Review Article

Ensuing New Derivatives in Developing Therapeutics for Alzheimer's Disease - A Review

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ABSTRACT

Alzheimer's disease (AD) is a tardily progressive disease of CNS, generally affecting older individuals and is the most common cause of dementia. The disease process is related with senile plaques and neurofibrillary tangles in the brain. In AD, the brain cells deteriorate and die inducing an even decline in memory and mental function. Despite of the established drugs for AD, scientists have been working on various moieties to produce multitarget-directed ligands. The review brings out the various active moieties and their derivatives against AD.

Keywords: Alzheimer's disease, AChE, BuChE, Multi-target, Metal-chelating, Aβ-aggregation.

INTRODUCTION

Alzheimer's disease (AD) is a neurodegenerative ailment of central nervous system with an intricate etiology. Therefore, the drug invention path is visualized to identify new agents when currently available single target drugs are unsuccessful.[1] AD is clinically outlined by memory impairment and progressive deficits in different cognitive slots related to the pronounced degradation of the cholinergic system accompanied by alterations in the glutamatergic and serotonergic systems. The number of accepted drugs is limited to only three acetyl cholinesterase (AChE) inhibitors,[2] the moderately active drugs rivastigmine, donepezil and galantamine and the *N*-methyl-D-aspartate receptor (NMDA) antagonist memantine Figure 1(a). Thus, a new concept of multitarget-directed ligands (MTDLs) design strategy has been developed. Here in a single molecule is combined with two or more molecules, possessing more than one pharmacological actions *i.e.* multitarget action, like antioxidant properties which are able to act at different targets in the neurodegenerative system, can acquire greater efficacy as compared to single-targeted drugs for examining AD.[3]

Scientists have been working extensively on MTDLs which can be achieved by developing hybrids of previously established drugs. This approach provides a great positive response in treatment of this disease. The article covers some of the active moieties and their derivatives with anti-Alzheimer's activity.

Diversity of Derivatives Used for Treatment

There are a number of moieties used for the development of drug candidates with activity against this disease. Recent development concerning these moieties is mentioned below.

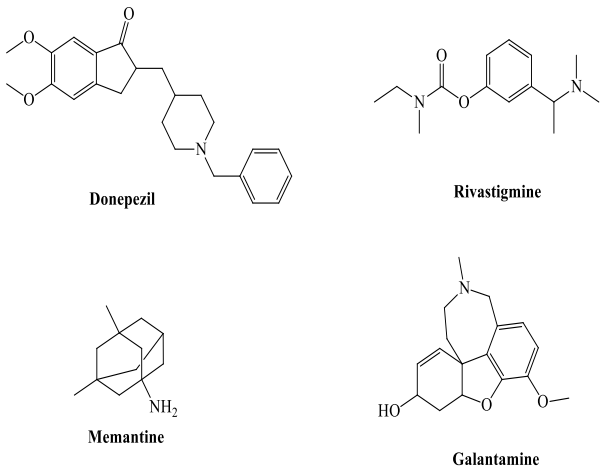


Figure 1 (a): Accepted drugs for Alzheimer's disease

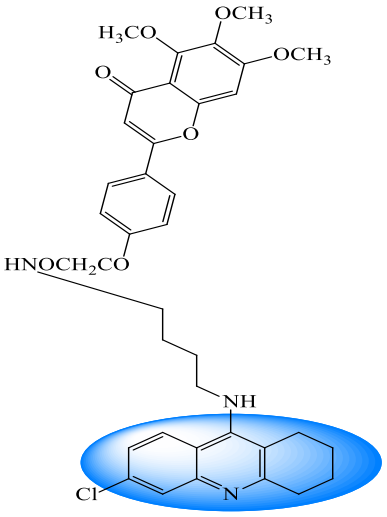
Tacrine Derivatives

Tacrine has been extensively used in recent research to establish hybrids or multi-target agents to produce other pharmacological actions with addition to its action on cholinesterase inhibition. This can be achieved by combining tacrine with other moieties.[2] Variety of new derivatives of tacrine have been synthesized, some of them have been shown below in Figure 1 (b). Liao *et al.* synthesized and assessed a series of 5,6,7-trimethoxyflavone-6-chlorotacrine compounds as multifunctional agents exhibiting inhibitory action on AChE, butyrylcholinesterase (BuChE) and amyloid-β (Aβ) aggregation, with antioxidant activities. Compound 1 showed high potency for treatment.[4] Another set of tacrine derivatives was designed and synthesized by combining caffeic acid (CA), ferulic acid (FA) and lipoic acid (LA) with tacrine by Digiacomo *et al.* Compound 2 was reported as an assuring lead ligand as AD

therapeutics.[5] Multifunctional agents were designed and synthesized by linking tacrine with trolox in a single molecule by Xie *et al. w*ith inhibitory action on cholinesterase and also possessing strong antioxidant action. Of all the compounds synthesized, compound 3 was established as the most promising lead.[6] Garcka-Font *et al.* synthesized and assessed 2-chloroquinolin-3-yl substituted pyrano tacrines (PTs) as multipotent tacrine analogues for AD. Amongst all the compounds, compound 4 and 5 showed high potency against AD. Hence, a new class of tacrine analogues, whose potent AChE inhibitory activity was combined with their Aβ-aggregating and tauphosphorylation inhibitory actions, were invented for the potential treatment of AD.[7] Twenty-six new tacrine-benzofuran hybrids were synthesized and assessed *in vitro* on key molecular targets for AD by Zha *et al.* Among the 26 compounds, compound 6 showed the most potent selective inhibitory activity on human AChE with half maximal inhibitory concentration (IC_{50}) of 0.86 µM and a good inhibitor of both β-amyloid aggregation (*h*AChE- and self-induced, 61.3% and 58.4%, respectively) and β-site amyloid precursor protein cleaving enzyme 1(BACE-1) activity.[8] Xie *et al.* designed, synthesized and evaluated a series of tacrine-coumarin compounds as multi-target agents for AD therapeutics. The compounds showed strong inhibition for AChE and BuChE and particular inhibition for monoamine oxidase B (MAO-B). Compound 7 was the most potent agent for treatment of AD.[9] Zhang *et al.* designed, synthesized and assessed a set of benzoates (or phenylacetates or cinnamates)-tacrine compounds as multi-target AD agents. Of all the compounds synthesized, compound 8 proved to be the most promising candidate for AD.[10] Khoobi *et al.* invented a series of tacrine-based AChE inhibitors by substituting the benzene ring of tacrine with aryl-dihydropyrano[2,3-*c*] pyrazole. Compound 9 possessing a 3,4-dimethoxyphenyl group was more active than reference drug tacrine.[11]

Coumarin Derivatives

Coumarins, also referred as benzopyran-2-ones, form an exclusive class of naturally occurring compounds with wide variety of actions. Various coumarin derivatives have profound anti-inflammatory, anti-HIV, anti-microbial, anti-viral, anti-Alzheimer's activities.[12] Some of the coumarin derivatives with anti-Alzheimer's activity are listed in Figure 1 (c). Ghanei-Nasab *et al.* synthesized and assessed a number of *N*-(2-(1*H*-indol-3-yl) ethyl)-2-oxo-2*H*-chromene-3-carboxamides against AChE and BuChE. The SAR study exhibited that the introduction of benzyloxy moiety on the 7-position of coumarin scaffold led to an increase the anti-AChE activity. Various amongst the different developed compounds, compound 10 showed the promising results with IC_{50} value of 0.16µM.[13] Sai-Sai *et al.* designed and synthesized donepezil coumarin hybrids by incorporating *N*-benzylpiperidine moiety of donepezil and coumarin into in a single molecule with AChE and MAO-B inhibitory activity. Of these compounds, compound 11 was the strongest inhibitor for *Electrophorus electricus* AChE (eeAChE) and equine BuChE (eqBuChE) (0.87µM and 0.93µM, respectively).[14]



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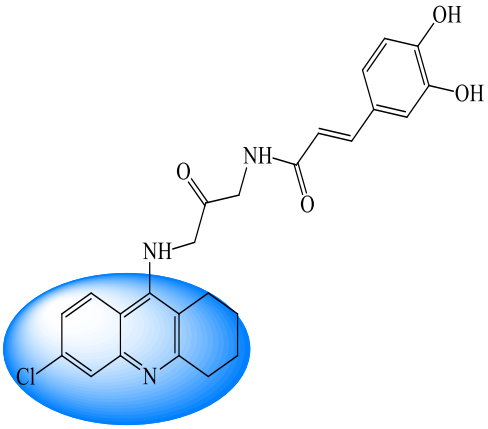

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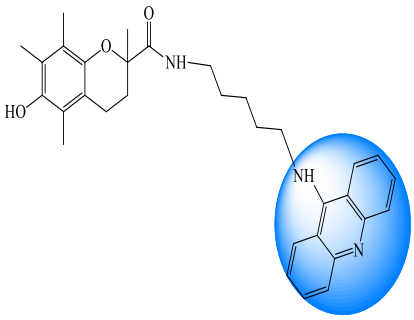

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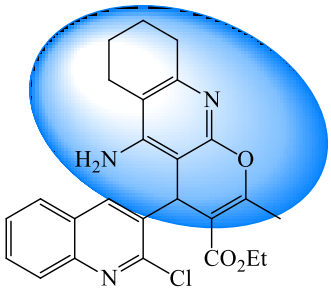

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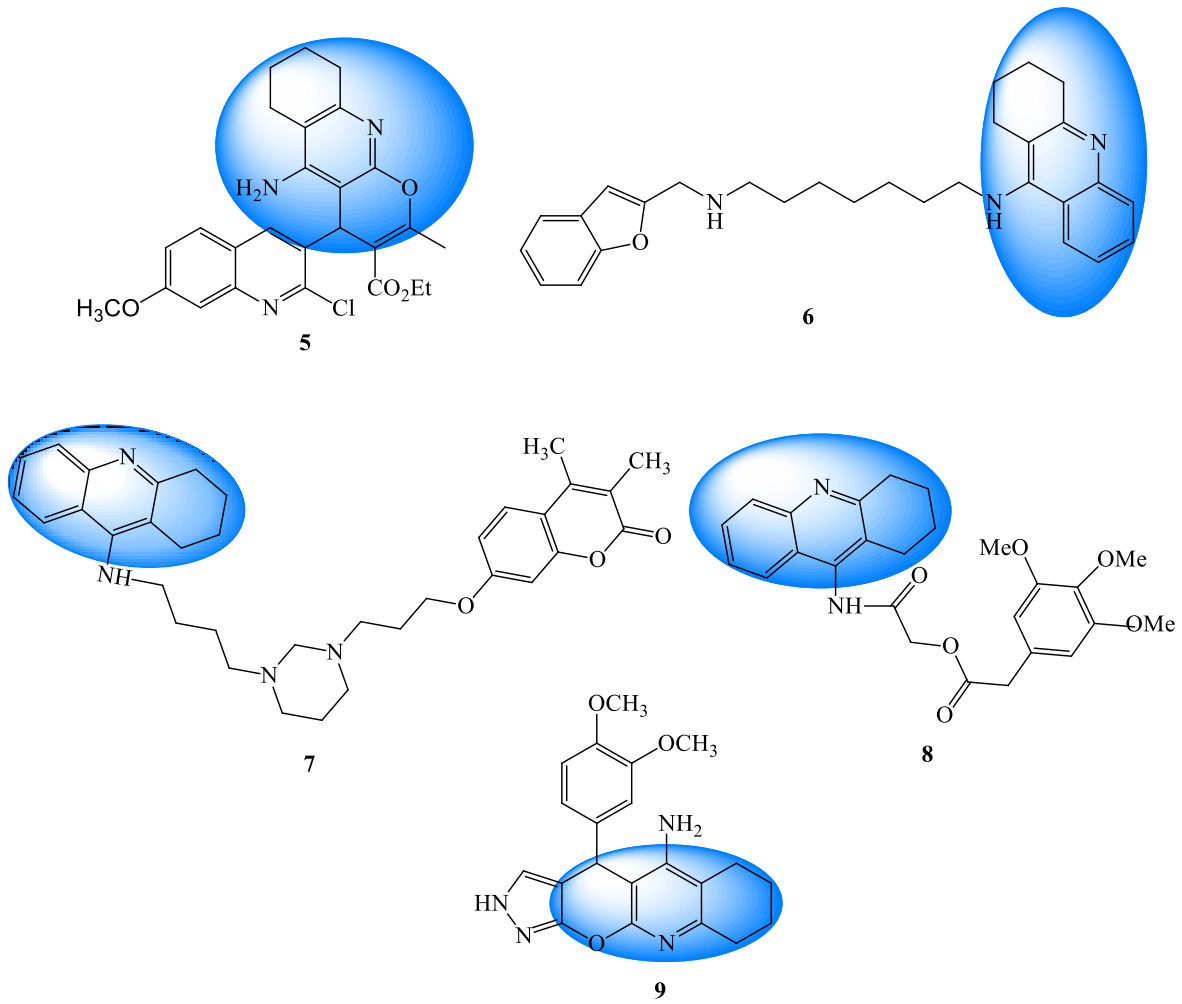


Figure 1 (b): Tacrine Derivatives with Anti-Alzheimer's Activity

A series of fused tricyclic coumarin derivatives were designed by Shaik *et al*. bearing iminopyran ring connected to various amido moieties as potential multifunctional anti-Alzheimer agents for their Compound 12 was found to be most active among them.[15] Huang *et al.* devised, synthesized and assessed multifunctional coumarin derivatives for treatment of AD. Among all the synthesized compounds, compound 13 cholinesterase inhibitory and radical scavenging property. was the most favourable agent for treatment of AD inhibition of MAO-B and $A\beta_{1-42}$ aggregation.[16]

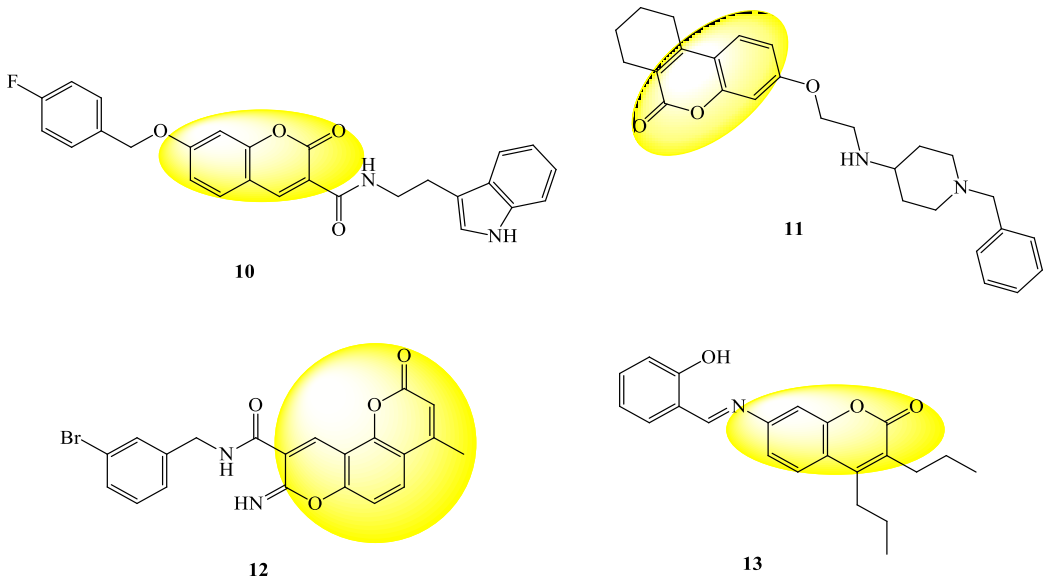


Figure 1 (c): Coumarin Derivatives with Anti-Alzheimer's Activity

Thiazole Derivatives

Thiazole, an important heterocyclic ring has drawn interest over the years because of its diverse pharmacological activities such as anti-convulsant, anti-inflammatory, anti-fungal, anti-bacterial and anti-Alzheimer.[17] A few thiazole derivatives with anti-Alzheimer's activity have been shown in Figure 2 (a). Kurt *et al.* synthesized and assessed a series of benzo-furanyl thiazole derivatives containing the aryl-urea moiety as AChE and BuChE inhibitors. Among all the synthesized compounds, 14 and 15 were most promising lead hybrids for treatment of AD.[18] A list of thiazole acetamides were synthesized by Sun *et al.* with AChE and BChE activity. Of all compounds synthesized, compound 16 was found to be the most promising molecule against AD.[19] Ghosh *et al.* devised, synthesized and evaluated β-secretase inhibitors containing a pyrazole or thiazole moiety. Of all the compounds synthesized, compound 17 was the most potent β-secretase inhibitor.[20]

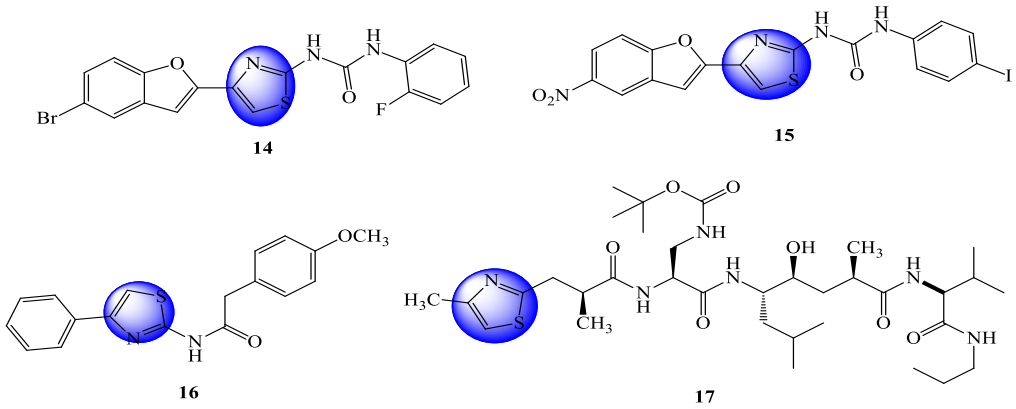


Figure 2 (a): Thiazole Derivatives with Anti-Alzheimer's Activity

Indole Derivatives

The indole nucleus is found in huge variety of natural and bioactive agents. It is recognized as an entitled scaffold for drug improvement.[21] Anti-Alzheimer's agents possessing indole nucleus have been shown in Figure 2 (b). Atanasova *et al.* synthesized and evaluated a series of galantamine derivatives with indole moiety with inhibitory action on Ach. Among the synthesized derivatives, compound 18 was the most excellent lead structure for treatment of AD.[22] Pettersson *et al.* designed and synthesized a series of indole-derived pyridopyrazine-1,6-dione ϒ-secretase modulators inhibiting presenilin. Among all the synthesized compounds, compound 19 showed pronounced action, for treatment of AD.[23] Fabritius *et al.* synthesized and defined a series of 1-sulfonyl-6-piperazinyl-7-azaindoles with strong antagonistic activity of 5-HT_6 receptor. Compound 20 was found to be most active among them.[24]

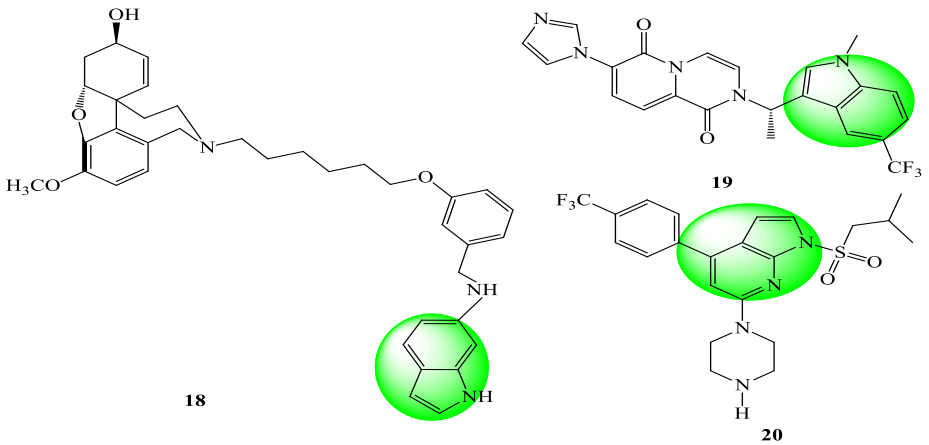


Figure 2 (b): Indole Derivatives with Anti-Alzheimer's Activity

Piperidine and Piperazine Derivatives

The piperidine nucleus plays a vital role in developing new derivatives with wide variety of activities. It has useful biological applications as anti-histaminic, anti-inflammatory, anticancer, anti-fungal, CNS stimulant and depressant activities.[25] They also showed profound activity in treatment of Alzheimer's disease, some of which are listed in Figure 2 (c). Wieckowska *et al.*

invented and synthesized 28 new derivatives of donepezil that possessing the *N*-benzylpiperidine moiety combined with phthalimide or indole nucleus. Compound 21, the most promising inhibitor of BuChE (IC_{50} = 0.72 µM) that has β-amyloid anti-aggregation activity (72.5% inhibition at 10 µM) and can cross the blood–brain barrier.[26] Takai *et al.* synthesized and assessed piperazine hybrids as ϒ-secretase inhibitors. The imidazolyl phenyl moiety of compound 22 was substituted with an oxazolyl phenyl moiety, which lead to development of most promising hybrid with selective $Aβ_{42}$ lowering action.[27] Meena *et al.* designed and synthesized a series of *N*-(4-benzylpiperidin-/piperazin-/benzhydrylpiperazin-1-yl) alkylamine derivatives with cholinesterases (ChEs), Aβ self-aggregation and also for their radical scavenging activity. Among all synthesized compounds, compound **23** was the most promising lead for developing AD therapeutics.[28]

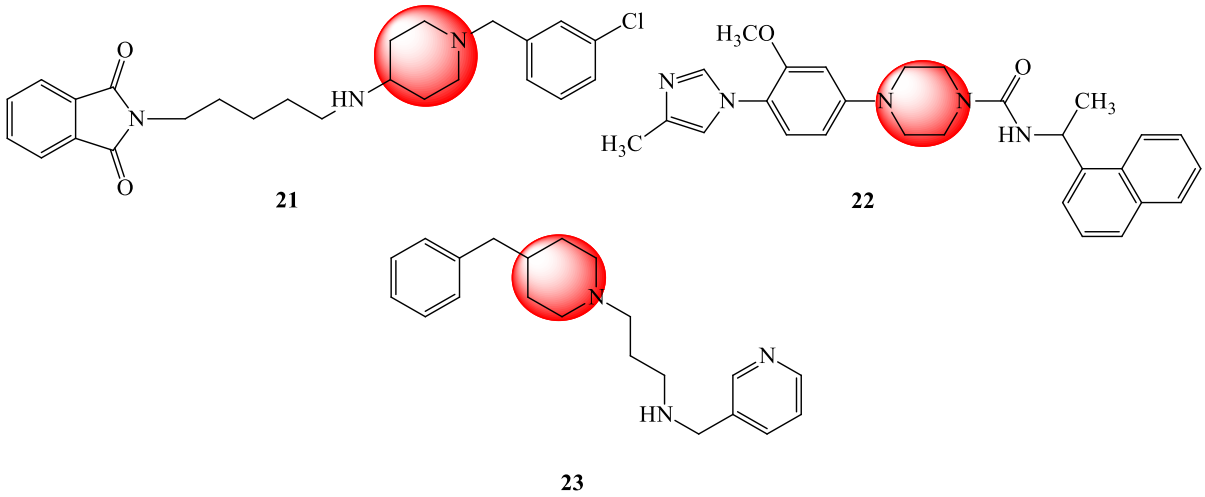


Figure 2 (c): Piperidine and Piperazine Derivatives with Anti-Alzheimer's Activity

Scutellarein Derivatives

Scutellarein is the main active ingredient of breviscapine (>85%), a clinic natural drug comprising of total flavonoids of *Erigeron breviscapus* (Vant.) Hand-Mazz. (Compositae), has been used for the treatment of cerebral infarction, coronary heart disease and angina pectoris.[29] They also constitute potential for Alzheimer's treatment. Some of the derivatives reported against AD are listed in Figure 3 (a). Sang *et al.* invented and synthesized scutellarein-*O*-alkylamine derivatives with multi target action on AD. Of all the synthesized derivatives, compound 24 was identified as a promising lead structure as anti-Alzheimer's agent having fair AchE inhibitory and anti-oxidant action, remarkable metal chelating properties and potent inhibitory effects on self-induced $Aβ_{1-42}$ aggregation, Cu^{2+}-induced $Aβ_{1-42}$ aggregation, human AChE-induced $Aβ_{1-40}$ aggregation and disassembled Cu^{2+}-induced aggregation of the well-organized $Aβ_{1-42}$ fibrils.[30] Sang *et al.* discovered and synthesized scutellarein-rivastigmine hybrids with multi-functional properties for treatment of AD. The study showed that compound 25 might be a promising lead for developing therapeutics for AD displayed dual inhibitory action on AchE and BuChE with IC_{50} values of 0.57 and 22.6µM, respectively, and satisfactory antioxidant activity, with a value 1.3-fold of Trolox. In addition to this compound showed neuroprotective and biometal chelating effects.[31]

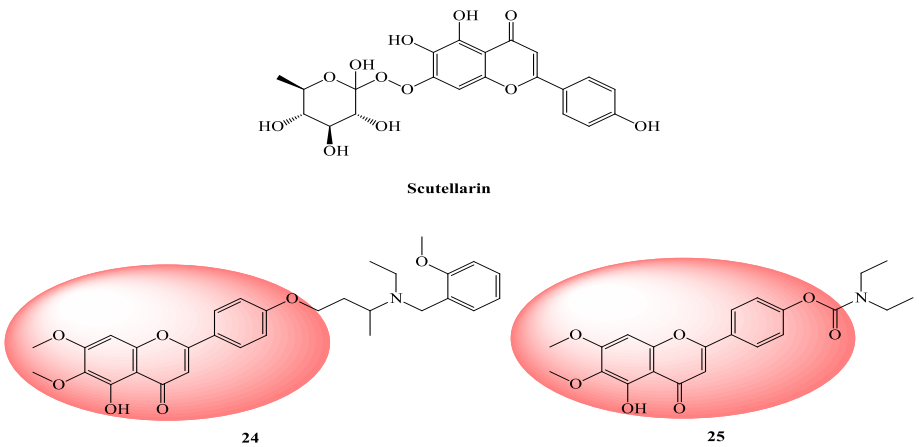
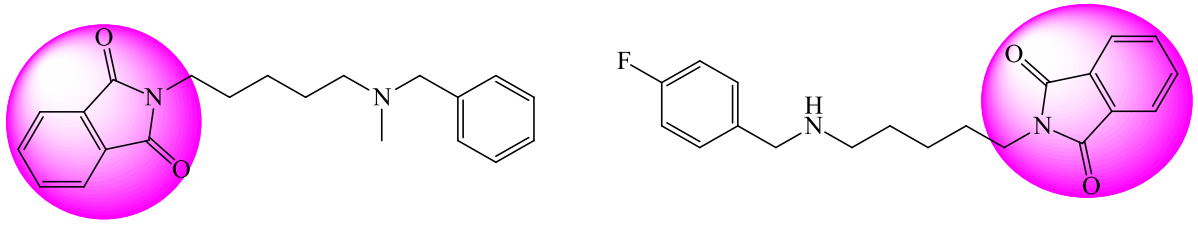


Figure 3 (a): Scutellarein Derivatives with Anti-Alzheimer's Activity

Isoindoline Derivatives

Isoindolines are heterocyclic compounds with biological activities such as anxiolytic, antipsychotic, anticonvulsive or anaesthetic. Some isoindolines possess nonsteroidal anti-inflammatory activity through selective cyclooxygenase-2 (COX-2) inhibition with IC_{50} varying from 0.1 to 1.0 µM and as antihypertensive drugs used in cardio-renal diseases.[32] List of derivatives with anti-Alzheimer's activity have been listed in Figure 3 (b). Guzior *et al.* synthesized isoindoline-1,3-dione derivatives possessing inhibitory action on AChE. Compound 26 was a potent lead structure for treatment of AD.[33] Isoindoline-1,3-dione derivatives with inhibitory action on AChE and β-amyloid aggregation were synthesized and assessed by Guzior *et al*. The study showed that the compound 27 was identified as the most active structure for treatment of AD.[34]

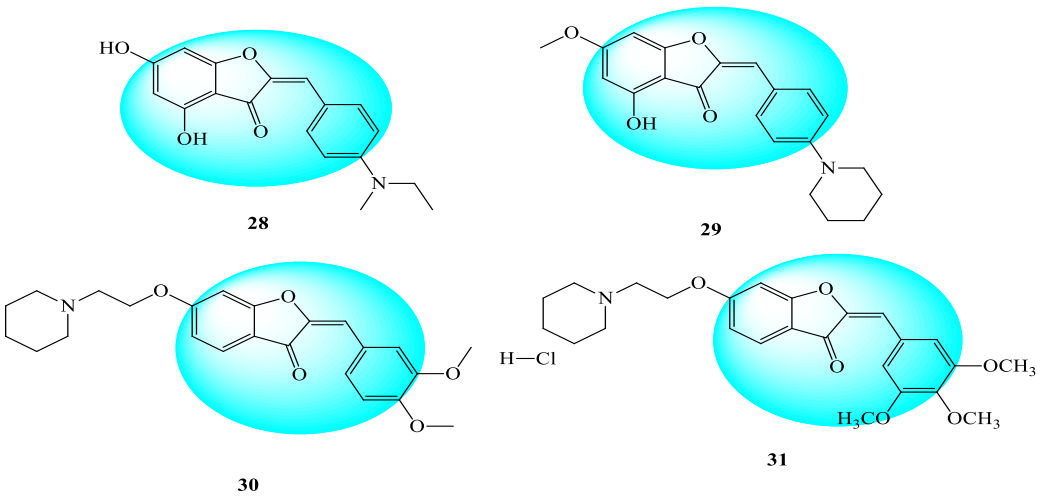


26 27

Figure 3 (b): Isoindoline Derivatives with Anti-Alzheimer's Activity

Aurone Derivatives

Aurones, (*Z*)-2-benzylidenebenzofuran-3-(2*H*)-ones are biosynthesized from chalcones by the chief enzyme aureusidin synthase and are important for the bright yellow color of some popular ornamental flowers. Natural and synthetic aurones have been shown so far to possess an extended spectrum of biological activities including anticancer, antioxidant, antiparasitic and neuroprotective.[35] Aurone derivatives also possess activity for treatment of AD, some of them are listed in Figure 3 (c). Li *et al.* devised, synthesized and assessed a series of 4-hydroxyl aurone derivatives with strong multifunctional action for treatment of AD. The compounds 28 and 29 showed good metal chelating potentiality and *in vitro* blood-brain barrier (BBB) permeabilities.[36] A set of aminoalkyl-substituted aurone derivatives were devised and synthesized by Lee *et al.* with inhibitory action on AChE. Among all synthesized derivatives, compound 30 showed higher potency than sulfuretin and galantamine.[37] Liew *et al.* designed and synthesized a series of aurones bearing amine and carbamate moieties possessing anticholinesterase inhibitory action. From all the synthesized derivatives, compound 31 emerged as the lead moiety for developing therapeutics for AD.[38]



28 29 30 31

Figure 3 (c): Aurone derivatives with anti-Alzheimer's activity

Benzofuran Derivatives

Benzofuran derivatives are functional biodynamic compounds that can be used to discover and develop useful therapeutic agents. They possess a wide variety of biological and pharmacological activities such as antimicrobial, antioxidant, anti-inflammatory, antifungal, anti-feedant, anti-HIV, anti-tumor and antiplatelet.[39] Along with the above activities they are also useful in treatment of Alzheimer's disease. Some of the

compounds are enlisted in Figure 4 (a). Mostofi *et al.* invented and synthesized a series of benzofuran-based chalconoids as potent AChE inhibitors. Of all the tested compounds, compound 32, which is a 3- pyridinium derivative bearing *N*-(2-bromobenzyl) moiety and 7-methoxy substituent on the benzofuran ring possessed superior activity with IC_{50} value of 0.027 µM.[40] Baharloo *et al.* designed and synthesized a series of benzofuran-based *N*-benzylpyridinium derivatives as AChE inhibitors. Compound 33, *N*-(3,5-dimethylbenzyl) derivative with IC_{50} value of 4.1 µM was the most potent compound among all the synthesized compounds.[41] Delogu *et al.* prepared and assessed a series of 2-phenylbenzofuran compound as cholinesterase inhibitors. Out of them, compound 34 possessed the highest BuChE inhibition with an IC_{50} value of 30.03 µM.[42]

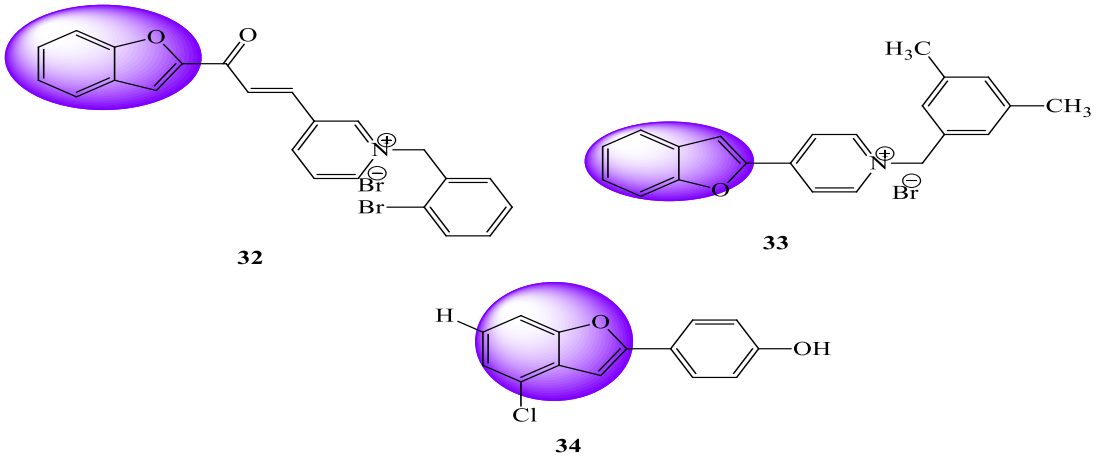


Figure 4 (a): Benzofuran Derivatives with Anti-Alzheimer's Activity

Donepezil like Compounds

Donepezil is an efficacious, selective, uncompetitive and reversible AChE inhibitor, acts by raising cholinergic function by increasing AChE levels in the CNS. However, the drug fails to treat the patients with moderate to severe Alzheimer's. Thus, various donepezil like compounds or donepezil hybrids are synthesized by combining it with different moieties.[43] Various donepezil compounds with anti-Alzheimer's activity have been listed in Figure 4 (b). Yerdelen *et al*. synthesized new donepezil-like secondary amide compounds that showed a potent inhibition of cholinesterases and Aβ with antioxidant and metal chelation activities. Based on the study, compound 35 was the most favourable structure in advanced research. [44] Wu *et al*. developed and evaluated a new series of donepezil-related compounds possessing metal chelating properties, capable of targeting different enzymatic systems related to AD (cholinesterases, and monoamine oxidase A). Among this set of compounds, compound 36 showed excellent ChEs inhibition and a selective MAO-A inhibition (MAO-B) coupled with strong complexing properties for zinc and copper ions, both known to be responsible in the progression of AD.[45] The synthesis of donepezil like-compounds for AChE and BACE-1 inhibition were designed by Costanzo *et al*., and in order to promote yields, regioselectively, and rate of each synthetic step and to minimize the coproduction of waste, different energy sources were used. Compounds 37 and 38 possessed promising dual inhibitory action for AD treatment.[46]

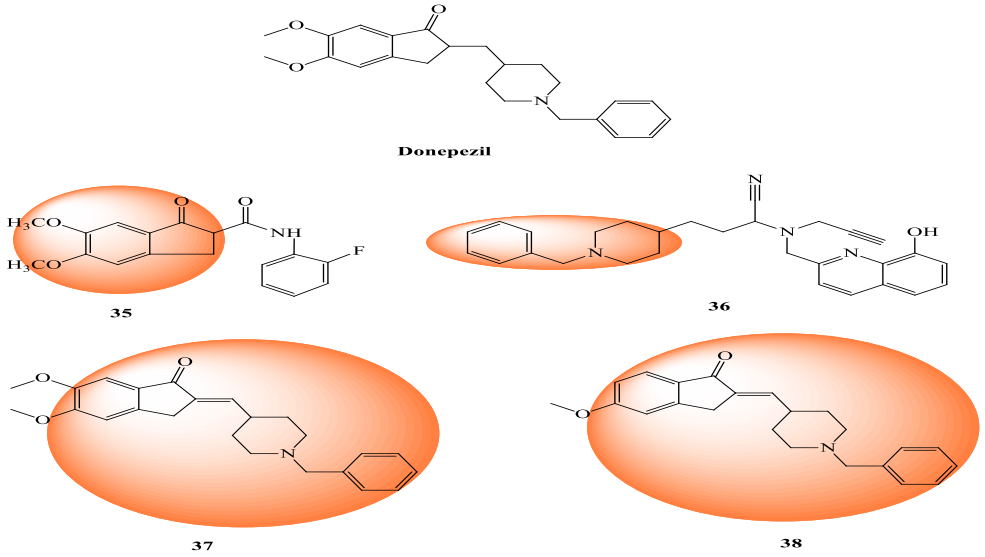
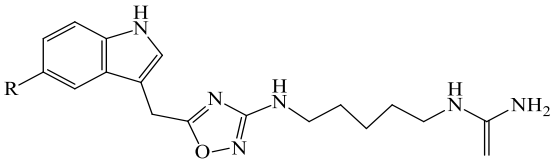


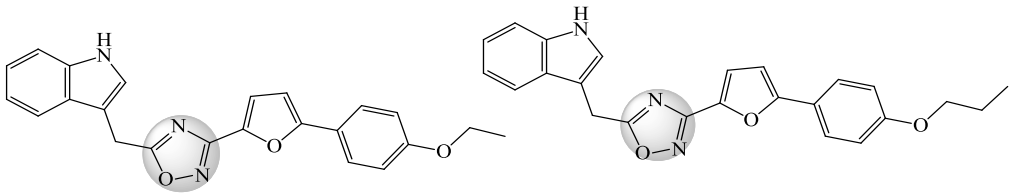
Figure 4 (b): Donepezil like Compounds with Anti-Alzheimer's Activity

Oxadiazole Derivatives

Oxadiazoles are important heterocyclic nucleus possessing two nitrogen atoms as isomeric forms. They have wide variety of biological activities such as antimicrobial, anti-inflammatory, anti-HIV, anti-parasitic, fungicidal, anticonvulsant, anti alfatoxigenic, as well as pyrophosphatases, phosphodiesterases and urease inhibitory properties.[47] Along with the above activities they are also active in treatment of AD. Oxadiazole derivatives with anti-Alzheimer's activity are enlisted in Figure 4 (c). Jiang *et al.* designed and synthesized naturally occurring marine derived compounds called Phidianidines, obtained from marine opisthobranch mollusk *Phidiana militaris* containing 1,2,4-oxadiazole moiety. Compounds 39 and 40 showed good activity among all the synthesized derivatives.[48]



R=Br phidianidine A
R=H phidianidine B



39 **40**

Figure 4 (c): Oxadiazole Derivatives with Anti-Alzheimer's Activity

Sulphonamide Derivatives

Sulphonamides are functional groups with immense importance. It is a constituent of various medicinal agents, dyes/pigments, polymers, and other structures.[49] The sulphonamide bearing moiety with anti-Alzheimer's activity are enlisted in Figure 5 (a). Bag *et al.* designed and synthesized a set of sulphonamide inhibitors as multi target agents AD, targeting Aβ self-assembly and cholinesterase inhibition and having free radical scavenging properties. The study showed that the compounds 43, 44 and 45 were the most favourable therapeutics for AD.[50]

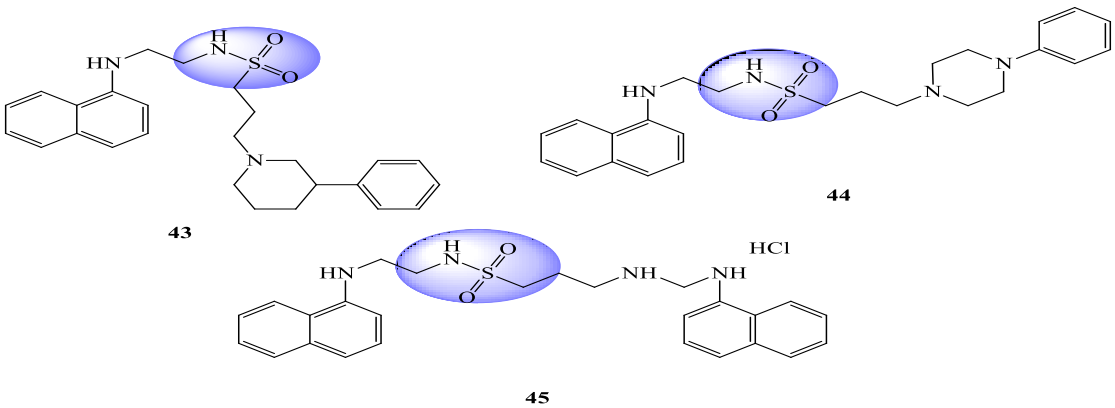


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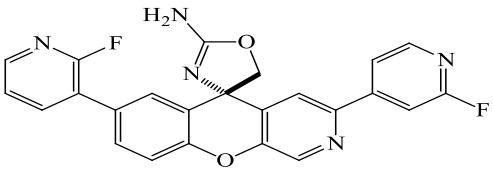
Figure 5 (a): Sulphonamide Derivatives with Anti-Alzheimer's Activity

Miscellaneous

Various miscellaneous agents with action on Alzheimer's disease have been illustrated in Figure 5 (b). Chen *et al.* developed and designed series of 2-aminooxazoline 3-azaxanthenes as β-secretase inhibitors, which convincingly reduced cerebrospinal fluid and brain Aβ levels in a rat pharmacodynamic model. Of all compounds synthesized, compound 46 possessed decreased potential for QT_c prolongation in non-human primate cardiovascular safety model.[51] Fischer *et al.* discovered and synthesized triazolobenzazepinones as ϒ-secretase modulators. These benzo-fused azepinone derivatives possessed inhibitory action on $Aβ_{42}$ aggregation. Compound 47 was the promising lead structure for treatment of AD.[52] Choi *et al.* invented and synthesized a series of 6-phenoxy-2-phenylbenzoxazole analogs as novel inhibitors of Receptor for advanced glycation end

products (RAGE). Moreover, recent studies suggest that the interactions between RAGE and Aβ peptides may be the convict behind AD. Inhibitors of the RAGE-Aβ interactions would prevent the accumulation of toxic Aβ in the brain, and progression of AD therefore, has the potential to provide a 'disease-modifying treatment'. Of all the compounds synthesized, compound 48 was the most promising lead for AD therapeutics.[53] Saxena *et al.* designed and synthesized a series of ethynylphenyl carbonates and carbamates with dual action on AChE and inflammation. Of all the derivatives synthesized, compound 49 was the most potent compound for AD.[54] Boy *et al.* invented, synthesized and assessed a list of acyl guanidines with inhibitory action on BACE. Compound 50 was the most potent lead from the list of derivatives.[55] Manral *et al.* invented and synthesized a list of diallyl disulphide (DADS) derivatives as multitarget agents possessing inhibition of cholinesterase (with more selectivity towards AChE than BuChE) and Aβ aggregation, antioxidant and metal chelating action. Compounds 51 and 52 showed most potent action against AD.[56] Knez *et al.* developed, synthesized and biologically evaluated a series of nitroxoline-based hybrids that were formed by combining the scaffold of 8-hydroxyquinoline with known selective BuChE inhibitor that has potent anti-Alzheimer activity. Compound 53 was the most potent lead for treatment of AD with inhibition of self-induced Aβ aggregation, BuChE inhibition and Cu^{2+} metal chelating action.[57] Wang *et al.* designed, synthesized and assessed a list of 2-arylethenylquinoline derivatives as potent multifunctional therapeutics for AD. Of all the compounds synthesized, compound 54 showed IC_{50} of 9.7 µM for self-induced $A\beta_{1-42}$ aggregation, antioxidant activity with a value of 3.9-fold of Trolox, potent inhibitory action for cholinesterase with IC_{50} of 0.2 µM (BuChE) and 64.1 µM (AchE). Thus, compound 51 might be a most favorable lead for AD treatment.[58] A list of selegiline derivatives with MAO inhibition and biometal chelation ability were invented and synthesized by Xie *et al.* The study showed that the compound 55 was the most promising agent against AD.[59] Liu *et al.* designed, synthesized and assessed naturally occurring marine product tasiamide B derivatives with blocking activity of BACE1. Among all synthesized compounds, compound 56 was the most potent lead for AD.[60] Pan *et al.* designed, synthesized and assessed ferulic acid-memoquin hybrids as multitarget agent for AD. Among all the synthesized compounds, compound 57 was most potent inhibitor of AChE and β-amyloid ($A\beta_{1-42}$) aggregation.[61] Zha *et al.* designed and synthesized αβ-unsaturated carbonyl based cyclohexanone derivatives for their actions on AChE, BuChE and Aβ aggregation. Of all compounds synthesized, compound 58 was the most favourable compound for treatment of AD.[62] Jain *et al*. designed and synthesized allylidene hydrazine carboximidamide derivatives as BACE-1 inhibitors. Among all synthesized compounds, compound 59 was the most promising lead structure with high docking score and IC_{50} value of 6.423µM.[63] A list of Pterostilbene-*O*-acetamido-alkyl-benzylamines derivatives were designed and synthesized by Li *et al*. with dual inhibitory actions on AchE and BuChE, β-amyloid aggregation and antioxidant properties. The study showed that the compound 60 possessed the best AChE inhibitory activity (IC_{50} = 0.06 µM) and good inhibition of BuChE (IC_{50} = 28.04 µM).[64]



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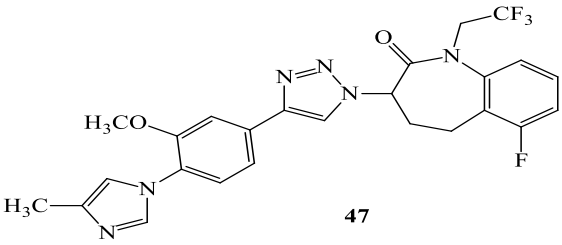

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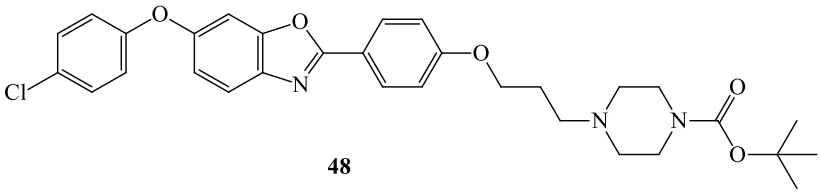

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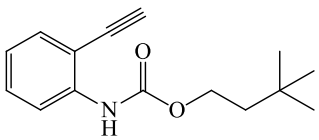

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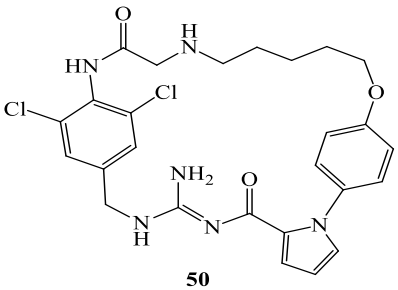

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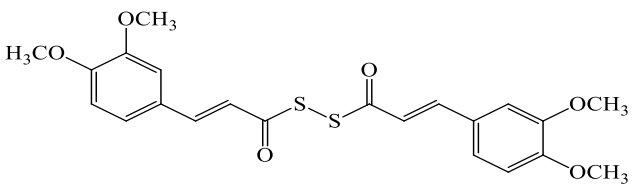

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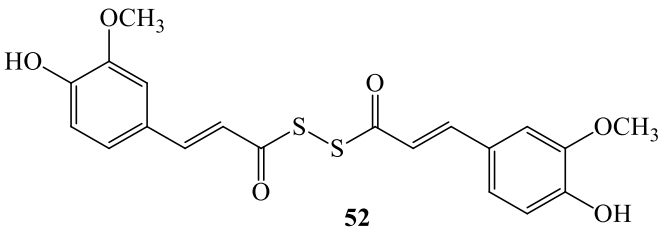

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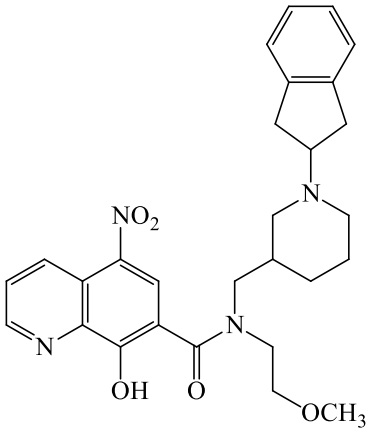

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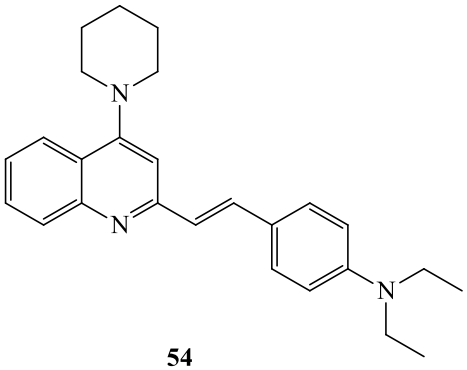

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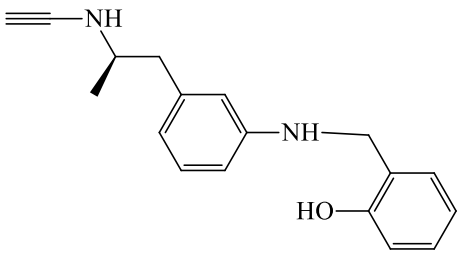

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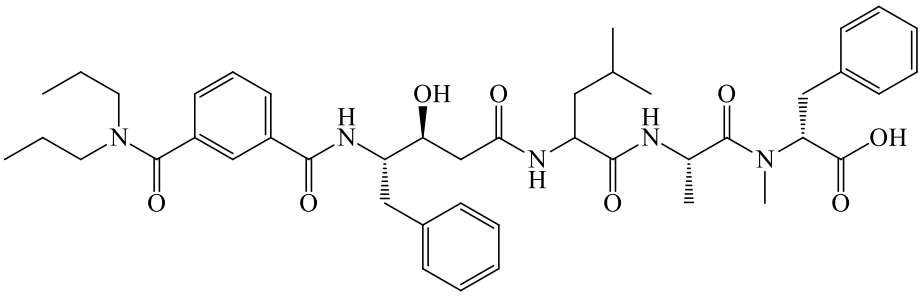

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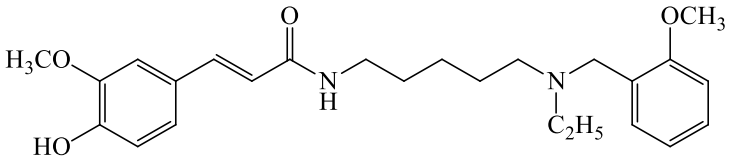

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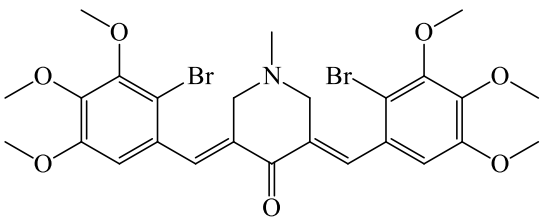

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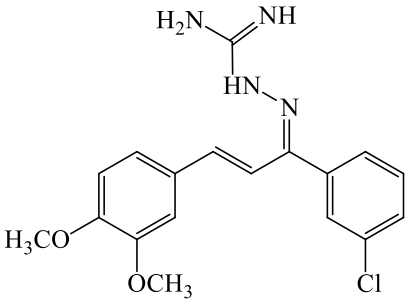

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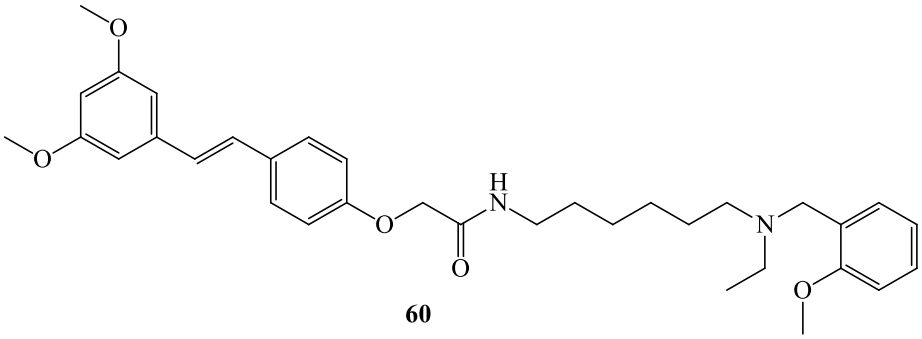

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Figure 5 (b): Miscellaneous Agents with anti-Alzheimer's Activity

CONCLUSION

Various moieties with potent activity against AD have been identified. There has been an increased interest in developing multitarget hybrids for AD. The review intends at highlighting the status of new moieties in developing drug candidates for AD.

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