

Donepezil: A review of the recent structural modifications and their impact on anti-Alzheimer activity

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Alzheimer disease (AD) is characterized by a low level of acetylcholine, beta-amyloid (A β) aggregation and oxidative stress. Donepezil is the core medicine used for the treatment of AD. Various structural modifications of donepezil have been carried out. Benzylpiperidine part of donepezil has been replaced with benzylpyridine, pyridyl methylpiperidine, benzylpiperazine, pyrimidyl piperazine. These derived molecules showed promising activities as anti-Alzheimer agents. Replacement of indanone part by other heterocyclic rings such as pyridine resulted in the formation of compounds which exhibited monoamine oxidase (MAO) as well as acetylcholinesterase (AChE) inhibition. Propargylamine containing derivatives displayed AChE as well as MAO inhibition properties. Attachment of donepezil with natural compounds like ferulic acid, flavonoids, and curcumin showed antioxidant activities in addition to inhibition of the AChE. Benzylpiperidine and benzylpiperazine have also been combined with condensed heterocyclic rings and these compounds displayed promising anti-Alzheimer properties. This review highlights the important structural modifications of donepezil and their influence on biological activities as anti-Alzheimer agents.

Keywords: Acetylcholinesterase (AChE). Butyrylcholinesterase (BuChE). Benzylpiperidine. Indanone. Hybrid compounds.

INTRODUCTION

The Alzheimer disease (AD) is a neurodegenerative disorder and is characterized by premature senile mental deterioration. It mainly affects the elder people aged above 65 years (Naj *et al.*, 2011). At present, 36 million people are affected due to this disease all over the world and according to some estimates, this number will increase up to 115 million in 2050 (Bolea *et al.*, 2011). Characteristic features of this disease are memory loss, cognitive impairment, behavioural changes and eventual death (Scarpini, Scheltens, Feldman, 2003). Low level of acetylcholine is one of the major causes in the development and progress of this disease (Talesa, 2001). Alteration in the dopaminergic, serotonergic and monoaminergic neurotransmission also contribute to some symptoms of Alzheimer disease. Beta-amyloid (A β) aggregation and oxidative stress are the other causes of this disease (Gella, Durany, 2009; Selkoe, Podlisny, 2002). Accumulation of

metal ions also results in fatal neurologic disorders and it is closely associated with abnormal A β plaques (Bush, 2008). Donepezil, rivastigmine, and galanthamine are the drugs which increase acetylcholine concentration by inhibiting cholinesterases and are effective in the treatment of AD (Birks, Harvey, 2006; Leon, Garcia, Marco-Contelles, 2013). An *N*-methyl-*D*-aspartate receptor antagonist, memantine is also approved for the treatment of this disease (David *et al.*, 2012). Donepezil is a selective inhibitor of AChE and this drug was approved for the treatment of AD in 1996 (Doody, Cummings, Farlow, 2012). Donepezil is a well tolerated and is most effective AChE inhibitor without causing hepatotoxicity. The benzylic portion of donepezil combines with the catalytic anionic site (CAS) and dimethoxy indanone part combines with the peripheral anionic site (PAS) of AChE enzyme (Cheung *et al.*, 2012). The AD is very complex in nature and involves many factors. Therefore, a drug molecule which interacts with a single receptor or enzyme is not sufficient for the treatment of this disease. Hybrid molecular strategy, in which the pharmacophoric parts of two drugs are combined in a single molecule,

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is widely being used for designing the new donepezil derivatives (Leon *et al.*, 2013). Over the last couple of years, a number of donepezil derivatives have been prepared and evaluated as anti-Alzheimer agents. To find the new derivatives, *N*-benzyl piperidinium and 5,6-dimethoxyindanone parts of donepezil have been attached as well as replaced by various other pharmacophores. In this review, an attempt has been made to summarize these derivatives on the basis of chemical structures and their biological activities as anti-Alzheimer agents.

DONEPEZIL DERIVED COMPOUNDS

Donepezil molecule comprises benzylpiperidine part which is connected to dimethoxy indanone through methylene group (Figure 1). It is used as a racemic mixture. Various structural modifications of this drug have been carried out and they are described in the following sections.

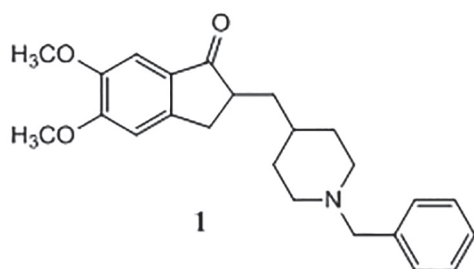


FIGURE 1 - Structural formula of donepezil.

Benzylpiperidine, benzylpyridine, pyridyl methylpiperidine fragments attached to indanone

Costanzo *et al.* (2016) carried out the synthesis of donepezil derivatives in which benzylpiperidine and indanone part were connected through the double bond. Compounds **2** (Figure 2) and **3** showed the most active inhibition of human erythrocytes AChE having IC₅₀ values of 0.058 ± 0.033 μM and 0.043 ± 0.007 μM respectively. These compounds were found to be selective for AChE as compared to butyrylcholinesterase (BuChE) with selectivity values of 81 and 132 for compounds **2** and **3** respectively (Costanzo *et al.*, 2016). Azzouz *et al.* synthesized bioxidiazable prodrugs of donepezil in which *N*-benzylpyridinium quaternary amine fragment was attached to indanone, tetralone and acetophenone fragments. Prominent activity was displayed by *N*-benzylpyridinium quaternary amine having the indanone ring. Compound **4** showed prominent inhibition of human AChE enzyme having

an IC₅₀ value of 0.36 nM. Docking studies of compound **4** showed that indanone part interacted with PAS while *N*-benzyl group interacted with CAS of AChE. Carbonyl group of indanone part formed hydrogen bonding with Phe295 of AChE (Azzouz *et al.*, 2018). Lan *et al.* carried out the synthesis of new donepezil derivatives in which 5,6-dimethoxy indanone part of donepezil was conjugated with *N*-benzylpyridinium moiety. Compound **5** presented activity as cholinesterase inhibitor having IC₅₀ values of 1.9 nM and 0.8 nM for electric eel AChE and human AChE respectively. Aβ aggregation inhibitory activity (53.7%) and antioxidant activity (0.54 Trolox equivalent) were also demonstrated by this compound. Compound **5** was also found to be neuroprotective at the dose of 1.56-12.5 μM. Compound **5** showed interaction with the CAS as well as with the PAS of AChE and showed the mixed type of inhibition (Lan *et al.*, 2017). Wang *et al.* modified the benzyl group of donepezil with various other heterocyclic rings such as pyridine, quinoline and hydroxyquinoline and small groups were also introduced at these heterocyclic rings. Compound **6** exhibited prominent inhibition of the AChE having IC₅₀ values of 85 nM and 73 nM for electric eel AChE and human AChE respectively. Compound **6** also inhibited the Aβ₁₋₄₂ aggregation (46.3%) induced by copper (Cu²⁺) and showed neuroprotective effects. Molecular modeling studies showed a strong binding interaction of this compound with the CAS and PAS of AChE (Wang *et al.*, 2016). Renou *et al.* (2016) synthesized four donepezil derivatives in which benzyl group of donepezil was replaced by 3-hydroxy pyridinaldoxime. Newly synthesized oxime derivatives showed the capacity to re-activate VX (an organophosphorous nerve reagent) and inhibited the human AChE better than the standard drug pralidoxime. Compound **7** showed the prominent activation of human BuChE (5 to 11 fold higher) as compared to pralidoxime (Renou *et al.*, 2016). Zurek, Szymański and Mikiciuk-Olasik (2013) synthesized donepezil derivatives by incorporating hydrazine nicotinate to the indanone part. Derivatives in this series showed a higher affinity for AChE than BuChE. Compound **9** was the most active AChE inhibitor (IC₅₀ = 1.087 × 10⁻⁵ μM) and also showed selectivity (selectivity index = 248.776) for this enzyme. An increased AChE inhibition was observed by replacing piperidine with benzylpiperidine and the resulting compound **9** appeared to be more active than compound **8**. Docking studies of compound **9** showed a binding score of -181.939 with AChE using cache software (Zurek, Szymański, Mikiciuk-Olasik, 2013).

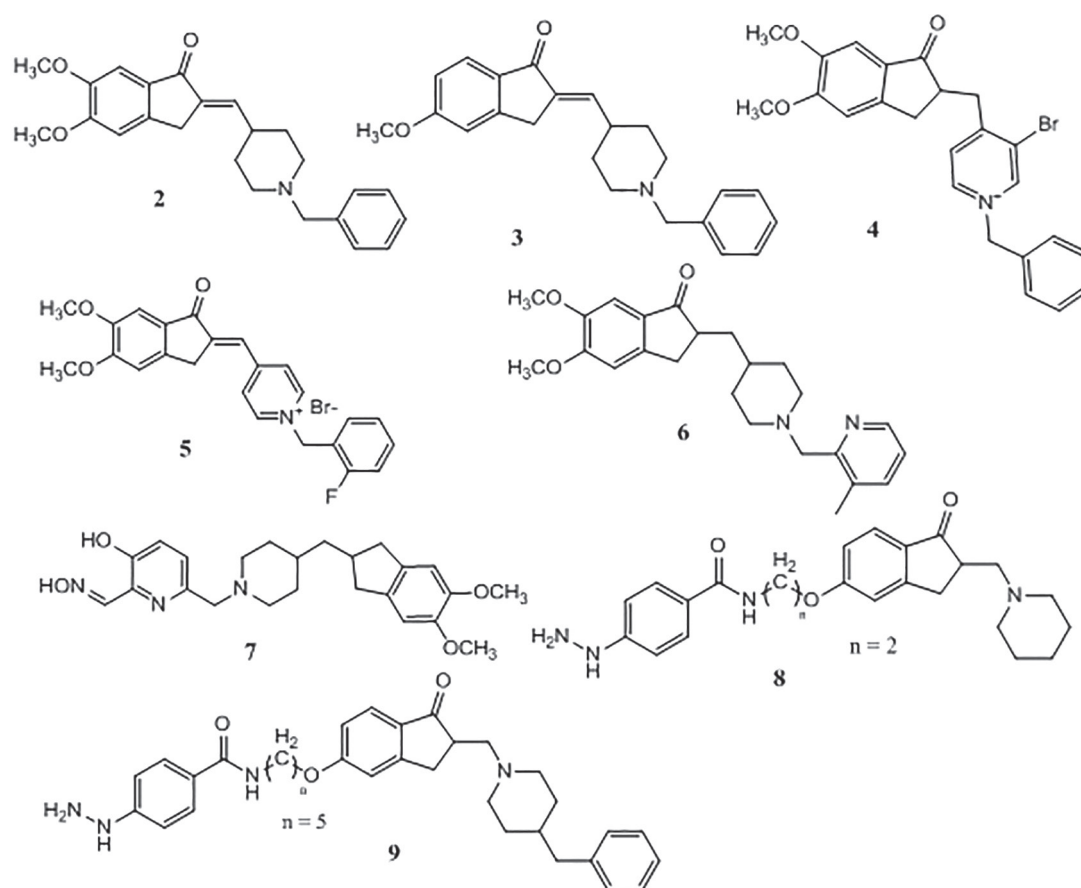


FIGURE 2 - Benzylpiperidine, benzylpyridine and pyridyl methypiperidine derivatives.

Benzylpiperidine attached to aromatic rings other than indanone

Özer *et al.* attached benzylpiperidine with the aromatic rings through an acylhydrazone group. These compounds were moderately active and nonselective as AChE and BuChE inhibitors. Compound **10** (Figure 3) was the most active in this series having IC_{50} values of $53.1 \pm 4.56 \mu\text{M}$ and $67.3 \pm 5.24 \mu\text{M}$ for AChE and BuChE enzymes respectively. Docking studies also showed the π - π interaction with PAS and CAS site of human AChE. These compounds showed excellent inhibition (69-80%) of the A β aggregation and have the potential for further modifications (Özer *et al.*, 2013). *N*-benzylpiperidine-aryl-acylhydrazone derivatives were prepared by Viegas *et al.* (2018) and among these, compound **12** presented excellent inhibition of electrophorus electricus AChE with an IC_{50} value of $8.65 \mu\text{M}$. Compounds **11** and **12** also exhibited the inhibition of COX-1 (51% and 64% for **11** and **12**) and COX-2 (65% and 53% for **11** and **12**) enzymes. The interaction with COX enzymes was also confirmed by molecular docking studies. These compounds also showed neuroprotective ability

(Viegas *et al.*, 2018). *N*-benzylpiperidine part of donepezil was attached with the beta-secretase (BACE-1) inhibitor through isophthalamide group to produce the new hybrid molecules. New molecules showed dual inhibition of AChE and BACE-1 enzymes and compound **13** was most prominent having IC_{50} values of $1.83 \pm 0.12 \mu\text{M}$, $0.567 \pm 0.159 \mu\text{M}$ for AChE and BACE-1 respectively. This compound also reduced the production of A β ($IC_{50} = 98.7 \text{ nM}$) and showed protection against hydrogen peroxide (H_2O_2) induced cytotoxicity (Zhu *et al.*, 2009). In 2017 attached the optical isomers of glutamic acid (D and L glutamic acid) with *N*-benzylpiperidine part of donepezil. L-glutamine derivatives were found to be more active than D-glutamine. Compound **14** showed prominent activity having IC_{50} values of $4.99 \pm 0.16 \mu\text{M}$ and $0.40 \pm 0.02 \mu\text{M}$ for AChE and BuChE respectively. Compound **14** contains carboxy benzyl side chain (Monjas *et al.*, 2017).

Benzylpiperidine attached with heterocyclic rings

Samadi *et al.* (2012) synthesized new pyridonepezil derivatives by linking the *N*-benzylpiperidine part

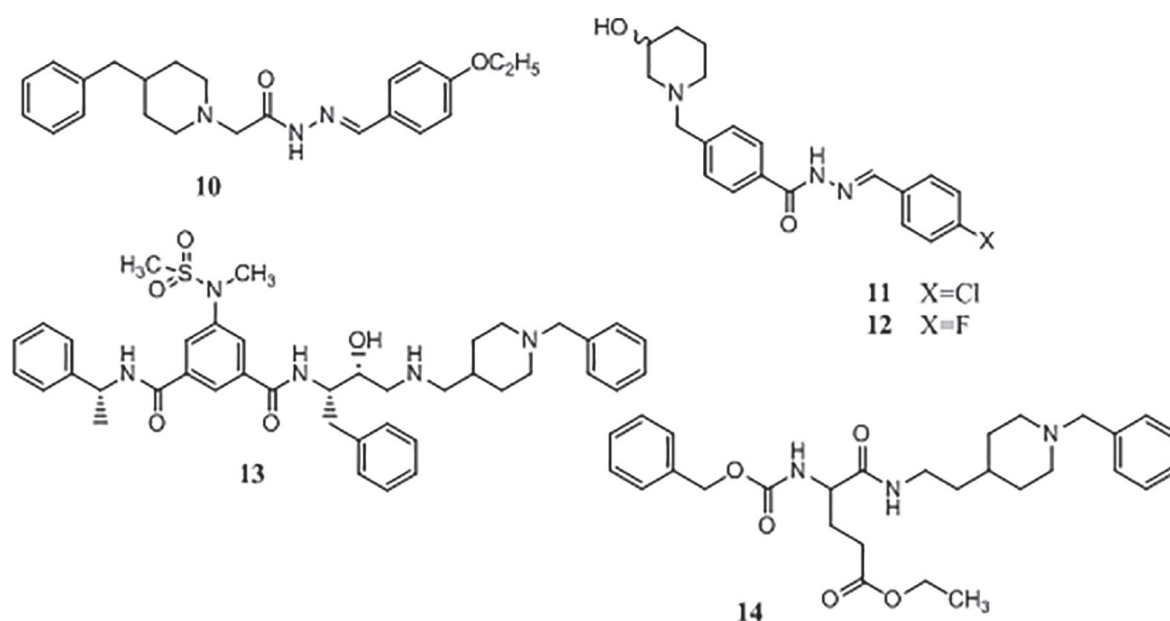


FIGURE 3 - Benzylpiperidine attached with aromatic rings.

of donepezil and 2-aminopyridine heterocyclic ring. Compounds **15** ($IC_{50} = 0.0094 \pm 0.0004 \mu\text{M}$) (Figure 4) and **16** ($IC_{50} = 0.070 \pm 0.005 \mu\text{M}$) showed prominent AChE inhibitory activity as well as selectivity (S.I. = 703, 24 for compound 15 and 16 respectively) for human AChE than human BuChE (Samadi *et al.*, 2012). An year later, Samadi *et al.* (2013) synthesized 6-chloropyridonepezil derivatives and compound **17** displayed the most active inhibition of human AChE ($IC_{50} = 0.013 \pm 0.002 \mu\text{M}$) and human BuChE ($IC_{50} = 8.13 \pm 0.0004 \mu\text{M}$). These compounds showed the ability to cross the BBB. Docking studies revealed that compound **17** interacted with the CAS and PAS of the AChE (Samadi *et al.*, 2013). Li *et al.* (2016) synthesized donepezil derivatives by linking the benzylpiperidine part of donepezil with benzamide and picolinamide moiety from an MAO inhibitor lazabemide. These compounds displayed AChE, BuChE, MAO-A and MAO-B inhibitory activities. Compound **18** presented

the most potent inhibition of cholinesterases having IC_{50} values of 0.220 μM , 1.23 μM and 0.454 μM for electric eel AChE, equine BuChE and human AChE respectively. This compound also showed inhibition of MAO-A and MAO-B having IC_{50} values of 3.14 μM and 13.4 μM . Compound **18** showed the capacity to cross the BBB and also exhibited metal chelating property. Docking studies of compound **18** with MAO-B demonstrated that 5-chloropicolinamide interacted with hydrophobic pocket while the *N*-benzylpiperidine bound via π -cation interaction with MAO-B (Li *et al.*, 2016).

Indanone derivatives having aromatic and heterocyclic rings

Yerdelen *et al.* (2015) attached the indanone part of donepezil with substituted aromatic rings through the amide group. Compound **19** (Figure 5) was the most prominent

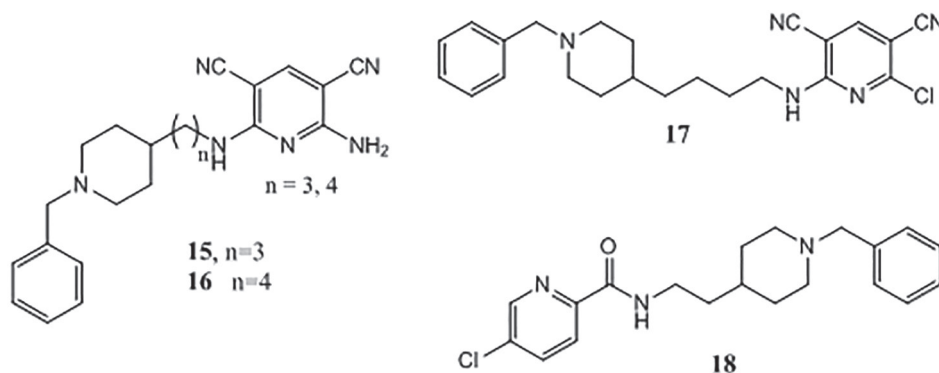


FIGURE 4 - Benzylpiperidine attached with heterocyclic rings.

inhibitor ($IC_{50} = 0.08 \pm 1.83 \mu\text{M}$) of AChE and it was most selective ($SI = 40.1$) for this enzyme. Compound **19** exhibited the most prominent inhibition of A β (55.3% at 25 μM) aggregation. Compound **19** also showed bonding interactions with CAS and PAS in the AChE binding sites (Yerdelen *et al.*, 2015). Meng *et al.* synthesized new donepezil derivatives in which the indanone part was connected to the pyridine ring through the double bond. Upon evaluation as AChE and BuChE inhibitor, compound **20** showed the most prominent inhibition of AChE having an IC_{50} value of 0.0018 μM and selectivity (5248.6) for AChE as compared to BuChE. It was more potent than the standard drugs donepezil and tacrine. Compound **20** also showed prominent metal chelating ability (Meng *et al.*, 2012). Nan DD *et al.* synthesized 6-methoxy indanone derivatives and evaluated them as probes for β amyloid plaques. Iodine (^{125}I) radiolabelled derivative (**21**) showed better binding to the β amyloid plaque, higher uptake in the

brain and rapid clearance. Compound **21** also showed better penetration across BBB having a partition coefficient of 3.45 (Nan *et al.*, 2016). Rizzo *et al.* (2010) attached indanone part of donepezil to the phenyl-*N*-methylbenzylamino fragment from AP2238. Compound **22** showed prominent inhibition ($46.8 \pm 2.0\%$) of AChE induced A β aggregation. Derivatives **23** and **24** showed prominent AChE inhibitory activities having IC_{50} values of $0.056 \pm 0.003 \mu\text{M}$ and $0.052 \pm 0.002 \mu\text{M}$ respectively. These compounds contain pentamethylene chain connecting diethylamine and piperidine group with the tetralone part. Compounds **23** and **24** also showed the A β aggregation inhibition induced by AChE having the inhibitory values of $42.9 \pm 0.8\%$ and $48.3 \pm 0.9\%$. Compounds **23** and **24** also inhibited the self-aggregation of A β . The long alkyl chain of these compounds having amino group showed a better interaction with PAS (Rizzo *et al.*, 2010). Mishra *et al.* carried out the synthesis of new 5,6-dimethoxy indanone-piperazine derivatives in which

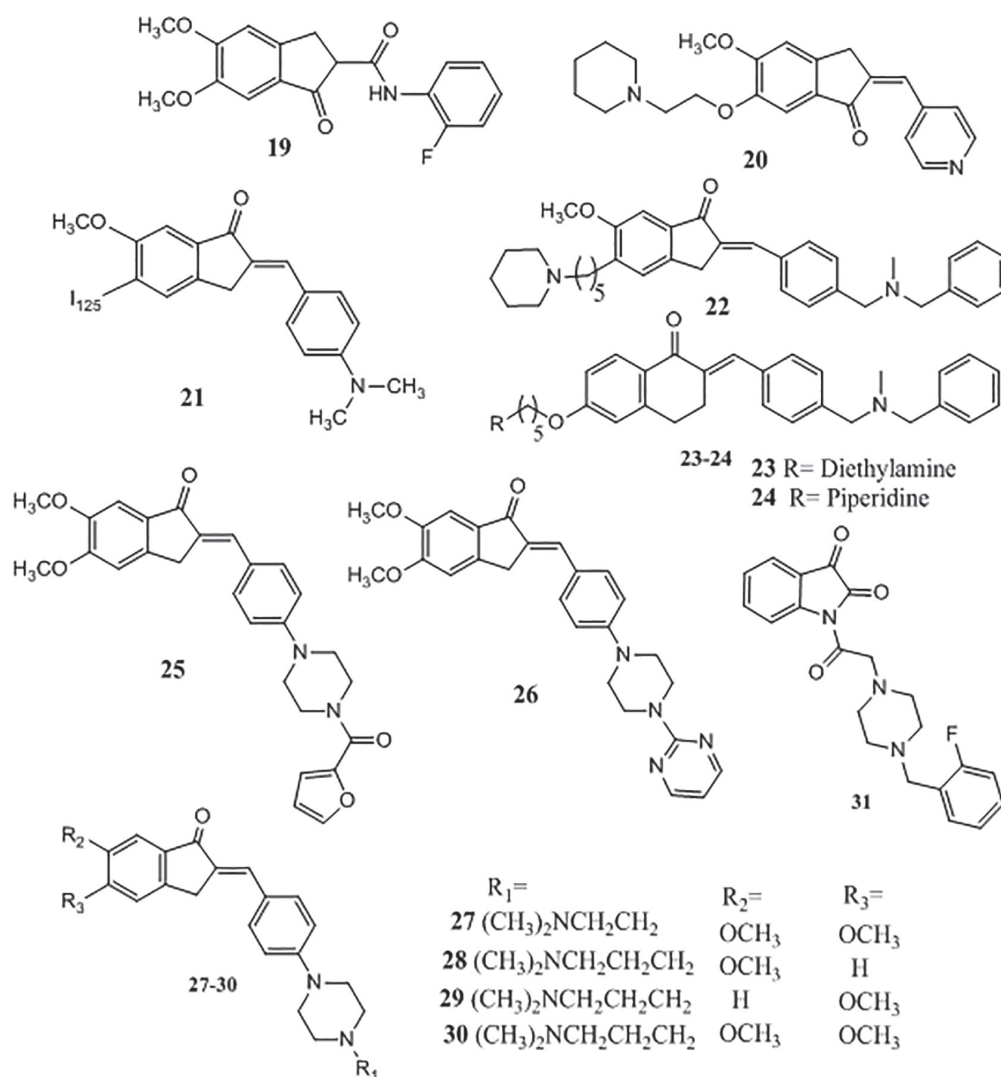


FIGURE 5 - Indanone derivatives having aromatic and heterocyclic rings.

structural parts of donepezil, curcumin and piperazine ring were combined to produce new molecules. Compounds **25** and **26** showed excellent AChE inhibitory potential having IC_{50} values of $0.034 \pm 0.002 \mu\text{M}$ and $0.025 \pm 0.001 \mu\text{M}$ and showed selectivity ($SI = 28.5$ and 97.3 for **25** and **26** respectively) for AChE than BuChE. Compounds **25** and **26** showed excellent inhibition of the A β aggregation ($80.4 \pm 1.08\%$, $81.6 \pm 0.78\%$ for **25** and **26** respectively) and antioxidant (3.89 ± 0.01 , 2.34 ± 0.03 for **25** and **26** respectively) activities. Molecular docking studies showed that these compounds have good interaction with AChE and A β peptide. Pyrimidine part of **26** binds through π - π interaction with PAS of AChE while the indanone part forms the hydrophobic interaction with CAS (Mishra *et al.*, 2017). Synthesis of new donepezil derivatives was carried out by Saglik *et al.* and their inhibitory effect on AChE was investigated. Compounds **27-30** displayed prominent inhibition of this enzyme (89.14 - 90.31% inhibition) and were found to be nontoxic ($IC_{50} = 78$ - $320 \mu\text{M}$) on NH/3T3 cell line. Side chains having another basic centre at the position # 4 of piperazine ring produced compounds with significant activity. Molecular docking studies also showed the interaction between these derivatives and targeted enzyme. Long chains of these compounds increased the van der Waals interactions with target enzyme (Sağlık, Ilgın, Özkay, 2016). Ismail *et al.* used indole molecule as the bioisosteric replacement of indanone part of donepezil. These compounds exhibited prominent AChE inhibitory

activity and compound **31** was the most active (55% inhibition) derivative in this series. Molecular docking studies of this compound also showed good energy score ($-23.4711 \text{ kcal/mol}$) in the active site of AChE. This was related to the additional 3-oxo and 2-fluorobenzyl groups in this compound (Ismail *et al.*, 2012a).

Phthalimide derivatives

Mohammadi-Farani *et al.* (2013) carried out the synthesis of donepezil derivatives in which the phthalimide ring was used in place of indanone part of donepezil. It was connected to benzylpiperazine through an alkyl chain. In this series, compound **32** (Figure 6) was the most prominent inhibitor of AChE having an IC_{50} value of $0.91 \mu\text{M}$. This compound contains ortho chloro substituent attached to the phenyl ring. Therefore electron withdrawing groups increased the activity of phthalimide derivatives. The molecular modeling study of this compound showed that piperazine, phthalimide and benzyl group occupied the same position at the AChE as the piperidine, indanone and benzyl group of donepezil (Mohammadi-Farani *et al.*, 2013). Ignasik *et al.* (2012) synthesized 2-(diethylaminoalkyl)-isoindoline-1,3-dione derivatives in which the phthalimide fragment was used as a substituent to indanone part of donepezil. Dialkylamine was used as a part which binds with the CAS. Compound **35** was the most prominent derivative in this series having

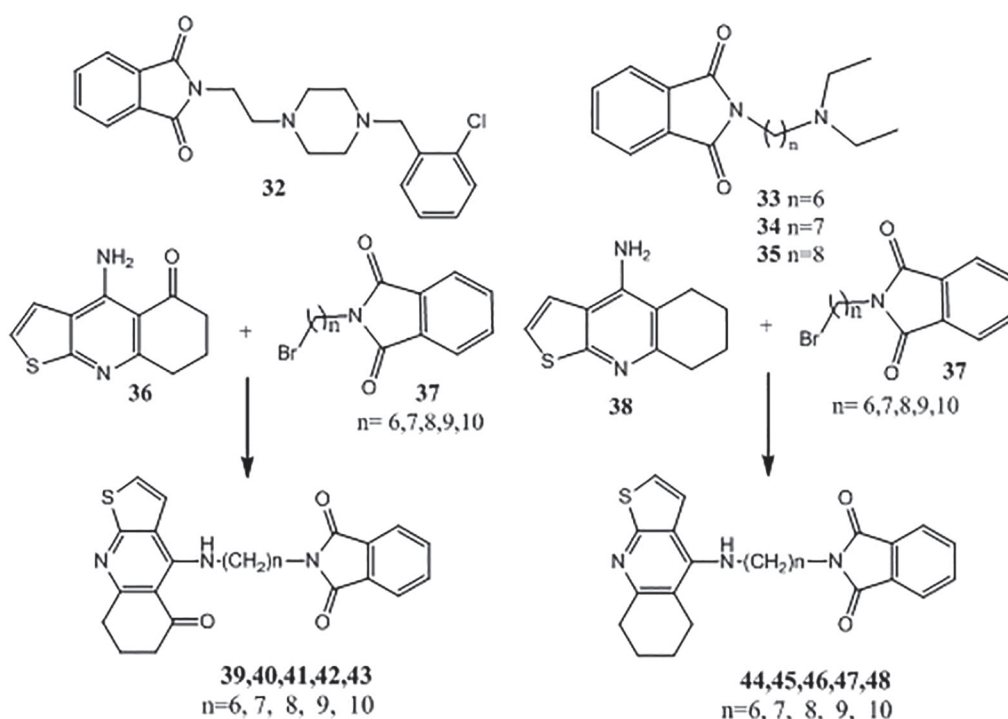


FIGURE 6 - Phthalimide derived compounds.

an IC_{50} value of 0.9 μ M for AChE. It contains an alkyl chain of eight methylene units. Compounds **33** and **34** also showed the promising and selective inhibition of AChE having IC_{50} values of 1.2 μ M and 1.1 μ M. Docking studies of these compounds also showed interaction with AChE only. Compounds **33** and **34** also exhibited the inhibition (33.8% and 39.4% for **33** and **34**) of A β aggregation (Ignasik *et al.*, 2012). Sang *et al.* (2017) carried out the synthesis of new molecules comprising phthalimide and 4-amino tetrahydrothienoquinoline. The reaction was done by direct alkylation of **37a-e** with **36** and **38**. These compounds have the potential for evaluation as AChE inhibitors (Song, Jo, 2009).

Donepezil and ferulic acid hybrid molecules

Ferulic acid is a phenolic compound which is found abundantly in plants. Donepezil and ferulic acid hybrids compounds were synthesized by Benchekroun *et al.* Resultant molecules showed prominent antioxidant activity and also showed selective inhibition of equine BuChE. Compounds **49** (Figure 7) and **50** were most active inhibitors of the BuChE having IC_{50} values of 10.39 ± 0.48 nM and 20.1 ± 1.9 nM respectively. Compounds **49** and **50** exhibited oxygen radical absorbing capacity of 8.71 ± 0.20 μ mol and 8.48 ± 0.33 μ mol respectively. These compounds contain ethylene and propylene linkers respectively and both of them contain melatonin as part of their structure (Benchekroun *et al.*, 2015). Dias *et al.* also synthesized donepezil-ferulic acid hybrid molecules by combining their pharmacophores. Compound **51** exhibited prominent activity against AChE having an IC_{50} value of 0.46 μ M. Molecular docking studies showed the interaction of this compound with AChE with the docking score of -16.129 with free AChE and -16.956 with acetylated AChE. Phenyl ring, the nitrogen atom of piperidine ring, a carbonyl group and 2-methoxyphenol

ring of this compound interacted with AChE enzyme. Compound **51** also showed anti-inflammatory potential by inhibiting COX-1, COX-2 and lipoxygenase (5-LOX) enzymes. This compound also showed metal chelating capacity with certain metals along with neuroprotective effects (Dias *et al.*, 2017). Sang *et al.* carried out the synthesis of ferulic acid-*O*-alkylamine derivatives by attaching the benzylpiperidine part of donepezil with ferulic acid and secondary amines by using methylene spacer. These compounds showed BuChE inhibitory and antioxidant activity. Compound **52** appeared as the most excellent inhibitor of BuChE (IC_{50} = 0.021 μ M) and AChE (IC_{50} = 2.13 μ M). Compound **52** also showed the inhibition of A β ($50.8 \pm 0.82\%$) aggregation. It also showed the ability to cross the BBB as well as less toxicity. Molecular modeling studies of compound **52** presented cation- π interaction, π - π interactions and hydrophobic interactions with BuChE but only hydrophobic interactions were observed with AChE which may be the reason for its selectivity for BuChE (Sang *et al.*, 2017). Xu *et al.* (2016) combined the pharmacophores of donepezil and ferulic acid to produce new hybrid molecules. Compound **53** displayed the prominent inhibition of electric eel AChE and equine BuChE having IC_{50} values of 0.398 μ M and 0.976 μ M respectively. Significant antioxidant activity (1.78 Trolox equivalents) was also observed for this compound. Molecular docking studies showed that compound **53** binds with PAS by polar contacts of phenyl propanoid group and with CAS by the π - π interaction of the phenyl ring (Xu *et al.*, 2016).

Donepezil and tacrine hybrid compounds

Tacrine was the first compound used for the treatment of AD but it was withdrawn from the market due to the toxic side effects. 7-Methoxytacrine is a less toxic derivative of tacrine (Soukup *et al.*, 2013). Alonso *et al.*

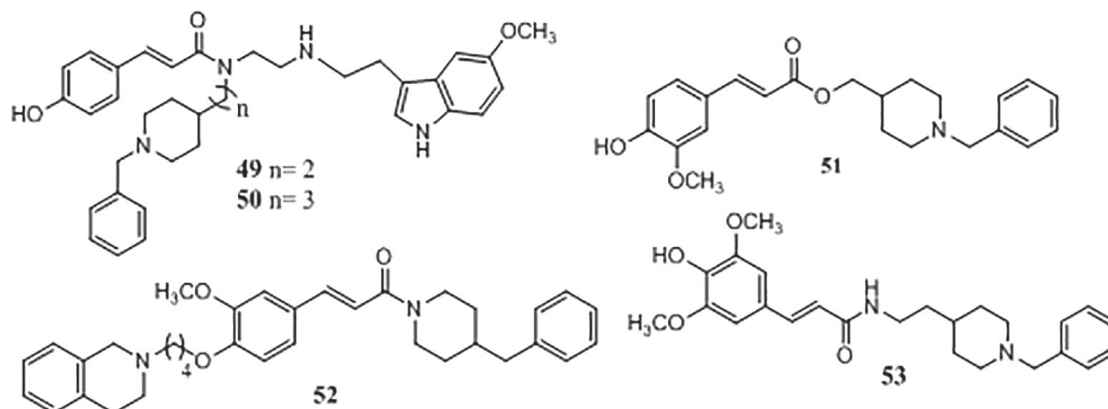


FIGURE 7 - Donepezil and ferulic acid hybrid molecules.

reported the synthesis of donepezil and tacrine hybrid compounds in which indanone part of donepezil was replaced by phthalimide ring. These derivatives showed more selectivity for AChE as compared to BuChE. Compounds **54** and **55** (Figure 8) displayed excellent inhibition of the AChE enzyme having IC_{50} values of 2.8 nM and 2.4 nM respectively. These compounds have the linker chain length of 9 and 12 methylene units between 9-aminoacridine and phthalimide scaffold. Molecular modeling of compounds **54** and **55** revealed that tetrahydroacridine/acridine rings of these compounds interacted with the catalytic site. Phthalimide ring attached with the peripheral site of AChE. Aromatic ring nitrogen formed hydrogen bonding while the chlorine atom interacted with hydrophobic pocket (Alonso *et al.*, 2005). Synthesis of donepezil and tacrine hybrid molecules was carried out by Camps *et al.* in which the 5,6-dimethoxy-

2-(4-piperidylmethyl) 1-indanone piperidine part of donepezil was attached to the tacrine. These compounds showed prominent inhibition of AChE and BuChE enzymes. Compound **56** was most potent having an IC_{50} value of 0.27 ± 0.03 nM for human AChE. Compound **57** was the most prominent inhibitor ($65.9 \pm 2.5\%$ inhibition) of A β aggregation. Tetrahydroacridine ring of compound **56** attached with the catalytic site of AChE while ring nitrogen formed hydrogen bonding with the carbonyl oxygen of His447 of enzyme and chlorine atom occupies the hydrophobic pocket (Camps *et al.*, 2008). Sepsova *et al.* (2015) evaluated 7-methoxytacrine and donepezil hybrid molecules for their interaction with AChE, with muscarinic and nicotinic acetylcholine receptors and these compounds presented activity in the micromolar range. They also showed the capacity to penetrate into CNS. Compound **58** ($IC_{50} = 1.38 \pm 0.15$ μ mol/litre) was the most potent

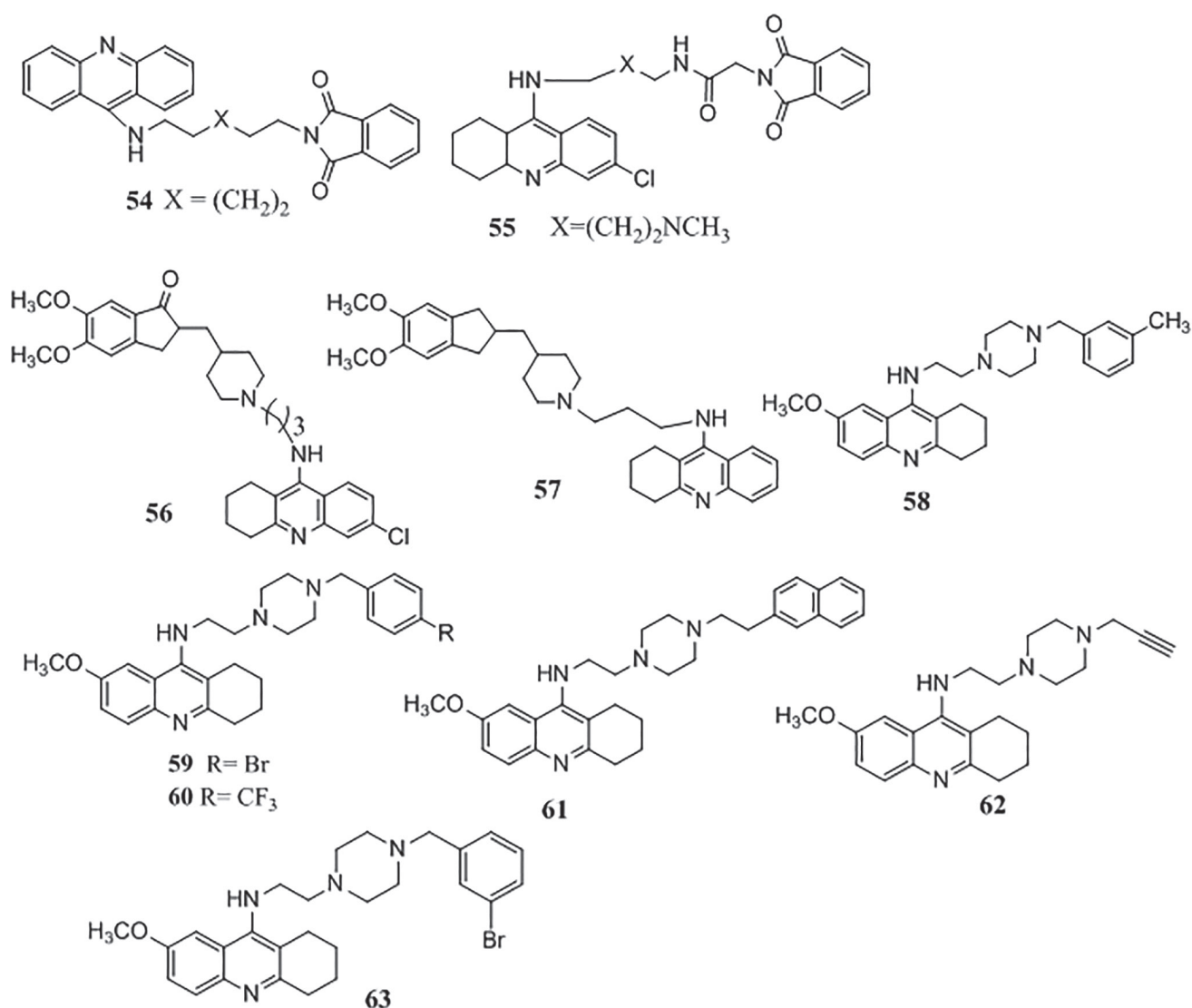


FIGURE 8 - Hybrid molecules comprising donepezil and tacrine fragments.

AChE inhibitor and showed a mixed type of inhibition i.e. competitive and non-competitive (Sepsova *et al.*, 2015). Hybrid molecules comprising 7-methoxytacrine and donepezil were synthesized by Korabecny *et al.* (2014) in which benzylpiperazine acted as isostere of the benzylpiperidine fragment of donepezil. The synthesized compounds exhibited excellent cholinesterase inhibitory activity against human and animal cholinesterases. Compounds **59**, **60**, **61** were prominent having IC_{50} values of $1.12 \pm 0.11 \mu\text{M}$, $1.16 \pm 0.22 \mu\text{M}$ and $1.94 \pm 0.26 \mu\text{M}$ against human AChE while **62** was the most active inhibitor of human BuChE with an IC_{50} value of $0.42 \pm 0.01 \mu\text{M}$. Molecular modeling investigations showed the interaction of these derivatives with the CAS and PAS of the AChE. 4-Bromophenyl group of compound **59** forms a new π - π interaction with enzyme and showed a binding energy of -13.8 kcal/mol (Korabecny *et al.*, 2014). Misik *et al.* (2015) evaluated 7-methoxytacrine and *N*-benzylpiperazine hybrid molecules as AChE inhibitors and compound **63** showed prominent inhibition (11.3%) of this enzyme as compared to donepezil (41%). Compound **63** contains benzylpiperazine group in place of benzylpiperidine fragment of donepezil (Misik *et al.*, 2015).

Donepezil hybrids with natural compounds

Compounds isolated from natural sources serve as lead compounds for new drug development (Koehn, Carter, 2005). Natural compounds have been combined with benzylpiperidine part of donepezil and these molecules demonstrated anti-Alzheimer activities. Xie *et al.*

combined *N*-benzylpiperidine part of donepezil with coumarin to produce new molecules having cholinesterase and MAO-B inhibitory activities. Compound **64** (Figure 9) appeared as the most active inhibitor of human AChE and human BuChE with IC_{50} values of $1.37 \pm 0.05 \mu\text{M}$ and $1.98 \pm 0.08 \mu\text{M}$ respectively. Compound **64** also showed inhibition of the MAO-B with an IC_{50} value of $2.62 \pm 0.81 \mu\text{M}$. Molecular modeling studies showed that phenyl group of coumarin ring binds with PAS through π - π interaction and carbonyl oxygen forms hydrogen bonding with PAS. *N*-benzylpiperidine forms π - π interaction with CAS of AChE. Compound **64** showed the capacity to cross the BBB and was found non-toxic for HepG2 cell line (Xie *et al.*, 2016). Yan *et al.* synthesized new molecules by combining pharmacophores of donepezil and curcumin. Compound **65** exhibited the prominent inhibition of AChE and it also showed selectivity for AChE ($IC_{50} = 0.187 \pm 0.015 \mu\text{M}$) than BuChE ($IC_{50} = 12.4 \pm 1.03 \mu\text{M}$). Compound **65** also showed inhibition ($45.3 \pm 3.58\%$) of $A\beta$ aggregation. This compound also penetrated BBB ($Pe = 11.85 \pm 1.00$) and showed antioxidant activity ($3.07 \pm 0.04 \mu\text{mol}$) (Yan *et al.*, 2017). Shen *et al.* (2009) linked *N*-benzylpiperidine part of donepezil to various flavonoids to produce the new hybrid molecules. Among these derivatives, Compound **66** exhibited the most effective inhibition of AChE with an IC_{50} value of $0.093 \mu\text{M}$. Compound **66** showed increased selectivity for AChE as compared to BuChE. Compounds having oxygen linker were found to be more active as compared to the methoxy group. Molecular docking investigations of this compound with AChE showed that isoflavone part

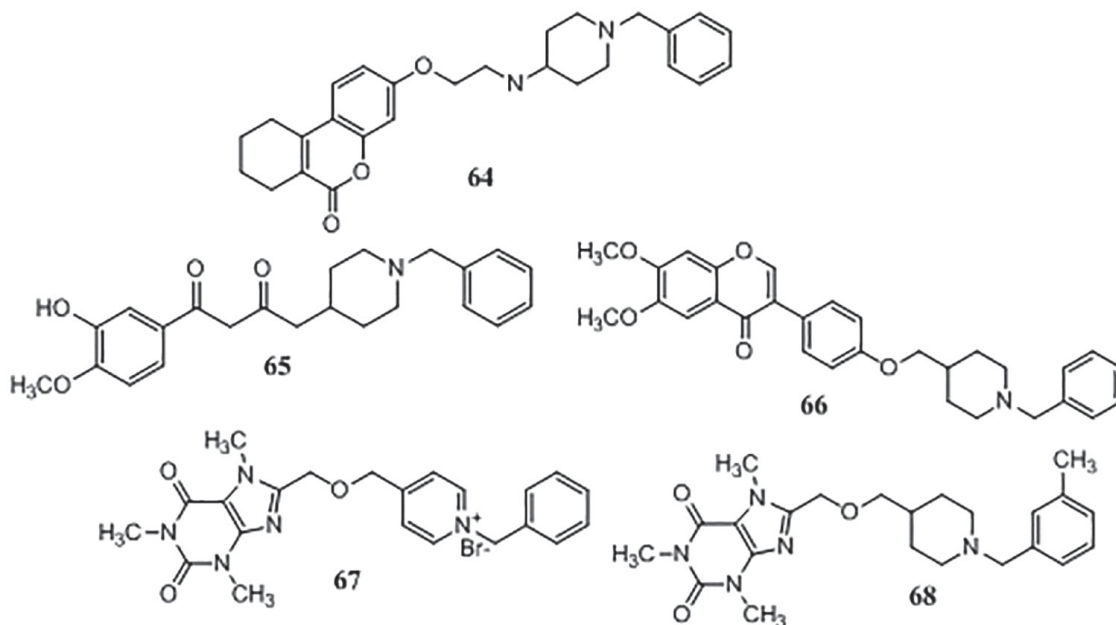


FIGURE 9 - Donepezil hybrids molecules with natural compounds.

of compound **66** joined the peripheral pocket through hydrophobic interactions. Two hydrogen bonds were also observed for this compound with Ser286 and Arg289. Compound **66** showed a binding free energy of -22.28 kcal/mol (Shen *et al.*, 2009). Rodriguez-Franco *et al.* (2005) also linked benzylpiperidine and benzylpyridine to 8-substituted xanthine derived from theophylline. Methoxymethyl group was used as a linker group between these two pharmacophores. These compounds exhibited AChE and BuChE inhibitory activities. Compound **67** showed prominent activity in this series presenting an IC_{50} value of $0.1 \pm 0.01 \mu\text{M}$ for AChE. Compound **68** was the most active inhibitor of the BuChE with an IC_{50} value of $0.4 \pm 0.01 \mu\text{M}$. Therefore it was noted that compounds having benzylpyridine part showed better interaction with AChE. The additional aromatic ring interacted with the aromatic amino acid of AChE (Rodríguez-Franco *et al.*, 2005).

Donepezil derivatives having propargylamine group

The presence of propargylamine group in certain drugs such as rasagiline and ladostigil confer neuroprotective, antiapoptotic and $A\beta$ aggregation inhibitory properties (Bar-Am *et al.*, 2010). Bautista-Aguilera *et al.* carried out the synthesis of new donepezil and indole hybrid molecules as anti-Alzheimer agents. In this compound, benzylpiperidine was attached to the position # 5 of indole through three methylene units and propargylamine group was attached at position # 2 of the indole ring. Compound **69** (Figure 10) was found to be the most potent agent in this class. It showed potent human MAO-A ($IC_{50} = 0.0055 \pm 0.0014 \mu\text{M}$) inhibitory activity as well as selectivity as compared to human MAO-B ($IC_{50} = 0.15 \pm 0.031 \text{nM}$). Compound **69** also exhibited AChE ($IC_{50} = 0.19 \pm 0.01 \mu\text{M}$) and BuChE

($IC_{50} = 0.83 \pm 0.16 \mu\text{M}$) inhibitory activities. Docking studies with AChE showed that propargylamine interacted via π - π bonding with Trp86. Phenyl ring interacted with the PAS and compound showed the binding free energy of -11.9 kcal/mol (Bautista-Aguilera *et al.*, 2014). Bolea *et al.* synthesized some multitarget molecules in which benzylpiperidine part of donepezil and indole propargylamine part of MAO inhibitor *N*-[(5-benzyloxy-1-methyl-1*H*-indol-2-yl)methyl]-*N*-methylprop-2-yn-1-amine were conjugated. Resultant compounds showed the capacity to interact with cholinesterases and MAO enzymes. Compound **70** exhibited prominent activity having MAO-A ($IC_{50} = 5.2 \pm 1.1 \text{nM}$), MAO-B ($IC_{50} = 43 \pm 8 \text{nM}$), AChE ($IC_{50} = 0.35 \pm 0.01 \text{nM}$), BuChE ($IC_{50} = 0.46 \pm 0.06 \text{nM}$) inhibitory activities. Compound **70** also showed the inhibition ($32.4 \pm 7.0\%$) of $A\beta$ aggregation. Molecular docking studies revealed that benzylpiperidine fragment attached with catalytic site and indole propargylamine part is stacked between aromatic rings with Trp279 and Tyr334. Propargylamine formed van der Waals interaction with phenyl ring of Tyr70 (Bolea *et al.*, 2011). Wang *et al.* (2014) synthesized hybrid compounds in which structural parts of donepezil, propargylamine and 8-hydroxyquinoline were combined. Compound **71** was the most active compound and showed simultaneous inhibition of MAO-A and MAO-B presenting IC_{50} values of $6.2 \mu\text{M}$ and $10.2 \mu\text{M}$ respectively. Significant AChE ($IC_{50} = 1.8 \pm 0.1 \mu\text{M}$) and BuChE ($IC_{50} = 1.6 \pm 0.25 \mu\text{M}$) inhibitory values were also observed for this compound. Compound **71** also showed excellent pharmacokinetic properties and displayed less toxicity to HepG2 cell line. Compound **71** contains 8-hydroxyquinoline and *N*-benzylpiperidine attached to the central propargylamine part having a nitrile group. This compound is a racemic mixture and both isomers showed binding at PAS and CAS of electric eel AChE (Wang *et al.*, 2014). Later on, Wu *et al.* (2016) also

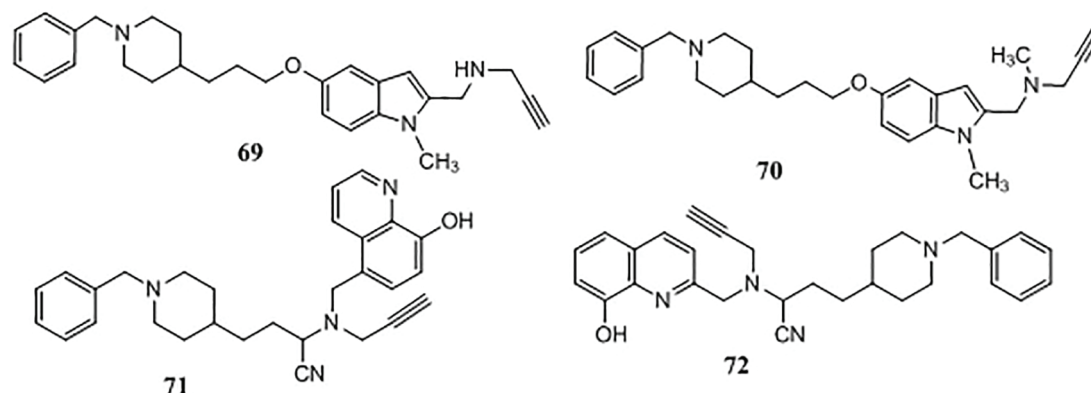


FIGURE 10 - Propargylamine derivatives of donepezil.

combined propargylamine group with benzylpiperidine and quinoline to produce new hybrid molecules. Among these derivatives, compound **72** showed excellent inhibition of AChE ($IC_{50} = 0.029 \pm 0.003 \mu\text{M}$), BuChE ($IC_{50} = 0.039 \pm 0.003 \mu\text{M}$) and selective MAO-A inhibition ($IC_{50} = 10.1 \pm 1.1 \mu\text{M}$). Compound **72** also showed metal chelating and antioxidant properties. The potency of compound **72** for cholinesterases was linked to the appropriate distance between the aromatic part and basic centre which are necessary for interaction with PAS, mid-gorge and CAS of AChE. Compound **72** is the bigger derivative in this series and cyano group can interact with mid gorge because of the correct length (Wu *et al.*, 2016).

Attachment of benzyl piperidine and benzyl piperazine with condensed heterocyclic rings

Vila *et al.* (2016) carried out the synthesis of donepezil analogues in which the indanone part of donepezil was replaced by the phthalazinone nucleus and the phthalazinone was connected to the *N*-benzylpiperidine fragment through the alkyl chain of two to three carbons. Compound **73** was prominently active and found to be the equipotent inhibitor of AChE and BuChE having IC_{50} values of $3.45 \pm 0.23 \mu\text{M}$ and $5.50 \pm 0.37 \mu\text{M}$. Compound **73** (Figure 11) contains *p*-toluyl group at position # 4 of the phthalazinone ring which gives an additional hydrophobic interaction with cholinesterases. Docking studies also showed dual binding of this compound with AChE as well as with BuChE (Vila *et al.*, 2016). Pudlo *et al.* connected quinoline carboxamide to the benzylpiperidine to produce the new hybrid molecules. These compounds exhibited the better inhibition of AChE as compared to BuChE. Compounds **74** and **75** were most active having

IC_{50} values of $0.11 \pm 0.03 \mu\text{M}$ and $0.48 \pm 0.14 \mu\text{M}$. Compound **75** also showed highest antioxidant activity ($EC_{50} = 12.2 \pm 0.4 \mu\text{M}$) and it contains catechol ring. Catechol ring was found to be important for antioxidant activity. Docking studies of compound **75** showed that phenyl group formed π - π interactions with CAS, piperidinium interacted with gorge and quinoline part was attached with PAS of AChE (Pudlo *et al.*, 2014). Synthesis of donepezil-Troxol hybrid molecules was reported by Cai *et al.* (2017). These compounds demonstrated activity against AChE and MAO-B enzymes. The most potent compound **76** showed inhibition of human AChE and MAO-B with IC_{50} values of $0.54 \mu\text{M}$ and $4.3 \mu\text{M}$ respectively. This compound also showed significant antioxidant activity ($IC_{50} = 41.33 \mu\text{M}$) and less hepatotoxicity to cell lines PC12, HePG2 and BV-2 (Cai *et al.*, 2017). *N*-benzylpiperidine fragment of donepezil and melatonin were fused together to produce the new molecules. Most of the compounds showed higher inhibition of BuChE as compared to AChE. Compound **77** was the excellent inhibitor of electric AChE and equine BuChE having IC_{50} values of 193 nM and 73 nM . This compound also displayed A β aggregation (56.3%) inhibition and antioxidant activities (3.28 Trolox equivalent). It also showed the capacity to penetrate into CNS. Molecular modeling studies showed that compound **77** interacted with CAS and PAS of AChE (Wang *et al.*, 2016).

Ismail *et al.* (2012b) carried out the synthesis of donepezil derivatives in which the indanone part of donepezil was substituted by tetrahydrobenzo[*b*]thiophine ring having carbonyl group at position # 3 of tetrahydrobenzo[*b*]thiophine. Acetamide group was introduced as a linker between the tetrahydrobenzo[*b*]thiophine and benzylpiperidine. Compounds **78** and **79**

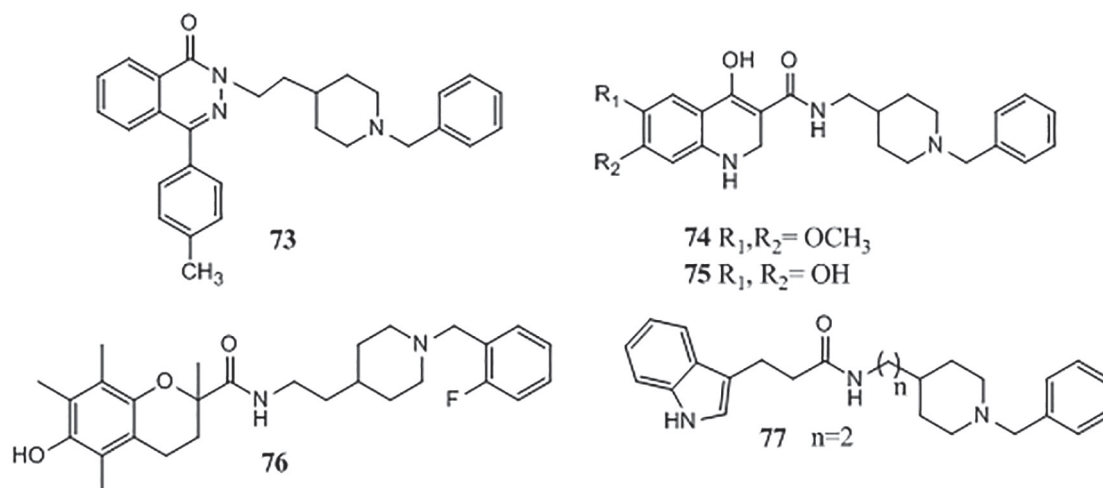


FIGURE 11 - Donepezil derivatives having condensed heterocyclic rings.

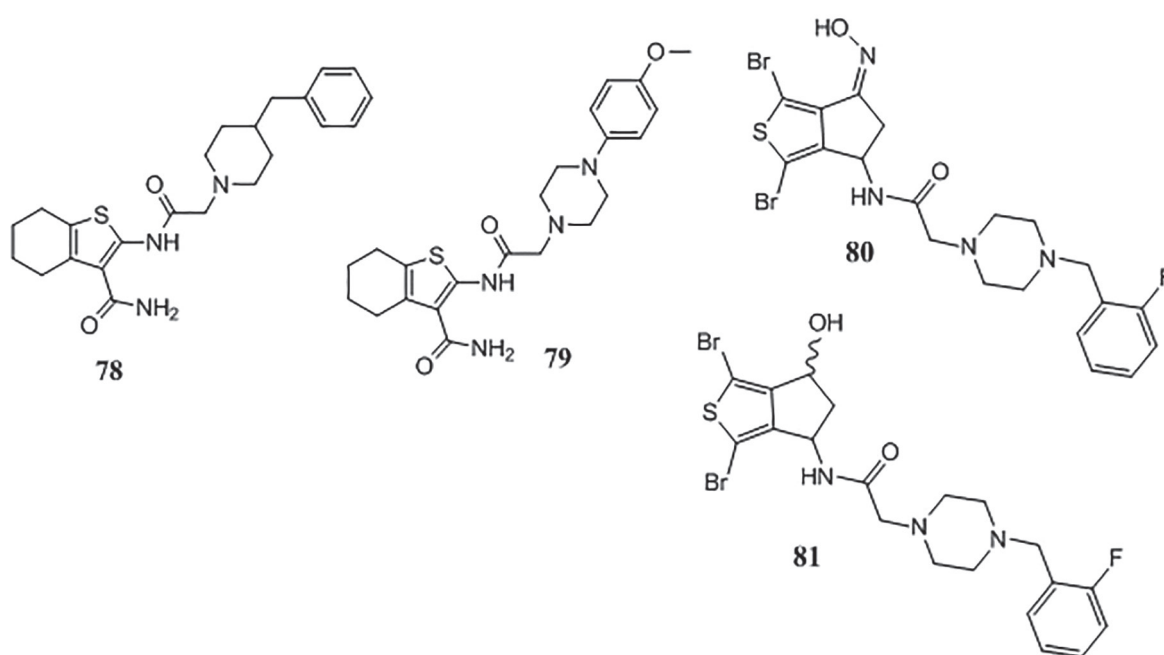


FIGURE 12 - Donepezil derivatives having condensed heterocyclic rings.

(Figure 12) exhibited prominent inhibition (56.67%, 60% for **78** and **79**) of AChE which was better than the standard drug donepezil (40%). In molecular docking studies, compound **78** presented strong hydrogen bonding than donepezil, which may be due to the amide group (Ismail *et al.*, 2012b). Omran *et al.* (2005) carried out the synthesis of new indanones and thiaindanones derivatives and evaluated their AChE inhibitory activity. Compound **80** exhibited excellent inhibition of AChE having an IC_{50} value of 0.06 μM as compared to donepezil ($IC_{50} = 0.02 \mu\text{M}$). It contains oxime group in the thiaindanone part and thiaindanone is attached to 2-fluorobenzyl piperazine through acetamide linker. Molecular modeling studies were also carried out and it was observed that fluorine atom at the ortho position of the benzyl group amplified the π - π interaction with the AChE enzyme (Omran *et al.*, 2005). Omran *et al.* (2008) carried out further modification and compound **81** was the most active inhibitor of AChE showing an IC_{50} value of 0.5 μM . It was observed that the replacement of the piperazine ring leads to the formation of inactive compounds. Replacement of hydroxyl group of this molecule with the bromine or fluorine produced less active compounds (Omran *et al.*, 2008).

DISCUSSION

A literature review of donepezil showed that benzylpiperidine part of donepezil can be replaced with benzylpyridine, benzylpiperazine, pyridyl methylpiperidine, aniline and phenylpiperazine motifs

with the retention of activity as anti-Alzheimer agents. Replacement of benzylpiperidine with unsubstituted piperidine produced less active compounds. 3-Hydroxy-6-(piperidin-1-ylmethyl)picolinaldehyde oxime derivatives were found to be reactivator of the AChE. Alkylamine, carboxamide and acylhydrazone are most commonly used linkers in these molecules. Attachment of benzylpiperidine with heterocyclic rings such as pyridine showed AChE and BuChE inhibitory activity while the picolinamide derivative showed MAO inhibition in addition to cholinesterase inhibitory activity. Benzylpiperidine part of donepezil has also been attached with condensed heterocyclic rings such as phthalazine, quinoline, tetrahydrobenzothiophine, indole and Trolox and these molecules showed anti-Alzheimer activities. Propargylamine derived compounds also exhibited MAO inhibition in addition to cholinesterase inhibition properties. In some derivatives, indanone part has been replaced with tetralone, oxindole, and phthalimide with retention of activity. Hybrid molecules of donepezil with ferulic acid showed higher BuChE inhibitory activity as compared to AChE inhibitory activity. These compounds also showed antioxidant as well as $A\beta$ aggregation inhibitory activities. Hybrid molecules of donepezil with tacrine produced compounds having AChE and BuChE inhibition. Donepezil hybrid molecules with natural compounds like flavonoids, coumarins, and curcumin presented antioxidant and MAO inhibitory activities in addition to cholinesterase inhibition. Amino acid derived compounds of donepezil showed dual inhibition of AChE

and BuChE enzymes. In this review, we have summarized the recent research progress of donepezil derived anti-Alzheimer agents. This review can help to provide some useful information for organic and medicinal chemists working in this field.

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