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The recent development of donepezil structure-based hybrids as potential multifunctional anti-Alzheimer's agents: highlights from 2010 to 2020

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Dementia is a term used to define different brain disorders that affect memory, thinking, behavior, and emotion. Alzheimer's disease (AD) is the second cause of dementia that is generated by the death of cholinergic neurons (especially acetylcholine (ACh)), which have a vital role in cognition. Acetylcholinesterase inhibitors (AChEI) affect acetylcholine levels in the brain and are broadly used to treat Alzheimer's. Donepezil, rivastigmine, and galantamine, which are FDA-approved drugs for AD, are cholinesterase inhibitors. In addition, scientists are attempting to develop hybrid molecules and multi-target-directed ligands (MTDLs) that can simultaneously modulate multiple biological targets. This review highlights recent examples of MTDLs and fragment-based strategy in the rational design of new potential AD medications from 2010 onwards.

1. Introduction

Alzheimer's disease (AD) is a progressive, chronic, and incurable neurological disorder that affects millions of people worldwide. According to the World Alzheimer report, there are currently more than 30 million people with Alzheimer's disease, with estimates that this number will increase up to 115 million in 2050.[1] The symptoms of this disease consist of memory loss, challenges in planning or solving problems, changes in mood and personality, and decreased judgment or decision-making abilities.[2] Cholinergic neuron death, diminishing

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neurotransmitter acetylcholine (ACh) levels in the brain,[3] metal dyshomeostasis, oxidative stress,[4] deficiency in steroid hormones, higher inflammatory mediators, deposition of β-amyloid (Aβ),[5] and tau-protein[6] have been mentioned as the main causes of AD.

Since this disease has a multifactorial nature, there is no effective treatment. Multi-target-directed ligands (MTDLs) are single molecules that can simultaneously modulate multiple targets in neurodegenerative disorders. Multi-target-directed ligands (MTDLs) generally are designed by connecting the pharmacophores of target ligands and are produced by chemical syntheses. Degeneration in the basal forebrain leads to a deficiency in central cholinergic transmission, which is believed to be a significant neurochemical and pathological characteristic of AD.[7] The cholinergic hypothesis is one of the oldest hypotheses that takes the role of ACh role into account in

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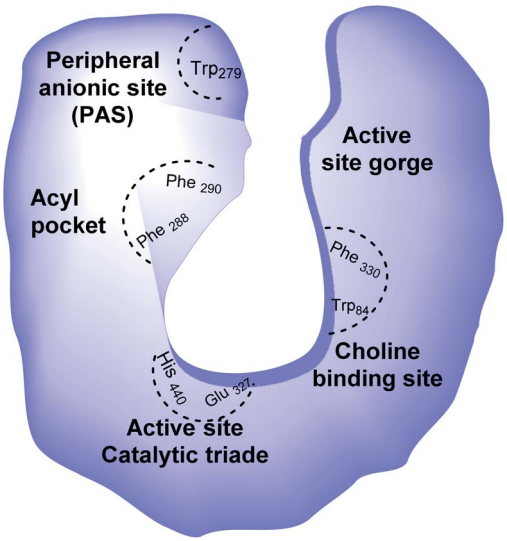

Fig. 1 Schematic representation of AChE binding sites; His: histidine, Glu: glutamate, Phe: phenylalanine, Trp: tryptophan.

animal and human behavior. Even though the cholinergic hypothesis is the most developed, the other hypothesis, Aβ peptide aggregation, describes how this aggregation could affect the AChE enzyme and is considered the most important. Hydrolysis of acetylcholine in the brain occurs by two types of cholinesterases (ChE): acetylcholinesterase enzyme (AChE) and butyrylcholinesterase (BuChE). Acetylcholinesterase enzyme (AChE) possesses two main binding sites for drug interaction, the catalytic site and the peripheral anionic site (PAS) (Fig. 1).[8]

In the amyloid aggregation process, the AChE anionic binding site is believed to be of paramount importance. Hence,

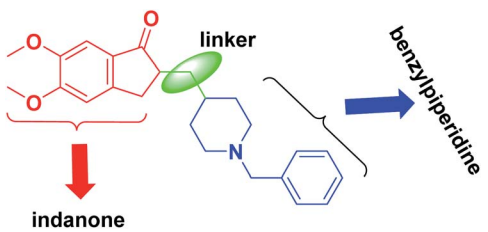

Fig. 2 Structure of donepezil.

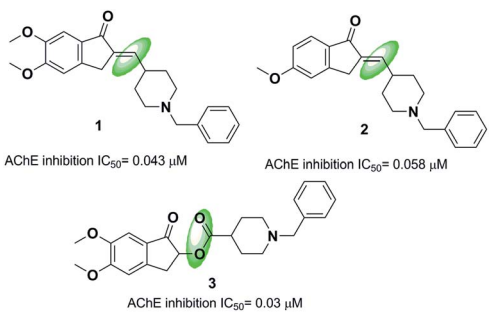

Fig. 3 Donepezil analogs with different linkers.

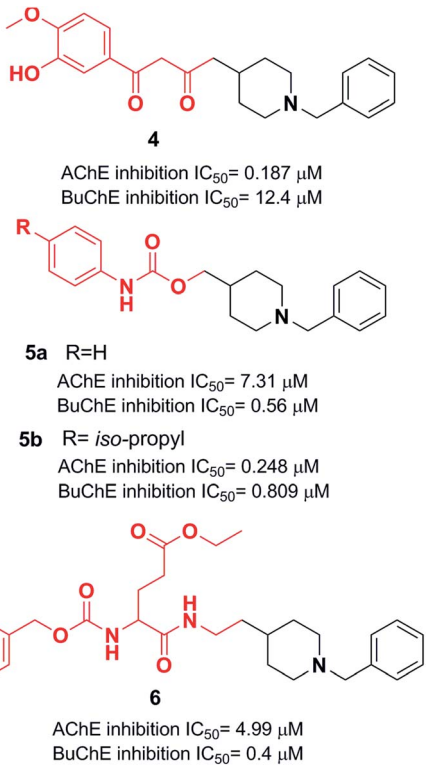

Fig. 4 Donepezil analogs with aromatic molecules.

this site is targeted as an alternative site by AChE inhibitors, which function as multi-target ligands that cause a decrease in the formation of senile plaque. Therefore, cholinomimetic therapy with anticholinergic drugs is the main approach in treating AD. The acetylcholinesterase enzyme inhibitor (AChEI) increases endogenous AChE levels and enhances cholinergic neurotransmission in the brain. Among the investigated acetylcholinesterase inhibitors, donepezil (2-((1-benzylpiperidin-4-yl)methyl)-5,6-dimethoxy-2,3-dihydro-1*H*-inden-1-one) is of most highly effective and well-known FDA-approved drug (Fig. 2).[9] Donepezil consists of dimethoxy indanone, which is connected to *N*-benzylpiperidine *via* a methylene linker.

A molecular docking investigation of donepezil showed that the indanone moiety fuses with the PAS of AChE, and the benzylic part links with the catalytic anionic site (CAS).[10] The *N*-

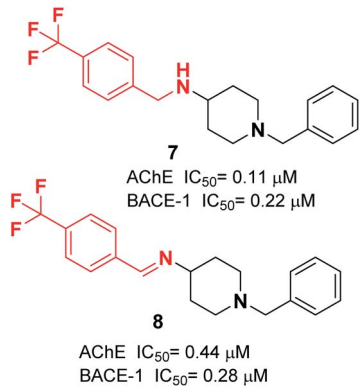

Fig. 5 Structure of donepezil-based benzylamine derivatives.

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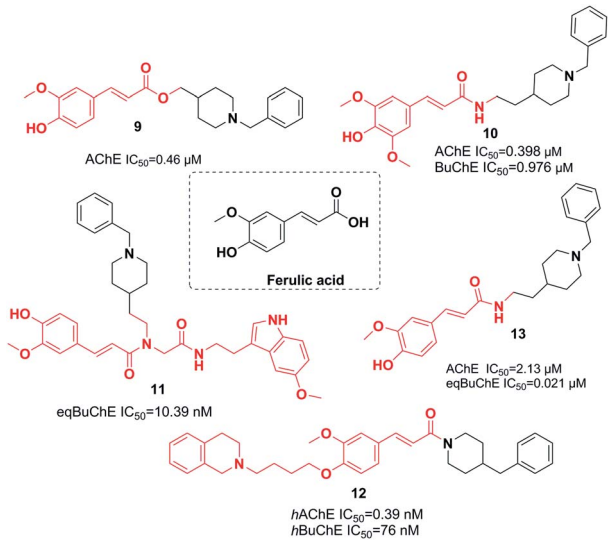

Fig. 6 Structure of most potent donepezil–ferulic acid hybrids.

benzylpiperidine group is situated onto the narrowest active-site cavity section. It interacts with four amino acid residues, Tyr-70, Asp-72, Tyr-121, and Tyr-334, in the anionic site.[11] A large number of reviews have been published on Alzheimer's topics.[12,13] Still, this review summarizes recent findings in AD research by emphasizing simple synthetic compounds with modified donepezil structures that act as MTDLs. We focused on the current literature and produced a collection of all hybrids of *N*-saturated heterocyclic compounds based on the structure of donepezil that were published from 2010 until now. We categorized this review into main sections of donepezil derivatives with different linkers for ease of reading, replacing indanone with heterocycles, and inserting piperazine/pyrrolidine instead of piperidine to produce donepezil-like structures. This current review will provide insights into the design and development of novel therapeutics for treating AD.

2. Donepezil-like derivatives with different linkers

One strategy in designing new acetylcholinesterase inhibitors (AChEI) is to create different linkers in the donepezil structure. Costanzo *et al.* synthesized indanonylidenyl precursors of donepezil through condensing the indanone nucleus and derivatives of *N*-benzylpiperidine-4-carboxaldehyde in the presence of a basic resin, Amberlyst A-26. The biological assessment indicated that compounds **1** and **2** demonstrated higher dual activity and decreased values of IC_{50} toward the AChE enzyme and BACE-1 enzyme as compared to donepezil (Fig. 3).[14] Greunen *et al.* synthesized two libraries of possible AChE inhibitors according to the AChE molecular skeleton by replacing the piperidine ring with N-saturated ring systems in different sizes and introducing various linker piperidine rings to the indanone in donepezil. Replacement of a methyl linker with an ester moiety resulted in a complete loss of activity in all but one case, where 5,6-dimethoxy-1-oxo-2,3-dihydro-1*H*-inden-2-yl-1-benzylpiperidine-4-carboxylate **3** yielded 0.03 μM IC_{50} towards AChE *in vitro* (Fig. 3).[15]

3. Donepezil-like derivatives with the replacement of the indanone part

As mentioned in the introduction, donepezil consists of an indanone moiety. Replacement of this part with various compounds has led to new hybrids of donepezil with various inhibitory activities.

3.1. Replacement of indanone with aromatics

Yan *et al.* produced a new series of derivatives by fusing donepezil and curcumin pharmacophores under aldol condensation.[16] They investigated the AChE inhibitor activity, Aβ-aggregation, metal chelation, and antioxidant activities. Among the synthetic targets, compound **4** showed the highest

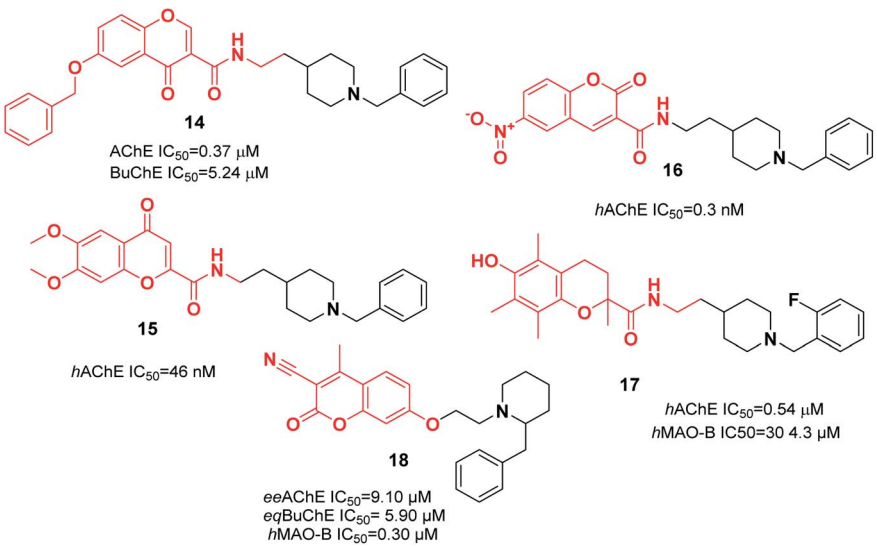

Fig. 7 Donepezil–flavonoid hybrids.

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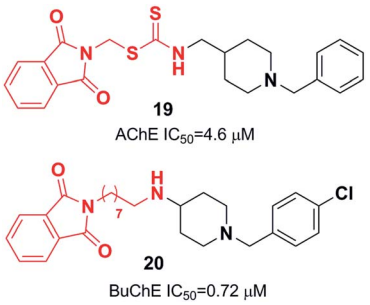

Fig. 8 Structure of phthalimide–dithiocarbamate hybrids.

selectivity ratio of 66.3 for BuChE/AChE, which was considerably better than the reference tacrine and galantamine with a selectivity ratio of 0.15 and 25.3 and slightly worse than donepezil with a selectivity ratio of 85.4. Compound **4** also demonstrated potent inhibition of self-induced Aβ aggregation (Fig. 4). Košak *et al.* developed a class of *N*-benzylpiperidine carbamates as viable anti-Alzheimer agents. Compound **5a** showed selective *h*BuChE and *h*MAO-B inhibitor activity (with an IC_{50} of 0.178 μM), but **5b** exhibited selective *h*AChE inhibition (Fig. 4).[17] In 2017, Monjas prepared L- and D-glutamic acid derivatives with the *N*-benzylpiperidine fragment in the γ-position in the presence of *Mucor miehei* and *Candida antarctica* lipases in high yield. The multifunctional profile of synthesized compound **6** exhibited stronger inhibition of human ChE activity (Fig. 4).[18]

At ambient temperature, the treatment of 1-benzylpiperidin-4-amine with disparate aromatic aldehydes under glacial acetic acid in absolute ethanol generated imine hybrids. The reduction of imines in $NaBH_4$ produced benzylamine derivatives in good yield (Fig. 5). These two series of amine derivatives were assessed as multi-functional AChE and BACE-1 inhibitors having moderate to excellent activities. Compared with donepezil, which exhibited 42.1-fold AChE selectivity (with an IC_{50} of 0.44 μM for AChE, and IC_{50} of 0.28 μM for BACE-1), the selective inhibition of compound **7** was 28.2-fold for AChE, and it displayed self-induced as well as AChE-induced Aβ aggregation inhibition in the thioflavin T-assay. Docking studies revealed that **7** and **8** elicited similar interactions at the PAS, except for additional π–π stacking and π–cation interactions with the Tyr341 residue. The benzyl portion of the compounds exhibited

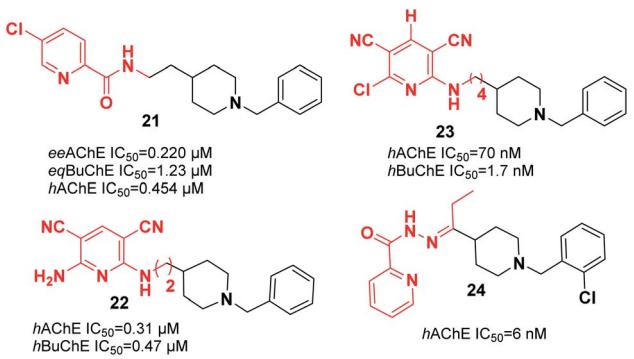

Fig. 9 Pyridine–donepezil hybrids with ChEI activity.

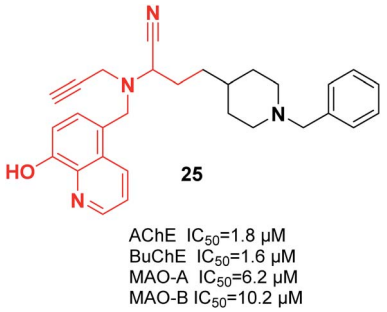

Fig. 10 Structure of a donepezil-8-hydroxyquinoline derivative as a mixed-type AChE inhibitor.

interactions with Trp86 (π–π stacking or π–cation) and Glu202 (electrostatic) residues at anionic subsites (Fig. 5).[19]

3.2. Replacement of indanone with ferulic acid derivatives

Ferulic acid, which is found in plant cell walls, is a hydroxycinnamic acid with pharmacological activities.[20] In a study carried out by Dias *et al.*, the synthesis, design, and pharmacological assessment of novel molecular hybrids of feruloyl–donepezil were reported. The *N*-benzylpiperidine pharmacophore of donepezil is responsible for its sufficient recognition through AChE and the subunit feruloyl, which exists in curcumin and ferulic acid. Based on the *in vitro* results, all the compounds mentioned demonstrated potent AChE inhibitory activity, moderate antioxidant properties, neuroprotection of neuronal cells against the oxidative process, and significant metal chelation of Fe^{2+} and Cu^{2+}. Compound **9** had the greatest AChE inhibitor potency (Fig. 6).[21]

In 2016, the design and synthesis of other donepezil–ferulic acid hybrids were carried out. The synthetic molecules were assessed as MTDLs against AD. An *in vitro* assay demonstrated that there was moderate AChE and BuChE inhibition by compound **10**. This compound exhibited considerable antioxidant activity (1.78 Trolox equivalents through the ABTS method, with an IC_{50} of 24.9 μM through the DPPH method) (Fig. 6).[22] Benchekroun *et al.* prepared donepezil–ferulic acid hybrids (DFAHs) through one-pot Ugi-4CR in low to moderate yield. They found that hybrid (*E*)-*N*-(2-(1-benzylpiperidin-4-yl)ethyl)-3-(4-hydroxy-3-methoxyphenyl)-*N*-(2-((2-(5-methoxy-1*H*-indol-3-yl)ethyl)amino)-2-oxoethyl)acrylamide **11** was a selective *eq*BuChE, and the oxygen radical-absorbing capacity of this compound was 8.71 μmol (Fig. 6).[23]

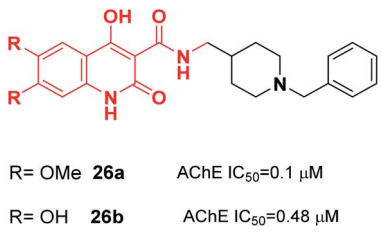

Fig. 11 Structure of a quinolone–benzylpiperidine derivative as a new acetylcholinesterase inhibitor.

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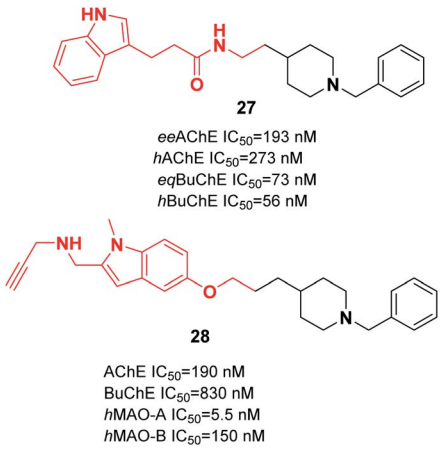

Fig. 12 Multitarget molecules based on donepezil–indole hybrids.

Sang *et al.* synthesized new derivatives of ferulic acid-*O*-alkylamine and then evaluated them against AD. Based on *in vitro* studies, all exhibited considerable inhibitory activity toward BuChE, acceptable self-induced aggregation (Aβ), and functioned as viable antioxidants. Specifically, compound **12** was a satisfactory AChE inhibitor with the greatest BuChE inhibition potency. It exhibited an inhibitory impact upon self-induced aggregation of Aβ1-42 (50.8%) and self-induced aggregation of Aβ1-42 (38.7%), moderate antioxidant activity with 0.55 eq. of Trolox, acceptable protection against H_2O_2-induced PC12 cell injury, and low toxicity (Fig. 6).[22] Estrada *et al.* linked cinnamic-related structures to *N*-benzylpiperidine. Compound **13** in series demonstrated moderate inhibition of *h*AChE with an IC_{50} of 0.39 and inhibition of *h*BuChE with an IC_{50} of 76 nM. The existence of the *p*-hydroxy group was necessary for inhibition of the cinnamic fragment (Fig. 6).[24]

3.3. Donepezil-like derivatives with replacement of indanone with heterocycles

3.3.1. Replacement of indanone with oxygen-containing heterocycles. The chromone structure, 4*H*-1-benzopyran-4-one, has been considered the pharmacophore of many active compounds in flavones and isoflavones. All of these structures are considered scaffolds that can be used to develop *h*MAO inhibitors. Combining the benzylpiperidine moieties of donepezil and

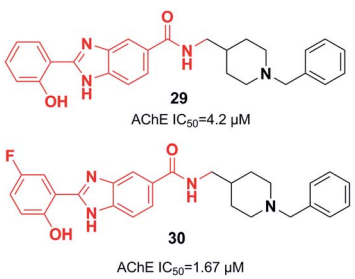

Fig. 13 Hydroxy benzimidazole–donepezil hybrids that are multi-target-directed ligands.

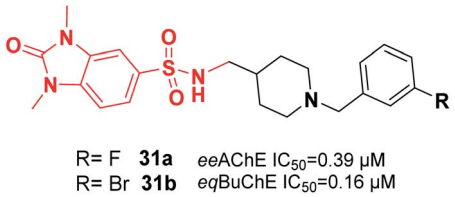

Fig. 14 Structure of a dimethylbenzimidazolinone–benzylpiperidine hybrid.

chromone resulted in the new dual inhibitors AChE and MAO-B. Among the synthetic targets, compound **14** exhibited the most proportionate probability of inhibiting ChEs and greatest *h*MAO-B selectivity (IC_{50} = 0.272 μM and SI of 247, respectively). Also, kinetic and molecular modeling indicated that compound **14** is a mixed type of inhibitor that simultaneously binds to the PAS and CAS of AChE and penetrates the blood–brain barrier (BBB). In addition, it exhibits low toxicity against rat pheochromocytoma (PC12) cells (Fig. 7).[25] In 2018, Estrada *et al.* explored neurogenic and neuroprotective donepezil–flavonoid hybrids (DFHs). These targets showed affinities toward the sigma-1 receptor (σ-1R), and inhibition of AChE, monoamine oxidases (MAOs), and 5-lipoxygenase (5-LOX). The most potent ligand was *N*-(2-(1-benzylpiperidin-4-yl)ethyl)-6,7-dimethoxy-4-oxo-4*H*-chromene-2-carboxamide **15**, which demonstrated a moderate 5-LOX inhibition with an IC_{50} of 74.3 μM and acceptable *h*AChE inhibition with an IC_{50} of 46 nM (Fig. 7).[26]

In a research study performed by Asadipour *et al.*, derivatives of coumarin-3-carboxamide were synthesized that were connected to *N*-benzylpiperidine. Based on the results, almost all the compounds exerted potent activity against AChE in the nM concentration range. Among them, compound **16**, with a *N*-methyl carboxamide linker and 6-nitro substituent, demonstrated the most potent activity and the highest selectivity of 26 300 with 46-fold more potency than the standard drug donepezil against AChE (Fig. 7).[27] To synthesize multifunctional anti-AD agents, donepezil and Trolox pharmacophores were fused into one molecule by Cai *et al.* Among the targets, *N*-(2-(1-(2-fluorobenzyl)piperidin-4-yl)ethyl)-6-hydroxy-2,5,7,8-tetramethylchromane-2-carboxamide **17** exhibited balanced functions with an acceptable inhibitory effect upon *h*AChE and *h*MAO-B, considerable antioxidant activity with an IC_{50} of 41.33 μM, outstanding copper chelation, $A\beta_{1-42}$ aggregation inhibition impact, and less hepatotoxicity toward cell lines HePG2,

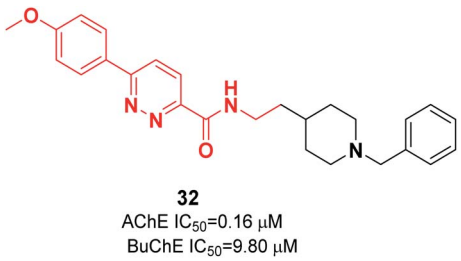

Fig. 15 Structure of a phenylpyridazine-3-carboxamide-benzylpiperidine hybrid.

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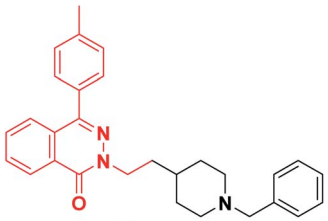
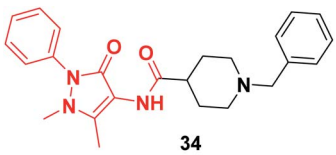


33
AChE IC_{50}=3.45 μM
BuChE IC_{50}=5.50 μM

Fig. 16 Structure of a phthalazin-1(2*H*)-one-donepezil hybrid.

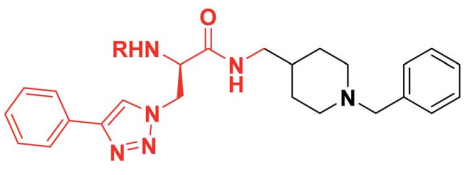


34
AChE IC_{50}=5.94 μM

Fig. 17 Structure of a pyrazole-benzylpiperidine derivative.

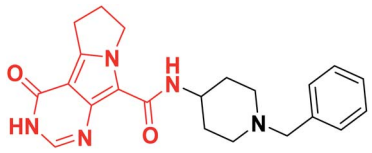
PC12, and BV-2 (Fig. 7).[28] The design and synthesis of 7-substituted coumarin derivatives were carried out by Joubert *et al.* These compounds retained the *N*-benzylpiperidine function of donepezil (ChE inhibitor) and the coumarin structure (MAO-B inhibitor) connected at the 7-position by an alkyl ether linkage. According to the biological assay results, compound **18** had the highest multifunctional agent potency, and exhibited a satisfactory *ee*AChE inhibition and potent selective *h*MAO-B inhibition (SI > 33). According to the molecular modeling, compound **18** simultaneously binds to the PAS, mid-gorge, and CAS of AChE and BuChE (Fig. 7).[29]

3.3.2. Replacement of indanone with nitrogen-containing heterocycles. The design and synthesis of phthalimide–dithiocarbamate hybrids were performed by Asadi *et al.* based on the donepezil pharmacophore. All lead compounds demonstrated cholinesterase inhibitory activity, and a benzylpiperidine derivative with methylene linker **19** had the greatest inhibitory impact with an IC_{50} of 4.6 μM. There was 2.5-fold greater activity of this compound as compared to rivastigmine (IC_{50} = 11.07 μM) (Fig. 8).[30] Więckowska *et al.* provided donepezil derivatives with an *N*-benzylpiperidine moiety mixed with indole or phthalimide moieties connected by an alkyl linker for mixing anticholinesterase and β-amyloid anti-aggregation activities in one molecule. Among the 28 targets, (2-(8-(1-(3-chlorobenzyl)



R=H **35a** *h*BuChE IC_{50}=9.94 nM
R=Ac **35b** *h*BuChE IC_{50}=0.17 nM

Fig. 18 Structure of an azido 1,2,3-triazoles-benzylpiperidine analog as a selective BuChE inhibitor.



36
*h*AChE IC_{50}=0.40 μM
*h*BuChE IC_{50}=0.129 μM

Fig. 19 Structure of a pyrrolizine–benzylpiperidine hybrid.

piperidin-4-yl amino)octyl)isoindoline-1,3-dione) **20** was a BuChE inhibitor with an IC_{50} of 0.72 μM, and it exhibited β-amyloid anti-aggregation activity with inhibition of 72.5% at 10 μM. It penetrates the BBB (Fig. 8).[31]

Substituting the indanone fragment of donepezil with the benzamide or 2-picolinamide moiety introduced a novel MTDL that exhibited potent inhibitory activities towards MAO-A, MAO-B, and AChE. Compound **21**, *N*-(2-(1-benzylpiperidin-4-yl)ethyl)-5-chloropicolinamide, was the most potent agent with moderate cholinesterase inhibition activity in comparison with galanthamine as a reference (Fig. 9). It showed satisfactory inhibitory activity toward MAO-B with an IC_{50} of 3.14 μM and IC_{50} of 13.4 μM for MAO-A. Also, **21** can be considered a metal chelator, and it has the ability to cross the BBB with a low level of toxicity to PC12 cells.[32]

Samadi *et al.* attached the *N*-benzylpiperidine moiety of donepezil to 2-aminopyridine derivatives and synthesized a novel series of considerably potent donepezil–aminopyridine hybrids. The most potent *h*AChE inhibitor was 2-amino-6-((3-(1-benzylpiperidin-4-yl)propyl)amino)pyridine-3,5-dicarbonitrile pyridonepezil **22**, and its activity was 2.6-fold less compared to donepezil for *h*BuChE (IC_{50} (*h*AChE) = 9.4 nM; IC_{50} (*h*BuChE) = 6.6 μM) (Fig. 9).[33] In 2013, Samadi *et al.* developed 6-chloro-pyridonepezils and evaluated them against *h*AChE and *h*BuChE.[34] According to the biological evaluation, the novel compounds are inhibitors of cholinesterase in the submicromolar range. Particularly, 6-chloro-pyridonepezil **23** was the most potent target, being 625-fold more selective for *h*AChE than *h*BuChE. It can be considered a selective dual AChEI for further pharmacological developments in AD treatment (Fig. 9). Novel molecules were produced through the interaction of the *N*-benzylpiperidine moiety of donepezil with pyridine hydrazide, which exhibited greater AChE inhibition and showed higher selectivity over BuChE. For the most active compound **24**, the IC_{50} was 6 nM with the capability to chelate cupric ion (Fig. 9).[35]

It was reported that a new hybrid of donepezil-8-hydroxyquinoline was a multifunctional molecule that can be used to treat AD. Among the molecules, racemic α-aminonitrile-4-(1-benzylpiperidin-4-yl)-2-(((8-hydroxyquinolin-5-yl) methyl)(prop-2-yn-1-yl)amino)butane nitrile **25** was the most promising compound and exhibited mixed-type AChE inhibitory effects and metal-chelating characteristics (Fig. 10).[36]

Donepezil-quinolone carboxamide analogs were synthesized by Pudlo *et al.* Derivative **26a** with the methoxy group and **26b**

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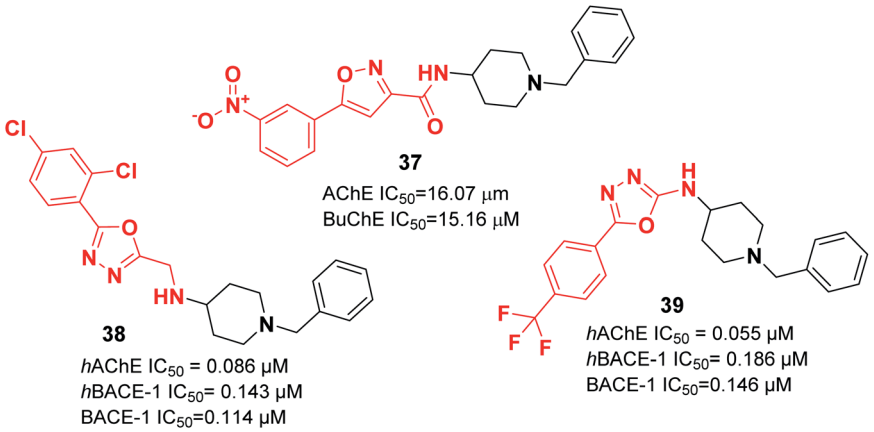

Fig. 20 Structure of isoxazole/oxadiazole–benzylpiperidine hybrids.

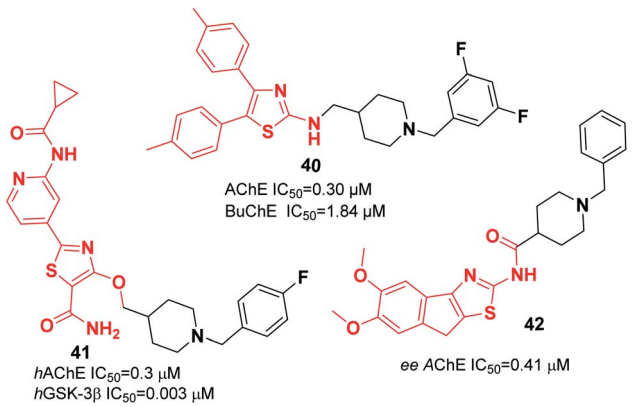

Fig. 21 Structure of thiazole-benzylpiperidine scaffolds.

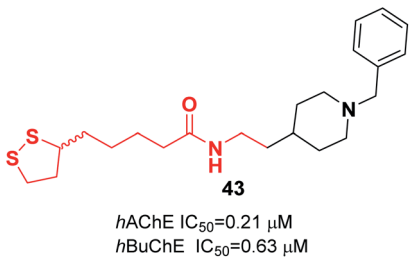

Fig. 22 A lipoic acid-based benzylpiperidine hybrid.

with the hydroxy group were potent and highly selective AChE inhibitors (Fig. 11).[37]

Wang *et al.* produced novel *N*-benzylpiperidine-indole hybrids with a carboxamide linker. Compound **27** with a two-carbon spacer exhibited satisfactory AChE and BuChE inhibition, with an average inhibition (56.3%) of Aβ aggregation at 20 μM, and satisfactory antioxidant activity (3.28 Trolox equivalent by ORAC assay). Moreover, **27** chelated metal ions, decreased the death of PC12 cells caused by oxidative stress, and was able to cross the BBB. The molecular docking of **27** represents a mixed-type inhibitor that simultaneously binds with the CAS and PAS of AChE (Fig. 12).[38] Based on the benzylpiperidine portion of donepezil and the indole derivative of propargylamine, various multi-target molecules were synthesized by Bautrisa-Aguilera *et al.* Among the synthetic compounds, *N*-((5-(3-(1-benzylpiperidin-4-yl)propoxy)-1-methyl-1*H*-indol-2-yl) methyl)prop-2-yn-1-amine **28** was the most potent inhibitor (Fig. 12).[39]

Piemontese *et al.* conjugated the benzylpiperidine part of donepezil with the benzimidazole bioactive molecule. The biological assessment showed that new targets have potential anti-Aβ aggregation capacity, antioxidant activity, and metal-chelating properties. The synthetic lead **29** showed satisfactory AChE inhibition activity and moderate inhibition of $A\beta_{1-42}$

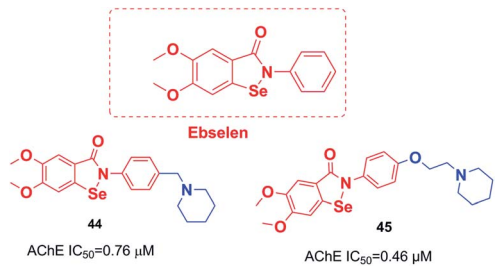

Fig. 23 Ebselen-piperidine hybrids with AChE inhibitor activity.

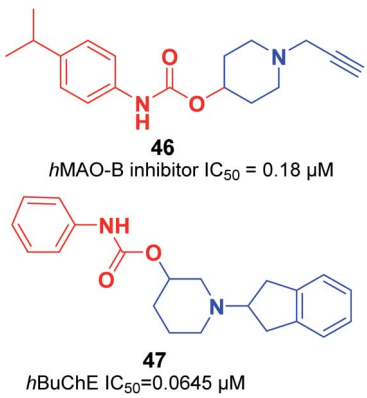

Fig. 24 *N*-alkylpiperidine carbamates as new inhibitors.

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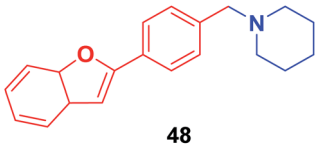
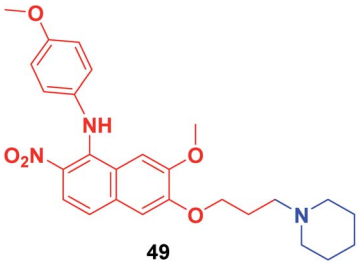


48

AChE inhibition=74%

Fig. 25 2-Arylbenzofuran derivative anticholinesterase agent.



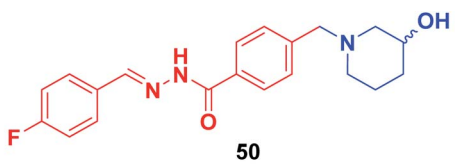
49

*ee*AChE IC_{50}=1.20 μM
*eq*BChE IC_{50}=18.52 μM

Fig. 26 Structure of 4-*N*-phenylaminoquinoline–piperidine hybrid.

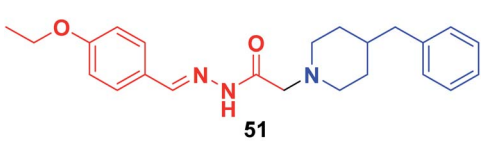
self-mediated aggregation, as well as metal-chelating ability. Benzimidazole hybrid **29** exhibited greater inhibition of Cu-induced aggregation of $A\beta_{1-42}$ as well as enhanced antioxidant capacity (Fig. 13)[40] based on the molecular docking assessment with compound **29** superimposed in the CAS as compared with donepezil. Recently, Chaves *et al.* synthesized 2-hydroxyphenyl benzimidazole derivative **30**. They illustrated that the fluorine atoms and hydroxy groups on the benzene ring resulted in higher cholinergic AChE activity and increased β-amyloid (Aβ) aggregation (self-induced 61%, Cu-induced 71%) (Fig. 13).[41]

Mo *et al.* reported the synthesis of benzylpiperidine-linked 1,3-dimethylbenzimidazolinones. The synthesized compounds **31a** and **31b** containing F or Br on the meta-position of the benzyl ring showed submicromolar IC_{50} values for AChE and BuChE. Additionally, these compounds demonstrated a neuroprotective



50

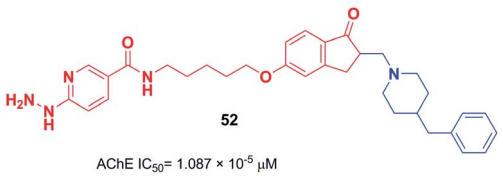
*ee*AChE IC_{50} =8.65 μM



51

AChE IC_{50} =53.1 μM
BuChE IC_{50}=67.3 μM

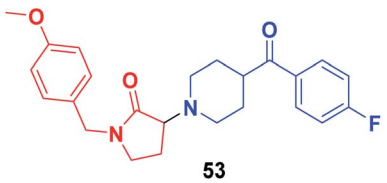
Fig. 27 Structure of aryl acyl hydrazones based on *N*-benzyl-piperidine.



52

AChE IC_{50}= 1.087 × 10^{-5} μM
BuChE IC_{50}= 2.659 × 10^{-3} μM

Fig. 28 Structure of donepezil–hydrazine nicotinate hybrid **52**.



53

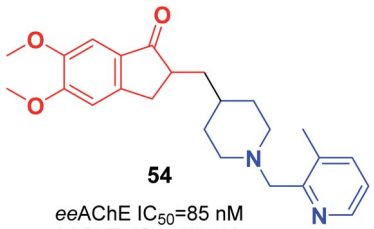
AChE IC_{50}= 0.018 μM

Fig. 29 Structure of *N*-benzylated-pyrrolidin-2-one-piperidine hybrid **53**.

impact upon H_2O_2-induced oxidative damage to PC12 cells as well as antioxidant activity based on the DPPH assay (Fig. 14).[42]

Kilic and colleagues focused on pyridazine derivatives. First, they synthesized 6-chloro-*N*-(2-substituted ethyl)pyridazine-3-carboxamide intermediates from 6-chloropyridazine-3-carboxylic acid and ethylamine derivatives. Next, they employed the Suzuki cross-coupling reaction for the carboxamide intermediate with a suitable phenylboronic acid derivative to obtain the corresponding *N*-(2-substituted ethyl)-6-phenylpyridazine-3-carboxamide derivatives. The biological assay revealed that pyridazine-3-carboxamide derivative **32** exerted dual cholinesterase inhibitory effects, with an IC_{50} of 0.16 μM for AChE and IC_{50} of 9.80 μM for BuChE (Fig. 15).[43] The molecular docking presents the interactions of a pyridazine ring with the active-site gorge of AchE and the Trp279 residue in the peripheral anionic site and an anisole ring with a water molecule.

Vila *et al.* reported synthesizing donepezil analogs using a phthalazin-1(2*H*)-one scaffold as potent human ChEIs. The biological assessment showed that the ChE inhibitory potency and selectivity of AChE/BuChE were affected by the structural modifications to a great extent. Also, the length of the chain between the *N*-benzylpiperidine fragment and the



54

*ee*AChE IC_{50}=85 nM
*h*AChE, IC_{50}=73 nM

Fig. 30 Structure of a 3-hydroxypyridinaldoxime-indanone derivative.

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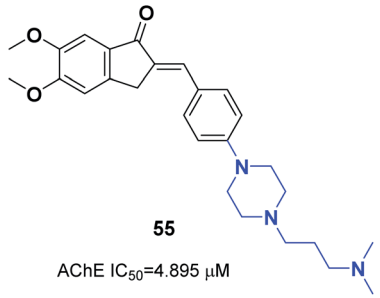

Fig. 31 Structure of indenone–piperazine hybrid **55**.

phthalazinone moiety impacted the inhibition of AChE. Compound **33** behaved as a dual cholinesterase inhibitor towards the AChE and BuChE enzymes (Fig. 16).[44]

In 2019, Greunen *et al.* attached the indanone part of donepezil to different commercial heterocycle amines under mild conditions in the presence of catalytic 4-(dimethylamino) pyridine (4-DMAP) to obtain carboxamide derivatives in low to good yield. Among the selected targets, 1-benzyl-*N*-(1-methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)piperidine-4-carboxamide **34** afforded *in vitro* AChE inhibition with an IC_{50} value of 5.94 μM (Fig. 17).[45]

De Andrade *et al.* replaced the 5,6-dimethoxy-1-indanone moiety of the donepezil structure with triazoles. This change resulted in a reduction in *h*AChE inhibition and an increase in *h*BuChE inhibitor activity. Compound **35** was the most potent (0.17 nM) selective *h*BuChE inhibitor (>58 000-fold) and showed no cytotoxicity (Fig. 18).[46]

In 2019, El-Sayed constructed pyrrolizine-benzylpiperidine hybrids. *In vitro* assay indicated that in this series, *N*-(1-benzylpiperidin-4-yl)-4-oxo-4,5,6,7-tetrahydro-3*H*-pyrimido[5,4-*a*] pyrrolizine-9-carboxamide **36** exhibited dual inhibitory impact upon *h*AChE and *h*BuChE in the submicromolar range. Also, compound **36** demonstrated cytotoxicity lower or similar to that of donepezil against a normal human hepatic (THLE2) cell line and human neuroblastoma (SH-SY5Y). Based on *in vivo* studies, the compound decreased the cognitive dysfunction of scopolamine-induced AD mice (Fig. 19).[47]

3.3.3. Replacement of indanone with isoxazole and oxadiazole derivatives. The synthesis and design of novel donepezil

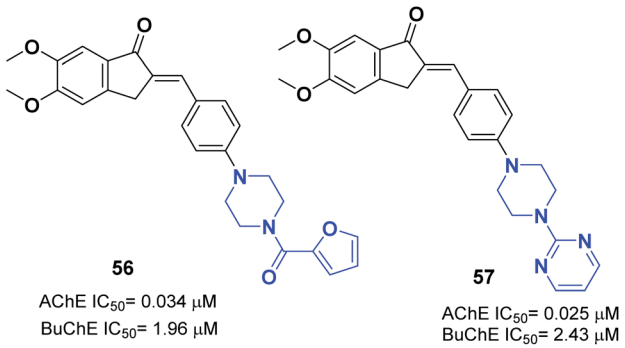

Fig. 32 The structure of piperazin–benzylidene hybrids.

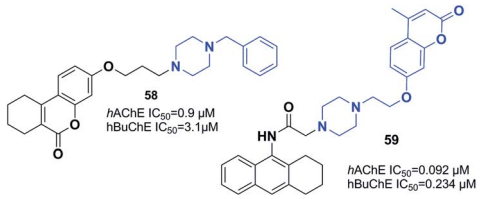

Fig. 33 Structure of chromene/coumarin–piperazine hybrids.

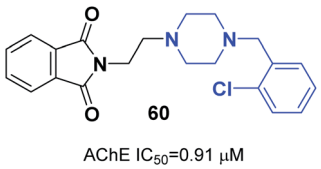

Fig. 34 Structure of phthalimide–piperazine hybrid **60**.

hybrids were performed by Saeedi *et al.*, where *N*-benzylpiperidine attached arylated isoxazole through a carboxamide linker. *In vitro* biological assessment showed that the synthetic compounds acted as multi-target ligands and, among them, *N*-(1-benzylpiperidin-4-yl)-5-(3-nitrophenyl)isoxazol-3-carboxamide **37** was the most optimal AChEI (IC_{50} = 16.07 μm for AChE; IC_{50} = 15.16 μM for BuChE) (Fig. 20).[48] Tripathi *et al.* connected *N*-benzylpiperidine and 5-phenyl-1,3,4-oxadiazole hybrids with –NH and $–NHCH_2$ linkers to synthesize multi-target hybrids. They found that the binding affinity was enhanced toward the PAS by the presence of 1,3,4-oxadiazole, and was responsible for the extension of the *N*-benzylpiperidine moiety deeper into the CAS of AChE and BuChE, which yielded viable dual inhibitors of ChE. Among the tested compounds, **38** and **39** displayed outstanding inhibition toward *h*AChE, *h*BuChE, and β-secretase-1 (hBACE-1). The anti-Aβ aggregatory activity of **38** was confirmed by the morphological property of incubated samples of Aβ aggregates in the absence

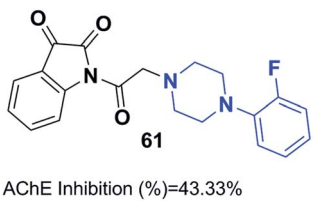

Fig. 35 Structure of (1-(2-(4-(2-fluorobenzyl)piperazin-1-yl)acetyl) indoline-2,3-dione) **61**.

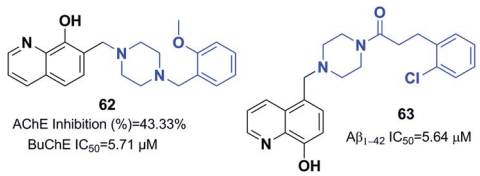

Fig. 36 Structure of 8-hydroxyquinoline-donepezil-like molecules.

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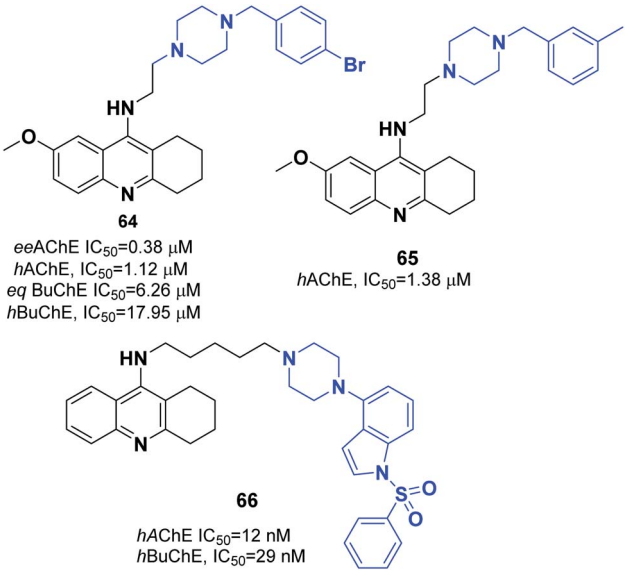

Fig. 37 Structure of acridine–piperazine hybrids.

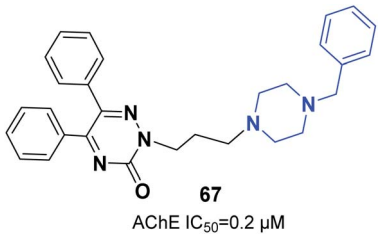

Fig. 38 Structure of 3-oxo-1,2,4-triazine-piperazine hybrid 67.

or presence of an inhibitor (Fig. 20). Compounds **38** and **39** lacked neurotoxicity towards the SH-SY5Y neuroblastoma cell line according to the MTT assay.[49]

3.3.4. Replacement of indanone with thiazole derivatives. Shidore *et al.* prepared diarylthiazole–benzylpiperidine hybrids and assessed their potential in AD treatment using various *in*

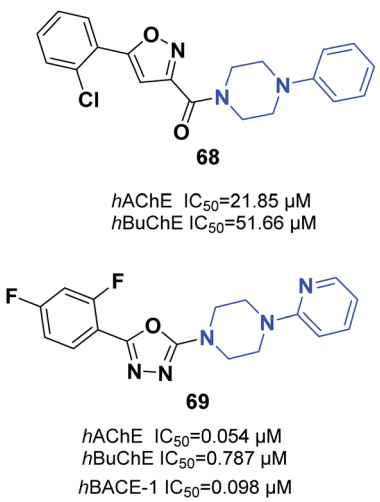

Fig. 39 Isoxazole/oxazole–piperazine hybrids.

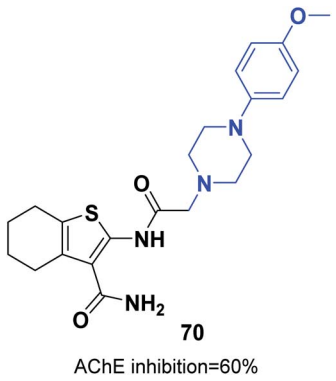

Fig. 40 Structure of thiophene-piperazine 70.

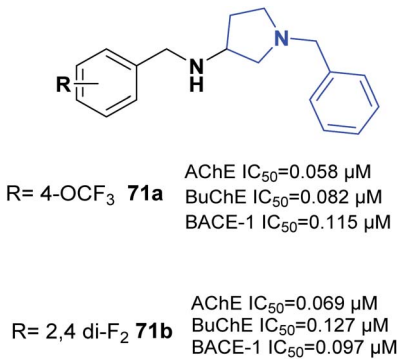

Fig. 41 Structure of benzylamine-pyrrolidine derivative 71.

vitro and *in vivo* experiments. Compound **40** exhibited the greatest inhibitory potency against AChE and BuChE and a mixed-type inhibition of AChE through binding to the PAS and CAS. This derivative also demonstrated reasonably acceptable inhibition of $A\beta_{1-42}$ aggregation induced by AChE (27% inhibition) (Fig. 21).[50] Glycogen synthase kinase-3β (GSK-3β) can be used as an indication that clinical efficacy has been achieved.

Recently, the design and synthesis of new types of pyridinethiazole with benzylpiperidine hybrids were carried out as GSK-3*β*/AChE dual-target inhibitors. Among these scaffolds, **41** was the most encouraging choice, with an IC_{50} of 0.3 μM for *h*AChE and IC_{50} of 0.003 μM for *h*GSK-3β (Fig. 21).[51] The Greunen group synthesized 1-benzyl-*N*-(5,6-dimethoxy-8*H*-indeno [1,2-*d*]thiazol-2-yl) piperidine-4-carboxamide **42**, which exhibited AChE inhibitory activity (IC_{50} = 0.41 μM) (Fig. 21).[45]

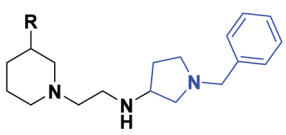

Fig. 42 Structure of piperazine-benzyl pyrrolidine derivatives.

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Table 1 Summary of multi-target-directed ligands

Compound number	AChE	BuChE	Inhibition of Aβ	BACE-1	Metal chelation	MAO	Non-toxicity	Reference
1	*			*				14
2	*			*				14
3	*							15
4	*	*	*					16
5	*	*				*		17
6	*	*						18
7	*		*	*				19
8	*		*	*				19
9	*		*		*		*	21
10	*	*						22
11		*						23
12	*	*	*					22
13	*	*						24
14	*	*				*	*	25
15	*					*		26
16	*							27
17	*		*			*	*	28
18	*	*				*		29
19	*							30
20		*	*					31
21	*	*	*		*	*	*	32
22	*	*						33
23	*	*						34
24	*	*			*			35
25	*	*			*			36
26	*							37
27	*	*	*		*		*	38
28	*	*			*	*		39
29	*		*		*			40
30	*		*					41
31	*	*						42
32	*	*						43
33	*	*						44
34	*							45
35		*						46
36	*	*					*	47
37	*	*						48
38	*	*	*	*			*	49
39	*	*	*	*			*	49
40	*	*		*				50
41	*							51
42	*							45
43	*	*						52
44	*							54
45	*							54
46						*		17
47		*						17
48	*							55
49	*	*						56
50	*							57
51	*	*						58
52	*	*						59
53	*							60
54	*		*					61
55	*						*	62
56	*	*	*					63
57	*	*	*					63
58	*	*						64
59	*	*	*		*			65
60	*							66
61	*							67
62	*	*	*				*	68
63			*		*			69

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Table 1 (*Contd.*)

Compound number	AChE	BuChE	Inhibition of Aβ	BACE-1	Metal chelation	MAO	Non-toxicity	Reference
64	*	*						70
65	*							71
66	*	*						72
67	*							73
68	*	*						74
69	*	*		*			*	75
70	*							76
71	*	*		*				77
72		*	*	*				78

3.4. Replacement of indanone with a lipophilic structure

Estrada *et al.* combined the lipoic acid structure with *N*-benzylpiperidine to obtain novel MTDLs. Lipoic acid-based hybrids were synthesized through coupling reaction between the corresponding amine derivative and (*R*,*S*)-LA or enantiopure (*R*)-LA or (*S*)-LA in a microwave oven at 120 °C, using 1,1′-carbonyldiimidazole (CDI) as an activating agent. The most potent ligand **43** demonstrated significant inhibitory activity against ChEs (Fig. 22).[52]

3.5. Miscellaneous MTDLs

An organoselenium compound with biological properties is ebselen (2-phenyl-1,2-benzisoselenazol-3(2*H*)-one).[53] Luo *et al.* connected ebselen to the pharmacophores of the AChEIs for producing novel hybrid molecules. Compounds **44** and **45** exhibited the highest potency against AChE (Fig. 23).[54]

Košak *et al.* developed a class of *N*-alkylpiperidine carbamates as viable agents against AD, with the most promising compounds being **46** and **47**. *N*-Propargylpiperidine **46** revealed *h*MAO-B inhibitor activity (IC_{50} = 0.18 μM), and compound **47** acted as a selective *h*BuChE inhibitor with an IC_{50} of 0.0645 μM (Fig. 24).[17]

Pouramiri *et al.* synthesized a library of 2-aryl benzofuran derivatives through four-step reactions from 2-hydroxybenzyl alcohol in good yield. In comparison with donepezil, the synthesized compound **48** with the piperidine moiety exhibited the most optimal AChE inhibition activity of 74% at 23 μM (Fig. 25).[55]

Cai *et al.* investigated the role of the 4-*N*-phenylaminoquinoline core in AChE and BuChE inhibition. They synthesized a series of novel derivatives of 4-methyl-piperidine-4-*N*-phenylaminoquinoline from the commercially available vanillic acid *via* ten steps. The biological evaluation indicated that compound **49** with a *para* methoxy group was more highly potent against AChE than galanthamine (Fig. 26).[56]

In 2018, the synthesis of a novel series of aryl acyl hydrazones was carried out by Viegas *et al.* according to the pharmacophoric *N*-benzyl-piperidine subunit of donepezil, the substituted hydroxy-piperidine fragment, and an acyl hydrazone linker. Among *N*-benzyl-piperidine acyl hydrazone derivatives, compound **50** showed satisfactory inhibition of electric eel (*Electrophorus electricus*) AChE, COX-1 (64%), and COX-2 (53%) (Fig. 27).[57] Özer *et al.* carried out the synthesis of *N*′-2-(4-benzylpiperidin-yl)acyl hydrazone derivatives. Based on the enzyme inhibition assay results, compound **51** with the 4-ethoxybenzylidene group was the most active, with an IC_{50} of 53.1 μM for AChE enzyme and IC_{50} of 67.3 μM BuChE enzyme (Fig. 27).[58]

The design and the synthesis of donepezil-hydrazine nicotinates were performed by Zurek *et al.* in 2013. All the products showed a higher affinity for AChE than BuChE. Compound **52** was the most effective inhibitor of AChE ($IC_{50} = 1.087 \times 10^{-5}$ μM). The molecular modeling was performed using Cache software and showed that compound **52** binds to AChE with a total score of −181.939 (Fig. 28).[59]

Gupta *et al.* replaced the 1-indanone moiety with *N*-benzylated-pyrrolidin-2-one and found that 3-(4-(4-fluorobenzoyl)-piperidin-1-yl)-1-(4-methoxybenzyl)-pyrrolidin-2-one **53** exhibited an excellent anti-Alzheimer's profile (Fig. 29).[60]

Wang *et al.* focused on modifying the benzyl group of donepezil using several disparate fragments, including quinolone, pyridine, and hydroxyquinoline, for better interaction with dual binding sites of AChE. Based on the screening results, all the compounds demonstrated a potent AChE inhibition with values of IC_{50} in the nanomolar range, satisfactory antioxidant activities, Aβ interaction, and BBB penetration. (5,6-dimethoxy-2-((1-((3-methylpyridin-2-yl)methyl)piperidin-4-yl)methyl)-2,3-dihydro-1*H*-inden-1-one) **54** displayed outstanding inhibition of AChE, satisfactory metal chelation, and inhibitory impact upon self-induced (18.5%), *h*AChE-induced (72.4%), and Cu^{2+}-induced (46.3%) aggregation of $A\beta_{1-42}$ at 20 μM (Fig. 30).[61]

4. Derivatives with replacement of the piperidine part of donepezil

4.1. Indanone–piperazine hybrids

The *N*-substituted piperazine moiety mimics the *N*-benzylpiperidine fragment from donepezil. In 2016, Saglik and coworkers synthesized novel donepezil analogs by replacing the piperidine part with 4-substituted piperazines. Among the compounds, 4-dimethylamino piperazine derivative **55** displayed prominent inhibition of AChE and nontoxicity towards the NH/3T3 cell line (Fig. 31).[62]

In 2017, Mishra attached the indanone part of donepezil to the 4-substituted piperazin-1-yl-benzylidene moiety from

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commercially available substituted piperazine and 4-fluoro benzaldehyde at 100 °C followed by the Knoevenagel condensation reaction to link the indanone moiety with various substituted piperazines through a methylene linker. Compounds **56** and **57** displayed excellent AChE inhibitory ability with an IC_{50} = 0.034 μM and 0.025 μM and Aβ fibril aggregation inhibition activity of 80.4 and 81.6%, respectively (Fig. 32).[63]

4.2. O-Heterocycle–piperazine hybrids

Gulcan designed and synthesized 6*H*-benzo[*c*]chromen-6-one and 7,8,9,10-tetrahydro-benzo[*c*]chromen-6-one derivatives (Fig. 33).[64] Replacement of indanone with chromene and piperidine with piperazine led to an increase in the inhibitory activity of compound **58**. In addition, a three-carbon atom spacer between the benzo[*c*]chromen-6-one moiety and piperazine is ideal for cholinesterase inhibition within this group of compounds.

Tacrine is another FDA-approved ChE inhibitor that has become an extensively used scaffold in recent years. In 2013, Xie *et al.* synthesized a novel MTDL by connecting tacrine, coumarins, and piperazine. Among the synthetic compounds, **59** with the methyl on the 4-position of chromene showed the greatest AChE inhibition, and an acceptable BuChE inhibition and Aβ aggregation inhibition (67.8%, 20 μM). Moreover, **59** was a satisfactory metal chelator. Based on molecular modeling and kinetic studies, **59** was a mixed type of inhibitor that binds to the CAS, PAS, and mid-gorge site of AChE at the same time (Fig. 33).[65]

4.3. N-Heterocycle–piperazine hybrids

Mohammadi *et al.* designed phthalimid-piperazine scaffolds. They employed the Gabriel synthetic reaction of phthalic anhydride with *N*-aminoethylpiperazine to obtain 2-(2-(piperazin-1-yl) ethyl)isoindoline-1,3-dione with 61% yield. In addition, equimolar quantities of isoindoline derivatives were reacted with the appropriate benzyl chloride to obtain the corresponding targets. Biological assessment of anticholinesterase activity determined that products with electron-withdrawing groups showed greater potency, and compound **60** with a chloro substituent on the *ortho* position of the phenyl ring exhibited the greatest AChE inhibition with an IC_{50} of 0.91 μM (Fig. 34).[66]

Replacement of the indanone part of donepezil with indoline-2,3-dione generated a novel scaffold with greater activity than that of donepezil. Compound **61** (1-(2-(4-(2-fluorobenzyl) piperazin-1-yl)acetyl)indoline-2,3-dione) demonstrated greater inhibitory activity compared to donepezil because of the 2-fluorobenzyl replacement and the acetamido spacer. This molecule remarkably binds to the H-bond receptor with Phe288, leading to more optimal pharmacological activity (Fig. 35).[67]

Prati *et al.* proposed and designed a new series of 8-hydroxyquinoline-donepezil-like hybrids with multi-targeting activities towards key AD targets. The new hybrid 7-((4-(2-methoxybenzyl) piperazin-1-yl)methyl)-8-hydroxyquinoline **62** inhibited Aβ self-aggregation, exhibited the highest potency for chelating copper(II) and zinc(II), and exerted the highest *in vitro* antioxidant activity. For compound **62**, significant BBB penetration, negligible cytotoxicity in T67 cells, and acceptable toxicity in primary human umbilical vein endothelial cells (HUVECs) accompanied its multi-target profile (Fig. 36).[68] The interaction of 8-hydroxyquinoline and donepezil hybrid molecules with cholinesterase and monoamine oxidase enzymes was evaluated by Yang *et al.*[69] Compound **63** had considerable inhibitory impacts against self-induced aggregation of $A\beta_{1-42}$ (IC_{50} = 5.64 μM) and potential antioxidant properties (2.63 Trolox equivalents) (Fig. 36). Furthermore, **63** was capable of chelating biometals, inhibiting aggregation of Cu^{2+}/Zn^{2+}, and penetrating the BBB *in vitro*.

Korabecny developed novel ChEIs based on 7-methoxytacrine-donepezil-like structures. The synthesized compounds showed cholinesterase inhibitory activity, and the values of IC_{50} were in the micromolar to sub-micromolar scale range toward enzymes of human and animal origin. *N*-(2-{4-[(4-Bromophenyl)methyl] piperazin-1-yl}ethyl)-7-methoxy-1,2,3,4-tetrahydroacridin-9-amine trihydrochloride **64** was the most promising compound (Fig. 37).[70] In 2016, Sepsova *et al.* evaluated the interaction of 7-methoxy-*N*-(2-(4-(3-methyl benzyl)piperazin-1-yl)ethyl)-1,2,3,4-tetrahydroacridin-9-amine with AChE and cholinergic (muscarinic and nicotinic) receptors. The results showed that compound **65** acts as an AChE inhibitor (Fig. 37).[71] Więckowska *et al.* designed (phenyl sulfonyl-1*H*-indol-4-yl piperazin-1-yl)hexyl)-1,2,3,4-tetrahydroacridin-9-amine, and biological evaluation indicated that compound **66** had a HT6 antagonist (K_b = 27 nM) (Fig. 37).[72]

Molecular hydrides of the 5,6-biphenyl-3-oxo-1,2,4-triazine nucleus and substituted piperazines were synthesized and assessed for inhibition of ChE. Compound **67** (5,6-diphenyl-3-oxo-2-(3-(4-benzylpiperazin-1-yl)propyl)-1,2,4-triazine) with three carbon atoms connected to the benzylpiperazine terminal group demonstrated inhibition potency toward AChE with an IC_{50} of 0.2 μM. Based on docking models, the benzyl group engaging at the lowest part of the enzyme gorge plays a crucial role in interaction with CAS residues of AChE (Fig. 38).[73]

4.4. Isoxazole/oxazole–piperazine hybrids

Saeedi and colleagues designed new isoxazoles linked to the moiety of phenylpiperazine and evaluated the AChE inhibitory effect of targets through Ellman's method as compared to donepezil and rivastigmine references. Among the synthetic compounds, (5-(2-chlorophenyl)isoxazol-3-yl)(4-phenylpiperazin-1-yl)methanone **68** was the most potent candidate (Fig. 39).[74] Tripathi *et al.* explored the synthesis of 2-pyridylpiperazine hybrids and 5-phenyl-1,3,4-oxadiazoles with considerable inhibitory possibilities for AD. Compound **69** with a 2,4-difluoro replacement at the end phenyl ring was considered the most viable lead, with cholinesterase inhibition and β-secretase-1 activity. Based on an analysis of enzyme kinetics, **69** demonstrated a mixed-type inhibition toward *h*AChE, with a K_i of 0.030 μM. Compound **69** showed considerable deposition of propidium iodide from the PAS of *h*AChE, penetration in PAMPA, neuroprotective capability against the SH-SY5Y neuroblastoma cell line, and outstanding BBB (Fig. 39).[75]

4.5. Thiophene–piperazine hybrids

The synthesis of new thiophene derivatives and evaluation of their biological inhibition were carried out by Ismail *et al.* 2-(2-

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(4-(4-Methoxyphenyl)piperazin-1-yl)acetamido)-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide **70** demonstrated inhibition of 60% in comparison with only 40% inhibition for donepezil (Fig. 40).[76] The amide linker in this scaffold led to extra binding to the receptor through three different H-bonds with Phe288 and resulted in increased pharmacological activity.

4.6. Modified scaffolds based on pyrrolidine

One of the latest studies on MTDLs was carried out by Choubey *et al.* They designed derivatives of *N*-benzyl pyrrolidine and biologically assessed their ability to treat AD. Among the synthesized leads, **71a** and **71b** demonstrated proportionate enzymatic inhibition against cholinesterases. They also showed significant PAS-AChE binding ability, outstanding BBB permeation, neuroprotective activity against Aβ-induced stress, and possible disassembly of Aβ aggregates (Fig. 41).[77]

Wichur *et al.* synthesized novel multifunctional ligands to investigate their inhibitory effects on BuChE, β-secretase, and amyloid-β (Aβ), and their antioxidant, aggregation of tau protein, and metal-chelating characteristics. All the targets exhibited dual anti-aggregating properties towards Aβ and tau protein (**72a**: 45% for Aβ, 53% for tau; **72b**: 49% for Aβ, 54% for tau). Compound **72a** with an IC_{50} of 2.39 μM and **72ab** with an IC_{50} of 1.94 μM exhibited the highest inhibitory potency against BuChE (Fig. 42).[78]

5. Conclusion

The enhancement of ACh would be considered an effective method to compensate for the deficiency of acetylcholine, and most treatment strategies for AD are focused on enhancing cholinergic neurotransmission. However, there are severe side effects to FDA-approved drugs for AD, including vomiting, nausea, diarrhea, bradycardia, abnormal dreams, and fatigue. Because of AD's complex pathophysiology, there is an urgent need to discover and develop efficient new therapeutic agents with minimal side effects to effectively combat AD.

In this review, we discussed the structural modification of donepezil as described in articles published from 2012–2020. This review is categorized into sections according to the changes made to the donepezil linker, replacement of the indanone moiety with O-containing heterocycles or N-heterocyclic moieties, and replacement of the piperidine moiety with piperazine or pyrrolidine structures. In addition, we tried to outline different synthetic small molecules based on the structure of donepezil and describe detailed structure–activity relationships.

Studies showed that attaching chromones with piperidine will produce ChE inhibitors and selective *h*MAO inhibition. Also, the type of spacer modulates additional activities, including metal-chelating characteristics. Furthermore, using hydroxyquinoline instead of the indanone part of donepezil leads to multi-target properties. Hybrid molecules from tetrahydroacridin-9-amines and piperazine will exhibit the best dual ChE activities and are vital for the effective treatment of AD. This review will assist researchers and medicinal chemists in designing novel, target-based, and advanced donepezil analogs with advantageous biological properties for effective AD therapy (Table 1).

Abbreviations

ABTS	(2,2′-Azino-bis(3-ethylbenzothiazoline-6-sulfonic acid)
ACh	Acetylcholine
AChE	Acetylcholinesterase
AChEI	Acetylcholinesterase inhibitor
AD	Alzheimer's disease
BACE-1	β-Secretase-1
BuChE	Butyrylcholinesterase
CAS	Catalytic anionic site
ChE	Cholinesterase
DFH	Donepezil–flavonoid hybrid
*ee*AChE	*Electrophorus electricus* acetylcholinesterase
FRAP	Ferric reducing antioxidant power
Glu	Glutamate
GSK-3β	Glycogen synthase kinase-3β
His	Histidine
5-HT	5-Hydroxytryptamine (serotonin)
5-LOX	5-Lipoxygenase
MAO	Monoamine oxidase
MAOI	Monoamine oxidase inhibitor
MTDL	Multitarget-directed ligand
PAS	Peripheral anionic site
Phe	Phenylalanine
QSAR	Quantitative structure–activity
SI	Selectivity index
σ-1R	Sigma-1 receptor
Trp	Tryptophan

Conflicts of interest

There are no conflicts to declare.

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