabilities were enhanced respect to **42**.

Xu *et al*. [199] integrated resveratrol and deferiprone (a known iron metal chelator) scaffolds in a novel series, with the aim of developing new MTDLs for AD. (Fig. **18**). The A*β* self-induced aggregation inhibition profile was tested by using the ThT based fluorometric assay. Compound **44** displayed stronger A*β* inhibitory activity in relation to resveratrol and curcumin (64.08% and 56.44%, respectively), while compound **43** exhibited similar behavior. The antioxidant activity was determined by the ABTS radical scavenging method employing Trolox as a positive control. Compound **43** showed higher antioxidant activity in relation to the reference (IC_{50} = 3.89 μM), while compound **44** exerted a similar effect. As expected, compound **43** demonstrated improved antioxidant properties. The pFe(III) values were determined by fluorescence spectroscopy along to deferiprone, which was used as a reference compound [200]. Compounds **43** and **44** displayed closely related Fe(III) scavenging properties in relation to deferiprone (pFe(III) = 20.60).

Yang *et al*. [201] investigated a series of pyridoxine-resveratrol hybrids by introducing Mannich base moieties. According to them, hybrids containing phenolic Mannich base moieties may exhibit good antioxidant properties [202], AChE inhibitory activity [203], and metal chelating properties [204]. Vitamin B6 (pyridoxine) has a critical function in cellular metabolism and stress response. Furthermore, it also behaves as a potent antioxidant that effectively quenches reactive oxygen species [205]. The inhibition of cholinesterases was evaluated *in vitro* using AChE from *electrophorus electricus* (*Ee*AChE) and BuChE from rat serum (Fig. **19**). Compound **45** was inactive as *Ee*AChEi, while compound **48** displayed the strongest *Ee*AChE inhibitory activity in the series even if lower than DPZ (IC_{50} = 23.0 nM). On the other hand, compound **46** bearing a piperidine unit showed stronger inhibition in *Ee*AChE than the structurally related compound **47**, differing only in oxygen in the morpholine moiety. In order to explore the mechanism of action of these hybrids, a kinetic study was carried out for compound **46**, indicating a mixed-type inhibition and supporting a dual-site binding to both CAS and PAS of AChE. All compounds were inactive or weak as BuChE inhibitors. The MAOs inhibition activity were evaluated using clorgyline (MAO-B IC_{50} = 8.85 μM; MAO-A IC_{50} = 7.9 nM), rasagiline (MAO-B IC_{50} = 0.044 μM; MAO-A IC_{50} = 0.71 μM), and iproniazid (MAO-B IC_{50} = 4.32 μM; MAO-A IC_{50} = 1.37 μM) for comparative purposes. All tested compounds showed much stronger inhibitory activities towards MAO-B than MAO-A. The intermediate **45** showed the highest MAO-B inhibition activity, followed by **47**, suggesting that the Mannich base moiety was detrimental for MAO-B inhibition (reminding us all the key importance of extending the biological assays to the intermediates). The antioxidant activity of those was evaluated by the ORAC fluorescein method. All compounds exhibited good ORAC values ranging from 1.76 – 2.56 compared to resveratrol (ORAC = 5.60 trolox eq.), also isopropylidene-protected derivative **48** showed slightly weaker antioxidant activity than **46**, what could be related to the hydroxyl of lacking the latter.

4. CHROMONE DERIVATIVES

Chromones are a group of oxygen-containing heterocyclic compounds (Fig. **20**), widespread and naturally occu-

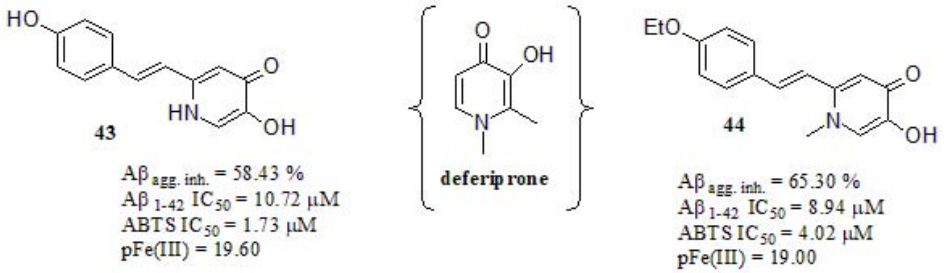


Fig. (18). Deferiprone-resveratrol hybrids.

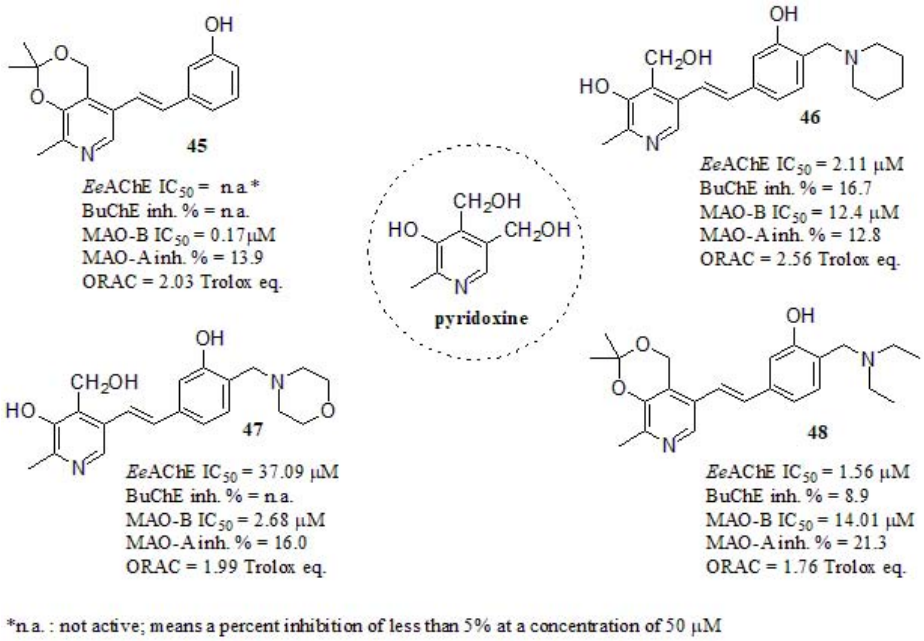


Fig. (19). Pyridoxine-Resveratrol hybrids Mannich base derivatives.

rring. It represents an unusual group of structurally diverse secondary metabolites, derived from the convergence of multiple biosynthetic pathways that are widely distributed through the plant and animal kingdoms [206]. Chromone scaffold ((4H)-1-benzopyran-4-one) has also been extensively recognized as a key pharmacophore [207-214]. The chromone ring is the core fragment of several flavonoid derivatives, such as flavones and isoflavones [215]. The structural diversity of chromones in nature allows their division into simple and fused chromones. These heterocycles have attracted much attention because they show a variety of pharmacological properties such as anti-inflammatory effect [216, 217], analgesic [218, 219], metal chelating ability [220], antioxidant [221, 222], antimicrobial [223-225], antifungal [226, 227] and neuroprotective effects [228, 229], among others [230-232]. In recent years, many research groups optimized their chemical structure in order to develop new derivatives for the potential AD therapy, being the main hallmark related to its neuroprotective capability, cholinesterases (ChEs) inhibitory capabilities, MAO inhibition, and amyloid β aggregation inhibitory activities [228, 233]. Furthermore, Reis and coworkers [234] showed that chromone is a privileged scaffold for the development of novel MAO-B inhibitors, highlighting the effect of the substituent nature located at C3- and/or C6-positions of the benzopyrone ring. Otherwise, chromone derivatives have also been applied to the preparation of fluorescent probes due to its photochemical properties [214]. The chromone core is found in flavones and isoflavones and they are preferential scaffolds for the development of MAO inhibitors [235].

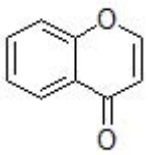


Fig. (20). Chromone.

Li *et al*. [236, 237] reported the synthesis of tacrine-flavonoids hybrids as multifunctional ChEs inhibitors. Their results showed that the chromone framework contributes to the bioactivities of flavonoids hybrids. Based on such findings, in recent work, Wang *et al*. [238] reported a series of chromone-donepezil hybrids (Fig. **21**) and their inhibitory activity against *eq*BuChE and *Ee*AChE were evaluated. Compound **49**, carrying a 6-methoxy substituent at the chromone moiety displayed the stronger inhibition, similar to DPZ in AChE but much stronger in BuChE (*eq*BuChE: IC_{50} = 2.47 μM, *Ee*AChE: IC_{50} = 0.032 μM). Compound **50** exerted significant inhibitory activity to both ChEs even though the effect was less. Indeed, since the only difference between both is the OBn group, the steric drawbacks of the latter turns clear. Both compounds endowed with N-ethylcarboxamide linker between the benzylpiperidine and chromone moieties exhibited higher inhibitory activity than the others lacking this spacer (data not shown). Regarding the MAOs, the position and nature of the substituents resulted in a shift of its inhibitory profile. Compounds **49** and **50** showed weak inhibition of MAO-A. However, in MAO-B the inhibitory strength was directly related to the length of the alkylene chain. Compound **50** displayed higher MAO-B inhibitory potency respect to iproniazid (IC_{50} = 6.93 μM) and similar to pargyline (IC_{50} = 0.12 μM) as reference compounds. Compound **50** was selected for kinetic study to the inhibition of ChEs and MAO-B. Interestingly, a mixed-type inhibitory behavior was found in AChE while in BuChE, a competitive mechanism was pointed out. In addition, the kinetic profile of **50** towards MAO-B was compatible with competitive inhibition. Molecular modeling supported the aforementioned outcomes. Moreover, compound **50** could penetrate the BBB to target the enzyme in the CNS and showed low cell toxicity in rat pheochromocytoma (PC12) cells *in vitro.* These results shed light on these multifunctional agents that may contribute to the field of multitarget directed ligands for potential AD therapy.

Pachón-Angona *et al*. [239] combined donepezil + chromone + melatonin as scaffolds, prepared by multicomponent reaction (MCR) synthetic strategy, transforming three or more starting material into new products in a one-pot procedure (Fig. **22**) [240, 241]. In a first trial, the antioxidant behavior of such compounds was carried out by the ORAC-FL method. Ferulic acid and Melatonin were used as positive references (ORAC values of 3.74 [242] and 2.45 [242], Trolox eq. respectively). Compound **51** exhibited strong antioxidant power, higher than melatonin and similar to Ferulic acid. However, the other compounds with a linker length of n = 1,2 displayed more potent antioxidant capabilities than Ferulic acid (ORAC = 6.52 Trolox eq.; n = 2 and **R** = H). The MAO activity was evaluated *in vitro*, by using clorgyline and pargyline as references. Compound **51** showed moderate MAO-A inhibition, less active than clorgyline (IC_{50} = 0.05 μM), and lower MAO-B inhibitory activity compared to pargyline (IC_{50} = 0.08 μM). The ChEs inhibitory activity was evaluated for *Ee*AChE and *eq*BuChE using DPZ and tacrine as references. Compound **51** showed strong *eq*BuChE inhibition, stronger than DPZ (IC_{50} = 840 nM) even though diminished respect to tacrine (IC_{50} = 5.1 nM). Regarding the structure-activity relationship, considering the same substituent, the most potent inhibitor was those with a n = 2 linker (IC_{50} = 6.29 nM, and **R** = $OCH(CH_3)_2$) while those with n = 3, and n = 4 displayed lower potency. On the other hand, **51** resulted a moderated AChE inhibitor. The most potent compounds were those bearing propoxy or isopropoxy substituents at the indole ring (IC_{50} = 0.08 μM and IC_{50} = 0.09 μM, respectively). Finally, in molecular docking simulation was noticed that in ChEs the chain ending in pyrrole and chromone ring were crucial for the binding to the active site of the enzyme. Furthermore, the MAO analysis revealed that the N-benzylpiperidine chain was a required feature to achieve good inhibitory profiles.

In 2017, Li *et al*. [229] described the synthesis of chromone derivatives combining the pharmacophore moiety **L1**, a previously reported to regulate metal-induced A*β* aggregation, ROS production, and neurotoxicity *in vitro* [243], and clioquinol (Fig. **23**). The inhibitory activities against MAOs were measured and compared to those of rasagiline (MAO-A IC_{50} = 49.7 μM and MAO-B IC_{50} = 7.47 μM) and iproniazid (MAO-A IC_{50} = 6.46 μM and MAO-B IC_{50} = 7.98 μM). Compound **52** displayed strong inhibitory values as MAOs inhibitors. The nature of substituent and their position generated changes regarding the structure-activity relationship. The most potent and selective MAO-A inhibitor was compound **53** (IC_{50} = 1.65 μM, R_1 = Cl, R_2 = H, R_3 = H, and R_4 =

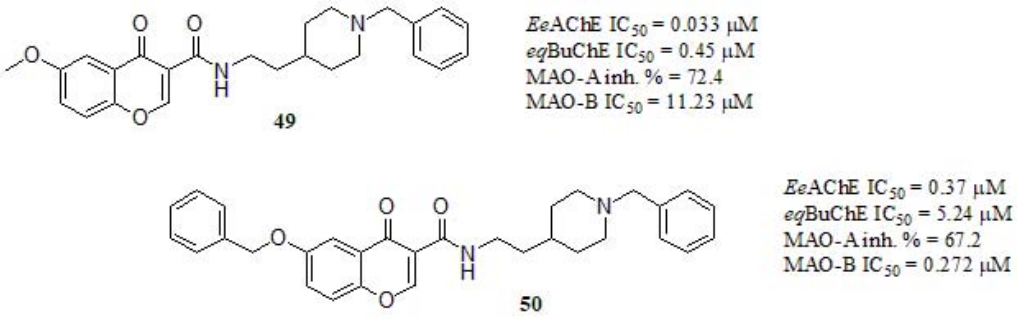


Fig. (21). Chromone and benzylpiperidine moieties of donepezil as multifunctional agents.

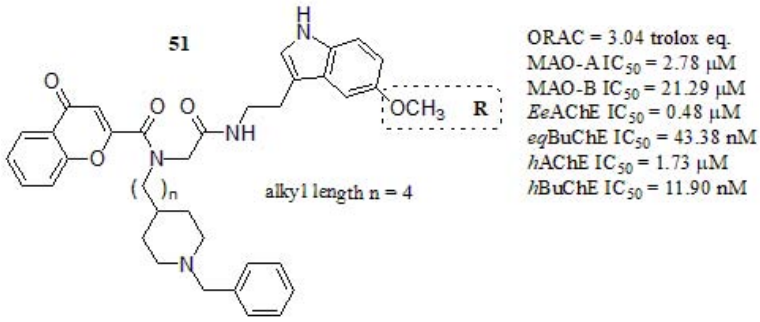


Fig. (22). Donepezil + chromone + melatonin hybrids as multitarget agents for AD.

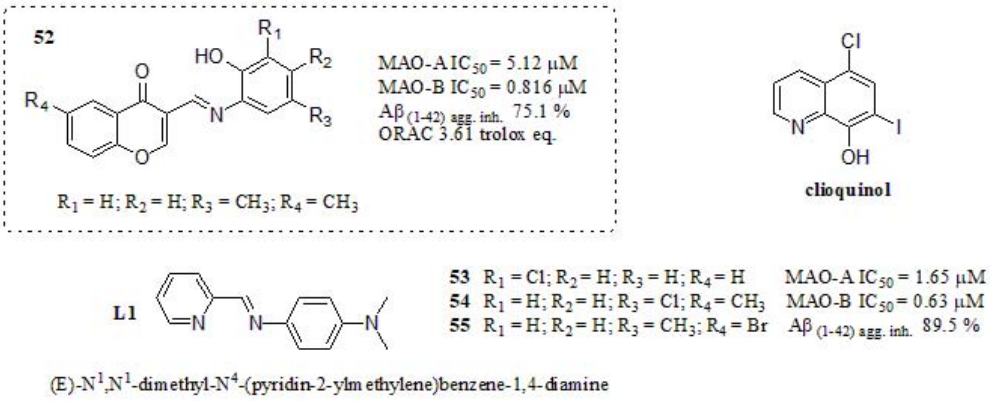


Fig. (23). Chromone derivatives reported by Li *et al*.

H). Moreover, **54** (IC_{50} = 0.634 μM, R_1 = H, R_2 = H, R_3 = Cl, and R_4 = CH_3) displayed the most potent inhibitory activity towards MAO-B. Compound **52** exhibited moderate A*β* aggregation inhibition even though stronger than curcumin and resveratrol (46.5% and 57.2%, respectively). The stronger A*β* aggregation inhibitor was compound **55**, exhibiting 89.5% inhibition (R_1 = H, R_2 = H, R_3 = CH_3, and R_4 = Br) even though it does not meet a multi-target feature. ThT binding assay and TEM were used to identify the degree of A*β* aggregation [244]. On the basis of the results, they concluded that compound **52** was capable of inhibiting Cu^{+2} induced A*β* aggregation, exhibiting significant antioxidant activity, metal chelation capabilities, H_2O_2-induced intracellular ROS accumulation reduction properties, and was able to cross the BBB (showed P_e values > 4.0). It is worth to mention that it did not show significant toxicity in PC12 cells, suggesting that further investigation and comprehension of this scaffold may achieve advancements in AD multitarget therapy.

Reis *et al*. [234] reported a series of chromone 2- and 3-phenylcarboximide derivatives (Fig. **24**). Regarding the inhibitory activity towards ChEs, compound **56** displayed submicromolar activity towards AChE and inactivity towards BuChE. Furthermore, compound **57** displayed bifunctional ChEs inhibitory activity in the low micromolar range, while compound **56** bearing a methyl group in the *para* position of the chromone exocyclic phenyl ring and two methyl group linked to the tertiary amine, also showed submicromolar MAO-A values and micromolar MAO-B values even though still far from clorgyline (IC_{50} = 0.0045 μM), and rasagiline (IC_{50} = 0.050 μM).

Compared with previous works of this group regarding similar structures, this result was less remarkable in regard to MAO-B inhibitory activity [245-248]. Compound **57** carrying no substituent at the exocyclic ring, resulted inactive in MAO-A and while acted as a selective MAO-B inhibitor. A kinetic study was performed in both MAO-A and MAO-B. The results showed that **56** and **57** behave as competitive MAO inhibitors. The evaluation of the AChE inhibition mechanism of **56** showed a mixture of competitive and non--competitive mechanisms. Most promising chromones were screened towards human BACE-1, however, none of the compounds displayed relevant potency (IC_{50} > 10 μM). The cytotoxicity profile was evaluated in differentiated human neuroblastoma (SH-SY5Y) and human hepatocarcinoma (HepG2) cell lines, being both clinically relevant. Compound **57** presented a wider safety profile and promising safety margin.

Starowicz *et al*. [249] studied the ability of various spices and herbs that are characteristic of European cuisine

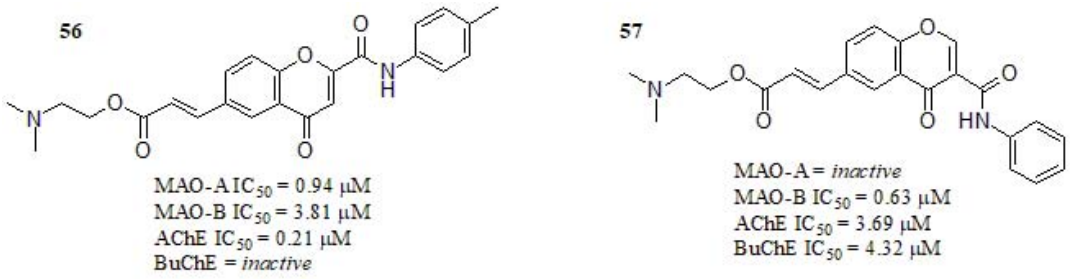


Fig. (24). Chromone 2- and 3-phenylcarboximide derivatives.

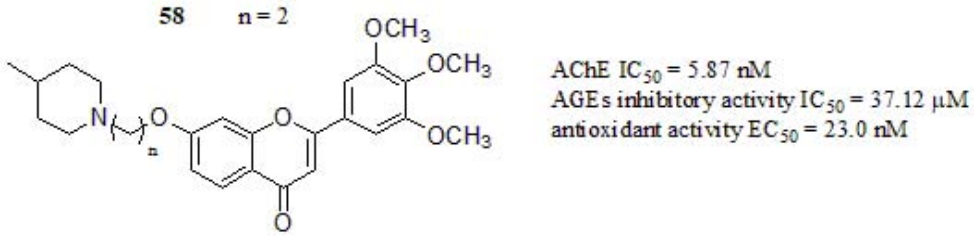


Fig. (25). MTDLs based on chromen-4-one reported by Singh *et al*.

to inhibit the formation of advanced glycation end products (AGEs) and their antioxidant capacity. Glycation is defined as a reaction that leads to the formation of an irreversible structure called AGEs and a high concentration of those could initiate actions leading to various disorders, such as AD, atherosclerosis, diabetes, kidney disease, and chronic heart failure [250, 251]. The research group of Singh and coworkers [59] focused their efforts on the design and synthesis of chromen-4-one derivatives, making modifications at different positions of the "skeleton key" [252]. The inhibition towards AChE was determined and compound **58** (Fig. **25**) exhibited the stronger inhibitory profile, higher than DPZ (IC_{50} = 12.7 nM) as standard. However, a further increase in carbon spacer (n = 6, 8) reduced the activity by 3--folds (IC_{50} range from 48.1 to 67.2 nM). Thus, n = 2 and n = 3 spacer chain length was optimal considering cyclic aminoalkyl groups for AChE inhibitory profile. Anti-glycation assay was performed according to the method reported by Matsuura *et al*. [253] with slight modifications. Compound **58** displayed significant inhibitory activity compared to aminoguanidine as reference drug (AGEs IC_{50} = 40.0 μM). Respect to *in vitro* antioxidant activity, compound **58** showed lower antioxidant activity compared to ascorbic acid (EC_{50} = 20.0 nM). Furthermore, the authors concluded that the conjugation system of chromen-4-one moiety appears to be crucial to their radical scavenging behavior. The kinetic study of compound **58** exhibited a mixed-type inhibition, which could bind with both CAS and PAS of the enzyme. Likewise, docking studies revealed the dual binding property as it interacted with both CAS as well as PAS via a hydrogen bond, π-π aromatic, and hydrophobic interactions, complementing the previous information.

Coumarin and chromone are two structural isomers that exhibit relevant pharmacological activities [230, 254, 263, 255-262]. Fonseca and coworkers [264] performed a comparative study of coumarin- and chromone-3-phenyl carboxamide scaffolds and its structure-activity relationship (SAR) as MAOs inhibitors (Fig. **26**). Firstly, the authors carried out a docking study of ligand-target recognition using the principal skeleton of both series of compounds. The binding modes analysis did not reveal significant differences in coumarin- and chromone- scaffolds. Consequently, the design of new derivatives was focused on *i)* the effects of the different substituents at the benzopyrone ring; *ii)* substituent position and its capabilities as electron-donating or withdrawing entities; *iii)* whether the position of the carbonyl group in the isomeric structures display some impact. Compounds **59** and **60** bearing a *meta* chlorine substituent at the benzamide portion showed stronger MAO-B inhibition compared to standard drugs deprenyl (IC_{50} = 16.73 nM) and safinamide (IC_{50} = 23.07 nM). The SAR analysis of remaining compounds (not presented here), bearing *para* substituents resulted in a decrease of activity, and the presence of a hydroxyl group either in *meta* or *para* position also resulted in activity decreasing. The position of the carbonyl group in coumarin or chromone moiety was apparently not relevant. Both compounds were inactive towards MAO-A. Eventually, the kinetic study of both compounds revealed a noncompetitive inhibition mechanism.

In a recent article, Shaikh *et al*. [265] designed a series of chromone-derived aminophosphonates in a one-pot reaction, catalyzed by porcine pancreatic lipase under solvent-free conditions. The α-aminophosphonates are a class of compounds with promising biological and pharmacological

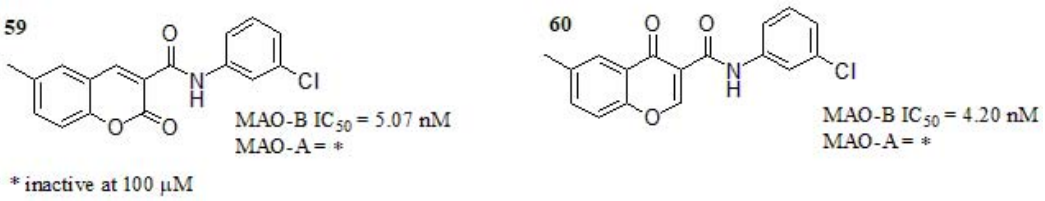


Fig. (26). Coumarin versus chromone scaffold reported by Fonseca *et al*.

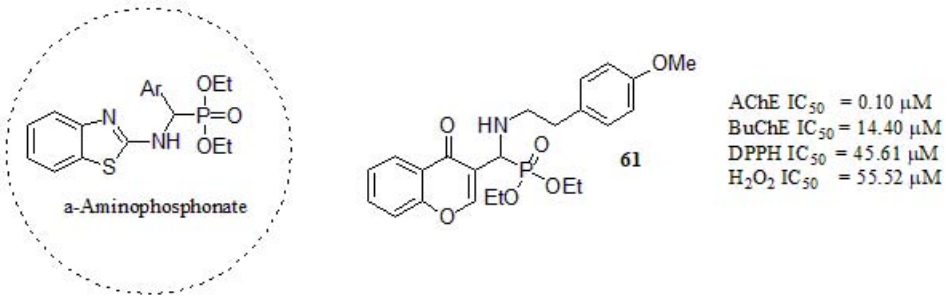


Fig. (27). α-Aminophosphonate -functionalized chromone as MTDLs.

importance as anti-AD agents [266]. Compound **61** (Fig. **27**) was the most potent AChE inhibitor compared to tacrine (IC_{50} = 0.29 μM), galantamine (IC_{50} = 3.64 μM) and rivastigmine (IC_{50} = 5.21 μM), showing higher activity towards AChE than BuChE. As an important observation regarding ChEs inhibitory activity, aliphatic amines displayed a stronger inhibitory profile towards AChE, while aromatic ones showed better performance in BuChE inhibition. The kinetic study of ChEs revealed a mixed-type inhibition, which is in agreement with the molecular docking results [237]. Besides, the antioxidant activity was evaluated against DPPH and hydrogen peroxide scavenging method. Compound **61** exhibited the greatest radical elimination and high scavenging activity comparable to Ascorbic acid (DPPH IC_{50} = 42.28 μM; H_2O_2 IC_{50} = 51.45 μM). Finally, **61** showed significant DNA damage protection activity.

5. INDOLE DERIVATIVES

Indole is a planar heterocyclic molecule in which a benzene ring is fused to a pyrrole ring through 2 and 3 positions of the latter (Fig. **28**). Due to the delocalization of π-electrons, it undergoes electrophilic substitution reactions, being a widely used chemical scaffold in medicinal chemistry. Its relevance in biological systems relies on being built into proteins through the indolic amino acid tryptophan [267]. Thus, indole moiety is considered a biologically accepted pharmacophore in medical compounds [268, 269].

Indole is a prominent phytoconstituent across various plant species and is produced by a variety of bacteria [270]. The indole-derived phytoconstituents and bacterial metabolites are a result of biosynthesis via the coupling of tryptophan with other amino acids. For this reason, it is a constituent of flower perfumes, pharmacologically active indole alkaloids, and some animal hormones or neurotransmitters such as serotonin [271] and melatonin [272]. Some naturally occurring indole alkaloids have gained FDA approval, including vincristine, vinblastine, vinorelbine, and vindesine for its anti-tumor activity [273, 274], ajmaline for its anti-arrhythmic activity [275-277], and physostigmine for glaucoma [278]. Taking inspiration from these natural compounds, several synthetic drugs were synthesized having reached the patient's bedside, such as indomethacin (NSAID) [279], ondansetron (chemotherapy-induced nausea and vomiting) [280], fluvastatin (hypercholesterolemia) [281], zafirlukast (leukotriene receptor antagonist) [282], etc. The success of the above-mentioned compounds indicates the importance of the ring system in multi-disciplinary fields, including the pharmaceutical and agrochemical industry.

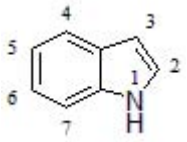


Fig. (28). Indole structure.

Luo *et al*. [283] reported the synthesis of multifunctional hybrids based on melatonin-benzylpyridinium bromides (Fig. **29**) and their cholinergic activities were evaluated. The most promising derivative was compound **63**, showing significant inhibitory activity in AChE even though 10-fold lower than DPZ as reference compound (IC_{50} = 0.014 μM). Otherwise, hybrid **62** exhibited a stronger inhibitory activity to BuChE, resulting in 70-fold higher than DPZ (IC_{50} = 5.6 μM). The authors highlighted the relevance of substituents

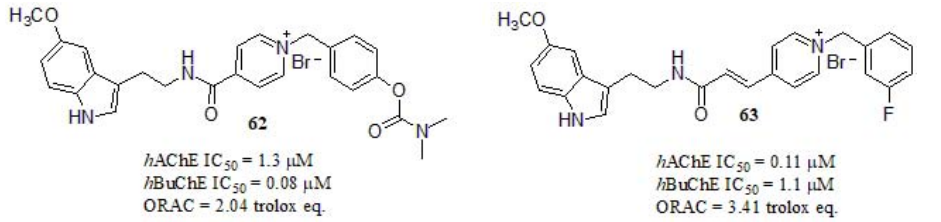


Fig. (29). Melatonin-benzyl pyridinium bromides derivates synthesized by Luo *et al*.

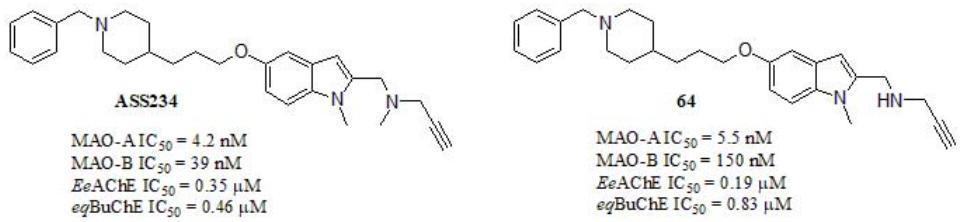


Fig. (30). MTDLs based on donepezil and indole scaffolds reported by Bautista-Aguilera *et al.*

at the main moieties, as different substitutions with varied electronic properties showed a little fluctuation on the inhibitory activity, except for the introduction of *-cyano* group at -*para* position in the benzylpyridinium moiety (AChE: IC_{50} = 22.9 μM; BuChE: IC_{50} >100 μM). On the other hand, regarding the indole moiety, 5-*methoxy* substituent had no influence on the inhibitory activity of ChEs compared to the corresponding unsubstituted hybrid. The evaluation of the antioxidant activity was carried out by using oxygen radical absorbance capacity by fluorescence (ORAC-FL) method [284]. Melatonin, an endogenous neurohormone with strong antioxidant properties [285], was tested as reference (2.34 trolox eq.), and compound **62** exhibited a comparable activity. Compound **63,** with an extra double bond within the spacer of both moieties, showed the most potent antioxidant activity. Furthermore, derivatives bearing such 5-methoxy group displayed enhanced activity respect to the unsubstituted one. A kinetic study was performed for compound **63**. In AChE, the Lineweaver-Burk plots indicated a mixed-type inhibition, which suggested that compound **63** could be able to interact with CAS and PAS of AChE. A different behavior was obtained for BuChE, showing different K_m and V_{max} at different concentrations; in this case, compound **63** might act as a competitive inhibitor of the BuChE isozymes. Cell viability and neuroprotection studies were assayed in the human neuroblastoma cell line SH-SY5Y. MTT assay was used to examine the potential cytotoxic effects with no toxicity displayed for **62** and **63** at the range of concentrations studied (1-50 μM). Furthermore, both compounds were tested for their capacity to protect human SH-SY5Y cells against oxidative stress-associated death induced by H_2O_2. Compounds **62** and **63** showed neuroprotective effects at concentrations ranging from 1 to 10 μM. While compound **62** showed higher protective capability in comparison with the reference melatonin (at 10 μM).

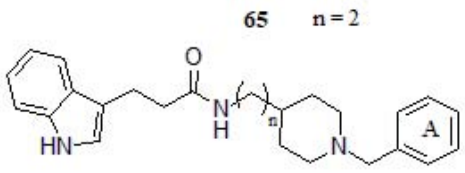
In addition to the aforementioned, another target that could play significant roles in the pathophysiology of the neurological diseases correspond to monoamine oxidase inhibitors (IMAOs). MAO is the enzyme that catalyzes the oxidative deamination of a variety of biogenic and xenobiotic amines [286], due to alterations in other neurotransmitter systems, especially serotoninergic and dopaminergic, which are also thought to be related to many behavioral disturbances observed in AD patients [287]. In this line, Bautista-Aguilera *et al.* [288] described the synthesis and pharmacological evaluation of novel hybrids designed through a combination of the previously reported [287] *N*-[(5-benzyloxy-1-methyl-1*H*-indol-2-yl)methyl]-*N*-methylprop-2-yn-1-amine and 1-benzylpiperidine, fragment present in DPZ (Fig. **30**). Among the synthesized hybrids, the most promising derivative exhibited potent and moderated values as both MAOs enzymes and ChEs inhibitors, respectively. Compound **64** resulted to be the stronger MAO-A and MAO-B inhibitor compared to DPZ (MAO-A IC_{50} = 850 μM; MAO-B IC_{50} = 15 μM) and as well as and BuChE inhibitor in relation to the same reference (*Ee*AChE IC_{50}: 0.013 μM; *eq*BuChE IC_{50}: 0.84 μM). The resulting pharmacological evaluation indicated the 1-benzylpiperidin-4-yl unit plays a key role in the AChE inhibitory activity, suggesting that this moiety mediates the binding to the enzyme. According to the design, the results showed that the linker length did not seem to be a decisive factor for the inhibitory potency against ChEs, whereas it seems to have a relevant effect in MAOs. Otherwise, the replacement of piperidine for bioisostere piperazine had a drastic reduction in the inhibitory activity, resulting in inactive compounds for ChEs (data not shown). A number of dual binding site AChE inhibitors have been found to exhibit a significant inhibitory activity on A*β* self-aggregation, thus compound **64** exhibits a significant inhibitory effect of A*β*-self-induced aggregation and hu-

man AChE-dependent aggregation, being more potent (human AChE-dependent) than the parent compound DPZ. The inhibition values of Aβ inhibition for compound **64** were 47.8% self-induced and 32.4% AChE-induced. This behavior may be explained through the kinetic study that exhibited a mixed-type inhibition. Molecular modeling suggests that **64** mimics the binding mode of DPZ in the crystal structure of AChE.

Several studies have documented the key activity of melatonin in scavenging a variety of reactive oxygen species, and moderate inhibition of Aβ aggregation affecting the synthesis and maturation of APP [289], which play an important role in AD. In this line, Wang *et al*. [290] described the synthesis and biological evaluation of donepezil-melatonin derivatives (Fig. **31**), focused on taking advantage of the potential neurogenic profile of melatonin-based hybrids, which are endowed with additional anticholinergic properties. The activity of compound **65** against *Ee*AChE showed a significant inhibitory profile, higher than tacrine (IC_{50} = 0.23 μM), although lower than DPZ (IC_{50} = 0.04 μM). Furthermore **65** showed a strong *eq*BuChE inhibition respect to donepezil (IC_{50} = 3.36 μM) and similar to tacrine (IC_{50} = 0.05 μM). According to the mentioned results, a modification in the indole ring with a methoxyl group showed a higher inhibitory potency than the compound without substituent (data not shown). Besides, the effect of the alkyl linker length influences the observed activities (*n* in (Fig. **30**). Kinetic analysis and molecular modeling studies revealed that compound **65** acted as a mixed-type AChE inhibitor, binding simultaneous CAS and PAS of the enzyme. The inhibition of $A\beta_{1\text{-}42}$ self-aggregation of **65** was improved respect to curcumin (45.2% at 20 μM) and resveratrol (43.5% at 20 μM). For the remaining compounds (not considered in this discussion), the effect of an electron-donating group at the benzene ring (A) might not be favorable for $A\beta_{1\text{-}42}$ aggregation inhibition. Likewise, compound **65** exhibited significant antioxidant activity by ORAC assay respect to melatonin (2.3 trolox eq.), it may chelate metal ions, reduce oxygen stress induced PC12 cell death, and penetrate the BBB.

Several studies reported that Phosphodiesterase's (PDE) inhibitors, such as sildenafil [291], tadalafil [292], and icariin [293], also displayed potent anti-AD effects in different mouse models of AD, significantly reversing cognitive impairment and improving learning and memory [294]. To illustrate this, Puzzo *et al*. [295] reported that sildenafil was beneficial against a mouse model of amyloid deposition, given that it produced amelioration of synaptic function and memory associated with a reduction of Aβ levels. In 2012, García-Osta *et al*. [296] revised Phosphodiesterase 5 (PDE5) inhibitors properties, and could act via anti-amyloid mechanisms, exhibit good BBB penetration, decrease p-Tau levels, shed light in their pharmacokinetics, safety and efficacy *in vivo* in animal models, but highlighted the lack of clinical trials in AD patients. Furthermore, Fiorito and coworkers [297] proposed PDE5 inhibitors as promising therapeutic agents for the treatment of AD. They synthesized quinoline derivatives with prominent outcomes in PDE5 inhibition and promising result in an *in vivo* mouse model of AD. In addition, Prickaerts *et al*. [298] carried out a study of rats in the object recognition task, suggested that PDE5 inhibitors improve processes of consolidation of object information, while AChE inhibitors improve processes of consolidation of object information. Therefore, AChE/PDE5 dual inhibitors could play a synergistic anti-AD effect and may supply a new perspective and breakthrough for the treatment of AD [294].

According to the aforementioned information, Mao *et al.* [294] described a series of novel tadalafil derivatives in order to seek dual-target AChE/PDE5 inhibitors as candidate drugs for potential AD therapy. The design of such derivates was based in PDE5 inhibitory activity presented in the tadalafil scaffold, by only varying the different substituent attached at the *N*-atom of piperazine-2,5-dione, incorporating different moieties such as morpholine, benzylpyridine, dimethylamine, benzylamine, and benzylpiperidine derivates. These results showed that the substituents in the R^1 group (Fig. **32**) and absolute configuration (R, R) remarkably affected the AChE inhibitory activities. Compounds **66** and **67** exhibited the strongest AChE inhibitory values, with nanomolar IC_{50} values. The results showed that the chain length (n= 2) between both moieties, tadalafil, and 1-benzylpiperidine, played a pivotal role in the AChE activities, so the optimal chain length was established as two methylenes (n = 2). Furthermore, the influence of stereochemistry on AChE inhibition was considered a key factor. The diastereoisomers **66** and **67** showed almost the same AChE inhibitory activity, comparable in potency to DPZ and huperzine A (IC_{50} = 0.013 μM and IC_{50} = 0.084 μM, respectively). However, both derivatives exhibited weak BuChE inhibitory activity. PDE5 inhibitory activity was determined by an IMAP-FP (immobilized metal ion affinity-based fluorescence polarization) assay [299, 300].



*Ee*AChE IC_{50} = 0.19 μM
*eq*BuChE IC_{50} = 0.07 μM
$A\beta_{agg.\ inh.}$ = 56.3 %
ORAC = 3.28 Trolox eq.
*h*AChE IC_{50} = 0.27 μM
*h*BuChE IC_{50} = 4.76 μM

Fig. (31). Donepezil-melatonin derivatives reported by Wang *et al.*

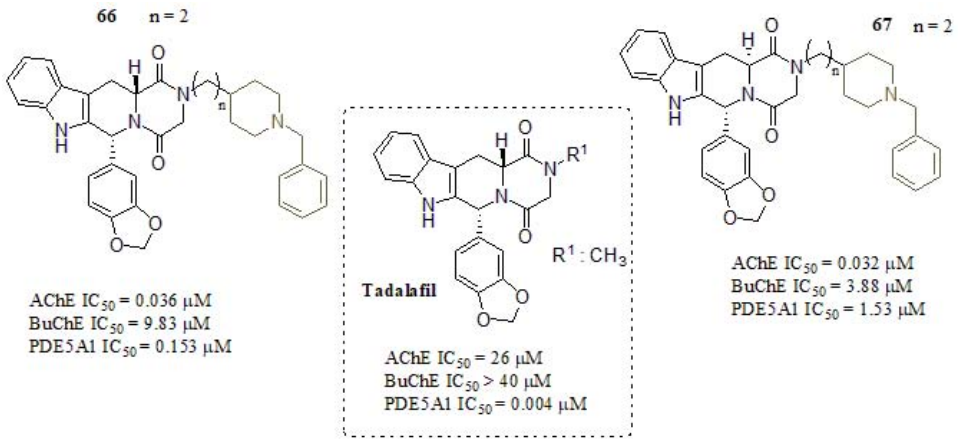


Fig. (32). Tadalafil derivates as AChE/PDE5 dual inhibitors.

The results showed that most of the tested compounds presented values ranging between 0.032 - 23.20 μM. In this context, the chain length presented no obvious influence on PDE5 type PDE5A1 inhibition. Moreover, compounds bearing aryl methyl and pyridyl substituents at piperidine nitrogen exhibited higher inhibitory activity than unsubstituted ones. Finally, **66** and **67**, exhibited good to moderate PDE5A1 inhibitory activity respect to the other derivatives studied. Besides, the BBB crossing capabilities, 7.67 and 9.25 Pe (10^{-6} cm s^{-1}) respectively, indicated that both compounds could be considered as potential dual-target AChE/PDE5 inhibitors.

The serotonergic system has been widely studied and well documented related to AD progression [301]. The modulation of 5-HT_4 and 5-HT_6 receptors have been recently proved to enhance cognition in AD models [302]. 5-HT_4 receptors (5-HT_4R) control brain functions, such as learning, memory, feeding, and mood behavior. In the AD context, activation of 5-HT_4R can promote the nonamyloidogenic cleavage (APP), leading to the formation of a neurotrophic protein, sAPPa [303-305]. On the other hand, 5-HT_6 receptors (5-HT_6R) play a role in functions like motor control, cognition, and memory [302].

A new proposal for combining $5HT_4$ affinity along with nanomolar AChE inhibition was reported by Lecoutey *et al.* [105] in 2014 with the design and synthesis of *donecopride* (Fig. **33**). RS67333 [306] is a potent $5HT_4$ antagonist that had been investigated as a potential antidepressant [307], nootropic [308], and as a potential treatment of AD [308]. Interestingly, RS67333 was also established as a low micromolar AChE inhibitor by the aforementioned authors [105]. This finding led them to pharmacomodulate it in order to enhance AChE inhibition profile with no significant effect on $5HT_4$ antagonism, while micromolar BuChE inhibition was also achieved (AChE IC_{50} = 16.0 nM; BuChE IC_{50} = 3.5 μM; $5HT_4$*Ki* = 6.6 nM). Moreover, sAPPα increasing capabilities of *donecopride* were also demonstrated (EC_{50} = 11.3 nM) [105]. According to the authors, donecopride is able to exert not only a symptomatic effect but also a disease-modifying effect against AD. Among a wide number of tested molecules [309], donecopride was selected for studies *in vivo*, showing no effect on the spontaneous locomotor activity at the maximum dose of 10 mg/kg. At 0.3 and 1 mg/kg a precognitive effect with an improvement in memory performances was observed, along with an antiamnesic effect by scopolamine-induced spontaneous alternation deficit. Moreover, they also suggested a slight antidepressant effect by a decreased time of immobility during a forced swimming test. Later on, donecopride was found to display potent anti-amnesic properties in AD animal models, preserving learning capabilities, including working and long-term spatial memories. Clinical trials will soon be undertaken to confirm these findings in a First in Human study [310].

Lalut *et al*. [305] designed a series of derivatives based on donecopride fine-tuning [105, 311] (Fig. **34**). By replacing the benzene ring by an indole residue, they obtained MTDLs with enhanced biological activities. Compounds **68**, **69**, **70**, and **71** were evaluated in their capacity to inhibit *h*AChE and to bind guinea pig (*gp*)5-HT_4R. All compounds displayed a decreased affinity for 5-HT_4R respect to donecopride (*Ki* = 9.5 nM) being **71,** which showed the strongest inhibitory profile. The SAR analysis revealed that a cycloalkyl or an alkyl substituent on the piperidine ring improved the affinity for this receptor compared to N-benzyl ring. Besides, substituents (chloro and methoxy) present in the indole moiety, did not significantly influence the activity. For AChE inhibition compounds **69**, **70**, and **71** displayed low IC_{50} values, in the same order of donecopride (IC_{50} = 16 nM) and DPZ (IC_{50} = 6.0 nM). In this case, N-Bn substituent greatly increased AChE inhibition in relation to a cycloalkyl or alkyl substituents. While substitution pattern or nature at the indole moiety seems to have little influence on activity, N-substituents can dramatically decrease it. Concerning kinetic studies, compounds showed non – competitive inhibitions type, therefore interacting with PAS and anionic subsite of AChE. Finally, compound **69** displayed a protective effect against dizocilpine-induced impairment in the passive avoidance test in mice [312, 313].

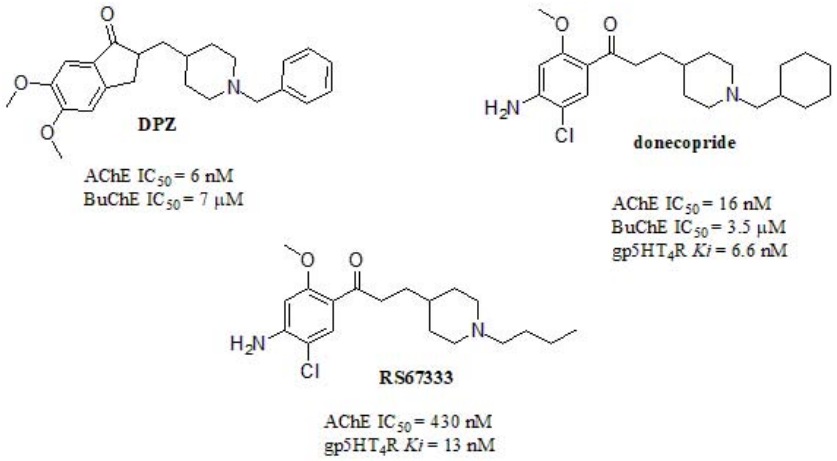


Fig. (33). Donecopride, RS67333 and donepezil hybrid designed by Lecoutey *et al*.

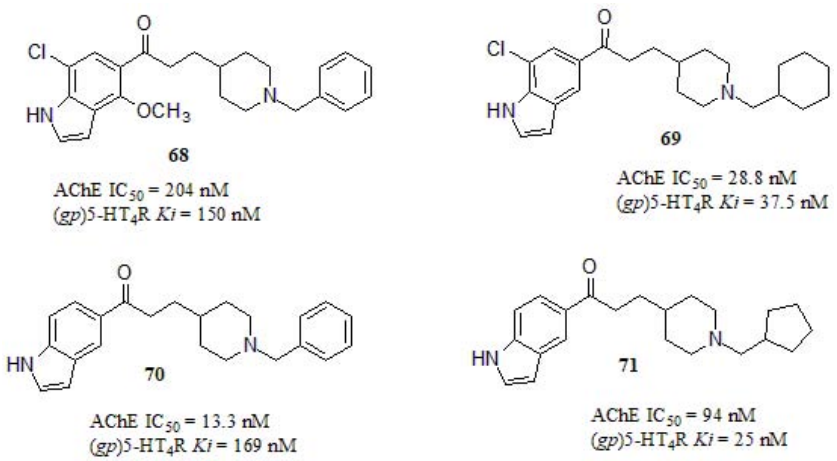


Fig. (34). Donecopride derivates as MTDL reported by Lalut *et al*.

Previous studies reported that C5-Substituted indole compounds containing a propyl spacer connected to different moieties such as piperazines and arylpiperazines, were endowed with serotoninergic activity [314-316]. Likewise, other studies have also reported AChE inhibitory activity in compounds containing these skeletons [104, 234, 317, 318]. Intending to combine such discoveries, Rodriguez-Lavado *et al*. [104] recently reported the synthesis, and *in vitro* evaluation of a new series of indolylpropyl benzamidopiperazines as promising MTDLs with dual activity against *h*SERT and *h*AChE (Fig. **35**). Compounds **73** and **74** displayed an inhibitory profile in AChE in the same order of magnitude as DPZ (IC_{50} = 2.17 nM). The substituents R_1 and R_2 remarkably affected the inhibitory profile in AChE. In this sense: *i*) the unsubstituted compound ($R_1 = R_2$ = H) showed no inhibitory response; *ii*) almost all compounds with a methoxyl group at the 5-indolic position were inactive; *iii*) R_1 = F or H resulted in a moderate to very active compounds depending on R_2 substituent, as in the case of compounds **73** and **74**. The authors thus explained how the appropriate substitution pattern can make a difference between inactive and very active compounds. On the other hand, compounds **72** and **75** showed a high affinity towards SERT, similar to citalopram (IC_{50} = 3.0 nM), both of them carrying R_1 = F (a small and electron-withdraw atom) and R_2 = 2-Br or 4-Br (bulky atom).

As expected, C5-Fluorine indole derivatives displayed nanomolar SERT affinity, being this an extensively reported property of fluorinated indoles [315, 319-321]. Interestingly, such fluorinated derivatives were also among the most active towards *h*AChE. None of the most active dual compounds resulted to be toxic at the studied concentration range in both HEK-293 and SH-5YSY cells. Molecular docking studies for both targets strongly supported the experimental results. Unfortunately, just one compound of the series resulted in significant *β*-amyloid self-aggregation inhibition (data not shown).

For clarity purposes, activities for some selected compounds endowed with promising multitarget capabilities are summarized in Table (**1**).

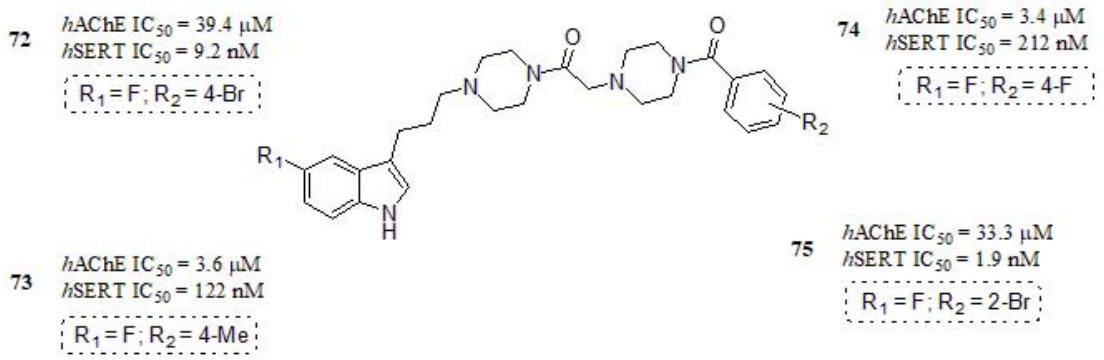


Fig. (35). Indolylpropyl benzamidopiperazines derivates with AChE and SERT activities reported by Rodríguez-Lavado *et al.*

Table 1. *In Vitro* Values for Selected MTDLs.

Comp.	AChE IC_{50} (µM)	BuChE IC_{50} (µM)	MAO-A IC_{50} (µM)	MAO-B IC_{50} (µM)	ORAC (Trolox Equivalent)	Other Activity	Refs.
1	0.187	12.4	*n.d.*	*n.d.*	3.07	A$\beta_{self\ agg.}$ 45.3%	[126]
2	0.228	9.78	*n.d.*	*n.d.*	2.49	A$\beta_{self\ agg.}$ 30.4%	[126]
3	0.149	2.33	*n.d.*	*n.d.*	1.10	A$\beta_{self\ agg.}$ 22.0%	[126]
21	0.09	0.16	*n.d.*	*n.d.*	0.4	*n.d.*	[152]
22	0.29	1.5	*n.d.*	*n.d.*	2.0	*n.d.*	[152]
23	0.08	0.22	*n.d.*	*n.d.*	2.4	*n.d.*	[152]
24	0.46[a]	24.97[b]	*n.d.*	*n.d.*	*n.d.*	DPPH EC_{50} = 49.41 µM	[153]
27	11.70	26.38	90.35	40.29	*n.d.*	A$\beta_{self\ agg}$ 49.8%	[178]
28	1.56	3.64	89.65	58.31	*n.d.*	A$\beta_{self\ agg}$ 53.5%	[178]
29	6.55	8.04	17.58	12.19	*n.d.*	A$\beta_{self\ agg}$ 57.8%	[178]
30	36.04	*n.d.*	8.19	12.16	4.72	Aβ IC_{50} = 7.56µM	[181]
31	6.27	*n.d.*	7.08	14.09	4.70	Aβ IC_{50} = 6.51µM	[181]
46	2.11[a]	16.7	12.8[c]	12.4	2.56	*n.d.*	[201]
47	37.09[a]	*n.a.*	16.0[c]	2.68	1.99	*n.d.*	[201]
48	1.56[a]	8.9	21.3[c]	14.01	1.76	*n.d.*	[201]
49	0.033[a]	0.45[b]	72.4[c]	11.23	*n.d.*	*n.d.*	[238]
50	0.37[a]	5.24[b]	67.2[c]	0.272	*n.d.*	*n.d.*	[238]
51	1.73 0.48[a]	1.19×10^{-2} 4.34×10^{-2}[b]	2.78	21.29	3.04	*n.d.*	[239]
62	1.30	0.08	*n.d.*	*n.d.*	2.04	*n.d.*	[283]
63	0.11	1.1	*n.d.*	*n.d.*	3.41	*n.d.*	[283]
64	0.19[a]	0.83[b]	5.5×10^{-3}	150×10^{-3}	*n.d.*	*n.d.*	[288]
65	0.19[a] 0.27	0.07[b] 4.76	*n.d.*	*n.d.*	3.28	A$\beta_{self\ agg}$ 56.3%	[290]
66	0.036	9.83	*n.d.*	*n.d.*	*n.d.*	PDE5A1 IC_{50} = 0.15 µM	[294]
67	0.032	3.88	*n.d.*	*n.d.*	*n.d.*	PDE5A1 IC_{50} = 1.53 µM	[294]

n.d.: non determined, *n.a.*: not active, [a]. *Electrophorus electricus Ee,* [b]. *equine,* [c]. MAO-A inhibition %.

CONCLUSION

AD is still an incurable disorder mainly due to its multifactorial nature and complex etiology. The more efforts are made by research groups and pharmaceutical companies to understand the underlying mechanism and find a disease-modifying treatment, the more AD-related targets are discovered. Therefore, there is no reason we can expect a solution provided by the 'one drug-one target' paradigm. Within the last years, the so-called multitarget paradigm has emerged to stay. In order to shed some light on the recent advances within this field, four biologically active scaffolds (curcumin-, resveratrol- chromone- and indole-) have been selected pointing to the simultaneous interaction towards many AD-related targets/functions, emphasizing on cholinesterases (AChE and BuChE), MAOs (MAO-A/B), 5-HT_4, SERT, β-amyloid self-aggregation and radical scavenging activity. While many of them are well known AD-related targets, others have not still been so deeply explored. We sincerely hope that this review will help other researchers worldwide to develop future improvements within this exciting field since much more efforts are needed to make this multitarget approach evolve into new drugs that can eventually be used in clinical trials and finally reach the market for the overcoming of such devastating disease.

LIST OF ABBREVIATIONS

WHO	=	World Health Organization
AD	=	Alzheimer's Disease
CNS	=	Central Nervous System
NMDA	=	N-methyl-D-aspartate
MTDL	=	Multi-target Directed Ligands
ACh	=	Acetylcholine
ChAT	=	Choline Acetyltransferase
AChE	=	Acetylcholinesterase
Aβ	=	Amyloid beta
APP	=	Amyloid Precursor Protein
NFTs	=	Neurofibrillary Tangles
MAO	=	Monoamine Oxidase
SRRIs	=	Serotonin Reuptake Inhibitors
5-HT_4R	=	5-HT_4R 5-HT_4 Receptor
BBB	=	Blood-brain Barrier
BuChE	=	Butyrylcholinesterase
DPZ	=	Donepezil
ORAC	=	Oxygen Radical Absorbance Capacity Assay
HEWL	=	Hen Egg White Lysozyme
IL-6	=	Interleukin-6
TEM	=	Transmission Electron Microscopy
ABTS	=	[2,20-Azinobis-(3-Ethylbenzothiazoline-6-sulfonic Acid)]
CAS	=	Catalytic Active Site
PAS	=	Peripheral Anionic Site
SIRT1	=	Silent Information Regulator 1
ROS	=	Reactive Oxygen Species
NO	=	Nitric Oxide
DPPH	=	2,2-Diphenyl-1-Picrylhydrazyl
FRAP	=	Ferric ion Reducing Antioxidant Power
*Ee*AChE	=	*Electrophorus Electricus* AChE
ChEs	=	Cholinesterases
*eq*BuChE	=	Equine BuChE
MCR	=	Multicomponent Reaction
AGEs	=	Advanced Glycation End Products
SAR	=	Structure-Activity Relationship
NSAID	=	Indomethacin
PDE	=	Phosphodiesterase's
PDE5	=	Phosphodiesterase 5
IMAP-FP	=	Immobilized Metal ion Affinity-based Fluorescence Polarization
GP	=	Guinea Pig.

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

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CONFLICT OF INTEREST

The authors have no conflicts of interest, financial or otherwise.

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