Multi-Target-Directed Ligand Approach in Anti-Alzheimer's Drug Discovery

Vaishali M. Patil, Neeraj Masand, Vertika Gautam, Shikha Kaushik, and Dee Wu

Abstract Alzheimer's disease is a multifactorial neurodegenerative syndrome and has raised concern related to global health and economy. Numerous targets have been analyzed toward discovery and development of potential therapeutics. Some of the single-target-based Food and Drug Administration (FDA) approved drugs include donepezil, galantamine, rivastigmine, and memantine which can improve the patient condition but fail to completely cure the disease. Single-target therapeutics have limitations to cure the disease due to complicated pathogenesis and complex network formed by the associated signaling pathways. Thus, the multi-target-directed ligand (MTDL) approach has gained importance as the potential anti-Alzheimer's drugs having the advantages of synergistic effect with improved cognition and regulating its progression. In the present chapter, multi-target-directed approaches are discussed with coverage of design strategies and promising compounds reported in recent years. Some of the well-explored targets like acetylcholine esterase (AChE), ß-site amyloid precursor protein-cleaving enzyme 1 (BACE-1), glycogen synthase kinase 3ß (GSK-3ß), monoamine oxidases (MAOs), metal ions in the brain, N-methyl-D-aspartate (NMDA) receptor, and phosphodiesterases (PDE)

V. M. Patil (✉)
Department of Pharmaceutical Chemistry, KIET School of Pharmacy, KIET Group of Institutions, Delhi-NCR, Ghaziabad, Uttar Pradesh, India

Faculty of Pharmaceutical Sciences, UCSI University, Kuala Lumpur, Malaysia

N. Masand
Department of Pharmacy, Lala Lajpat Rai Memorial Medical College, Meerut, Uttar Pradesh, India

V. Gautam
Institute of Pharmaceutical Research, GLA University, Mathura, Uttar Pradesh, India

S. Kaushik
Department of Pharmaceutical Chemistry, KIET School of Pharmacy, KIET Group of Institutions, Ghaziabad, Uttar Pradesh, India

D. Wu
Department of Radiological Sciences, Section of Medical Physics, University of Oklahoma, Norman, OK, USA

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are described focusing on their contribution toward cognitive neurodegeneration leading to Alzheimer's disease (AD).

Keywords Alzheimer's disease (AD) · Multi-target-directed ligand (MTDL) · Acetylcholine esterase · BACE-1 · Natural compounds

Abbreviations

5-HT	5-Hydroxytryptamine
AChE	Acetylcholine esterase
AChEI	Acetylcholine esterase inhibitor
AD	Alzheimer's disease
APOE	Apolipoprotein E
BACE!	ß-site amyloid precursor protein-cleaving enzyme 1
BBB	Blood–brain barrier
BuChE	Butyrylcholinesterase
CB1	Cannabinoid-based 1
ChAT	Acetyltransferase
FDA	Food and drug administration
GSK-3ß	Glycogen synthase kinase 3ß
JNK	c-Jun N-terminal kinase
MAO	Monoamine oxidases
MTDL	Multi-target-directed ligand
NFT	Neurofibrillary tangles
NMDAR	N-methyl-D-aspartate receptor,
NQO1	NAD(P)H quinone oxidoreductase
PAMPA	Parallel artificial membrane permeation assay
PDE	Phosphodiesterase
ROCK	Rho-associated protein kinase
ROS	Reactive oxygen species
α-M	α-Mangostin

1 Introduction

Alzheimer's disease (AD) is a progressive, multifaceted, and multifactorial neurodegenerative disease (Yilmaz 2015). It has phylogenic nature and possesses cross-talk among various signaling cascades. The complex pathophysiology of AD consists of aggregation of pathological proteins, impaired neurotransmission, increased oxidative stress, and/or microglia-mediated neuroinflammation. Various AD hypotheses supported by experimental data have been proposed, and they play an important role in its pathogenesis (Fig. 1) (Hardy and Higgins 1992; Selkoe and

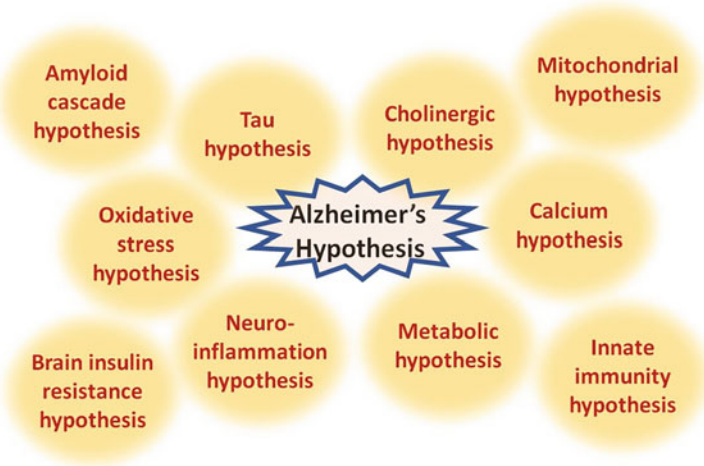


Fig. 1 Various proposed hypotheses for Alzheimer's disease

Hardy 2016; Iqbal and Grundke-Iqbal 1996; Iqbal et al. 2016; Perry et al. 1977, Bartus et al. 1982; Moreira et al. 2010; Swerdlow et al. 2010; Coyle and Puttfarcken 1993; Zhu et al. 2004; McGeer et al. 1994; de la Monte 2009; Deng et al. 2009; Hoyer 2000; Iqbal and Grundke-Iqbal 2005; Gong et al. 2016; Khachaturian 1994; Guillot-Sestier et al. 2015; Masand et al. 2017; Gupta and Patil 2020).

Several hallmarks of AD involved in pathological progression are oxidative stress, neuroinflammation, synaptic dysfunction, deprivation of cholinergic function, amyloid plaques, and neurofibrillary tangles (NFTs) (Canter et al. 2016; Busche et al. 2019). Thus, it can be defined as a disorder regulated by enzymes/receptors like acetylcholinesterase (AChE), butyrylcholinesterase (BuChE), N-methyl-D-aspartic acid (NMDA), ß-secretase 1 (BACE1), and muscarinic and signaling pathways (c-Jun N-terminal kinase (JNK)) (Martin et al. 2013). In addition to this, based on the review of clinical studies, some of the important targets are amyloid, tau, apolipoprotein E (APOE)/lipids and lipoprotein receptors, neurotransmitter receptors, neurogenesis, inflammation, oxidative stress, cell death proteostasis/proteinopathies, metabolism and bioenergetics, vasculature, growth factors and hormones, synaptic plasticity/neuroprotection, gut–brain axis, circadian rhythm, and epigenetic regulators which were of interest for clinical studies in 2022 (Fig. 2) (Turgutalp et al. 2022; Cummings et al. 2022). Drugs acting as antagonists of these enzymes/pathways have limited success to control the symptoms and fail to stop or reverse the disease progression (Savelieff et al. 2019).

The prevalence of AD is increasing, and $>$ 50 million elderly are living with it (Li et al. 2022b). Research efforts have focused on the reported AD-related subpathogenesis without any success to put forward disease-modifying therapeutics. Unfortunately, no effective therapy for the prevention or treatment of AD is available. No disease-modifying drugs are available in the market, and very low clinical success is reported for this class of drugs. In addition to this, aspects related to the

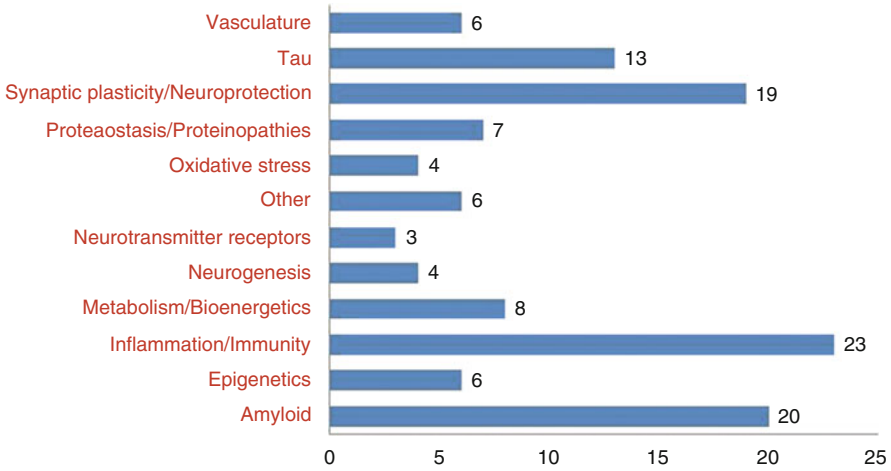


Fig. 2 Number of agents entered in the clinical phase of evaluation (during the year 2022) and their anti-AD mechanisms

onset and progression of this neurodegenerative disease are still unexplored. Researchers are focusing on newer therapeutic targets toward their efforts to identify definite and direct therapeutics. Despite the huge number of preclinical and clinical studies (> 4000), only a few drugs have been approved for clinical use and there is requirement for drugs to prevent, delay the onset of neurodegeneration, slow the disease progression, and improve the AD-associated symptoms (Cummings et al. 2022). Earlier FDA approved only five drugs for the treatment of AD, which include tacrine, donepezil, galantamine, rivastigmine, and memantine with recent addition of Leqembi (lecanemab-irmb) through accelerated approval pathway (https://www.fda.gov/news-events/press-announcements/fda-grants-accelerated-approval-alzheimers-disease-treatment). Tacrine has been discontinued due to its hepatotoxicity (Watkins et al. 1994). Among the various reported approaches, multi-target-directed ligands (MTDLs) have several advantages when compared to single-target or combination therapeutics, but none of the reported agents have entered the clinical phase of development. In this chapter, an overview of the MTDL approach for the development of anti-AD therapeutics has been discussed along with its potential to address the associated limitations with various examples from the preclinical phase of development.

2 Single-Target, Multi-Target, and Combination Therapeutics

For AD drug development, the most promising strategies are combination therapeutics, MTDL therapeutics, and drug repurposing (Barthélemy et al. 2020). Among them, the drug repurposing approach consumes less time and requires less

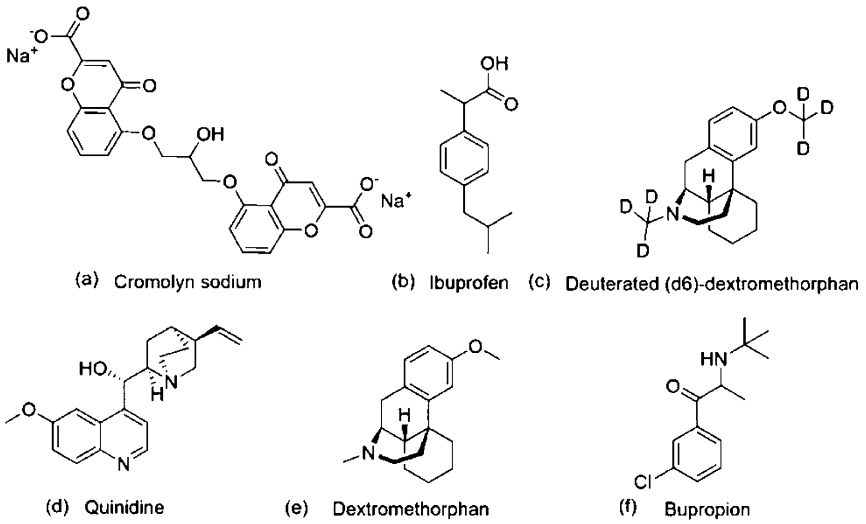


Fig. 3 Chemical structures of compounds used for anti-AD combination therapeutics (**a**, Cromolyn sodium; **b**, Ibuprofen; **c**, Deuterated (d6)-dextromethorphan; **d**, Quinidine; **e**, Dextromethorphan; **f**, Bupropion)

Table 1 Details of anti-AD combination therapeutics in phase III of clinical studies

Clinical trial ID	Details of combination	AD target	Ref.
NCT02547818	ALZT-OP1 (cromolyn and ibuprofen)	Amyloid and inflammation	Panza et al. (2016), Hori et al. (2015), Brazier et al. (2017), Pasqualetti et al. (2009), Weggen et al. (2001), Zhang et al. (2018)
NCT02442765, NCT02442778, NCT02446132	AVP-786 (deuterated (d6)-dextromethorphan and quinidine)	Agitation	Garay and Grossberg (2017), Wilkinson et al. (2019)
NCT03226522	AXS-05 (bupropion and dextromethorphan)	Agitation	O'Gorman et al. (2019), Ahmed et al. (2019), Stahl (2019)

investment, while a few combination therapeutics have been selected for phase III clinical studies (Fig. 3 and Table 1). In case of multi-target approach, drug combinations are used to prepare a single formula. There are some challenges associated with combination therapeutics such as drug–drug interactions due to the release or blockage of certain enzymes involved in metabolism. It alters drug concentrations leading to absence/reduced efficacy or toxic effects. In case of elderly patients taking several drugs, it increases the chances of drug–drug interactions.

In the last decade, multi-target or multifunctional drugs have gained importance as potential therapeutics for various diseases having complex and multifactor pathophysiology and drug resistance cases (Talevi et al. 2012; Koeberle and Werz 2014;

Talevi 2015). In case of complex disorders or diseases having resistance issues like AD, cancer, malaria, mycobacterium tuberculosis, and diabetes, simultaneous modulation of multiple targets can help to heal or reduce the disease condition (de Freitas et al. 2018; Makhoba et al. 2020; Benek et al. 2020). MTDLs are based on the use of one active ingredient (Zhou et al. 2019). In AD, MTDLs are helpful as they can focus on more than one subpathologies simultaneously and to establish a better approach. The current single-target anti-AD therapeutics have limitations like low efficacy and inability to control associated symptoms. Due to the diverse pathogenesis, the single-target anti-AD drugs have limitations and there is requirement of understanding the multifunctional or multi-target strategies for the development of potential drugs.

3 Multi-Target-Directed Strategies

The causative factor behind AD is characterized as a disease caused by the systemic breakdown of physiological networks of the brain (Hopkins 2008; Barabási et al. 2011). The complex pathophysiology observed with AD and lack of success with single-target strategies has emphasized the need for "one drug/ligand, multiple targets" as a better approach. Murphy et al. (2004) have emphasized on rational designing of multi-target directed ligands which can modulate multiple targets of interest related to the pathological condition. These are developed with the objectives to improve efficacy and/or safety and thus may provide wider application in clinical practice. Some of their merits compared to combination therapy include retention of all advantages of combination therapy with some additional benefits like absence of/less drug–drug interactions, reduced risk of adverse effects due to reduced polypharmacy, simplified dosage regimen causing better patient compliance, and requirement of less number of clinical trials (Proschak et al. 2019; Bolognesi 2013; Woodcock et al. 2011; Center for Drug Evaluation and Research 2013; Ibrahim and Gabr 2019). In addition to this, single-target agents demonstrate short and temporary effects and multiple target agents have chances of higher success rate (Rossi et al. 2021).

Among the well-reported anti-AD MTDLs, cholinesterase inhibitors present an interesting category. In addition to cholinesterase inhibition, the other biological properties targeting the factors involved in the intertwined pathogenesis are important to design and develop MTDLs. AChE inhibition along with antioxidant properties is an interesting strategy (Cruz et al. 2017).

In the past decade, studies focusing on the design and synthesis of multifunctional ligands targeting different AD pathways have been reported (Cabrera-Pardo et al. 2020; Bhatia et al. 2021). Hybridization of pharmacophores is another interesting approach where each of them is retained its nature for interaction with specific targets and thus can produce multiple pharmacological activities. It has the advantage to overcome the administration of multiple drugs and thus provides patient-friendly dosage regimen. Numerous hybrid analogs using bioactive pharmacophore moieties have been found useful (Uddin et al. 2021).

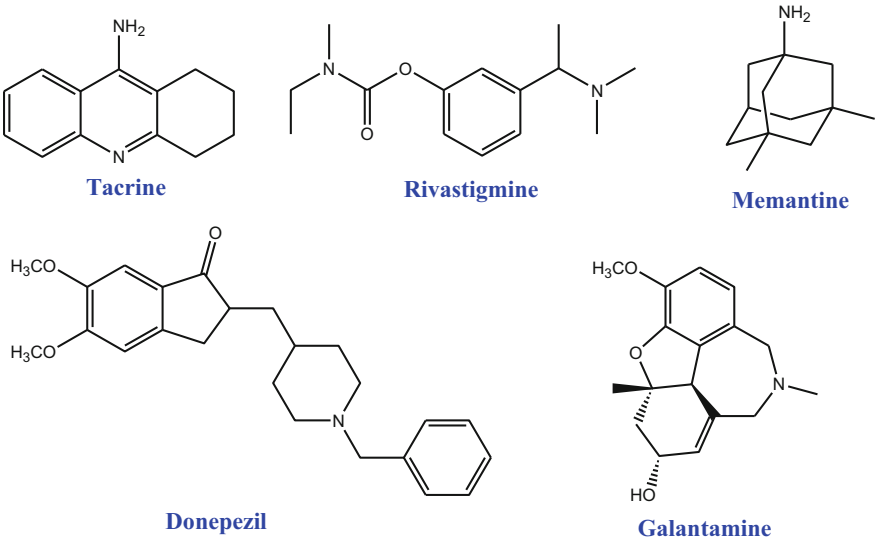


Fig. 4 Chemical structures of approved anti-AD AChEIs (Tacrine, Rivastigmine, Memantine, Donepezil, and Galantamine)

3.1 AChEI-Based MTDLs

Among Alzheimer patients, varying levels of acetylcholine, acetyltransferase (ChAT), and acetylcholinesterase (AChE) have been observed and has served as vital target in the development of first-generation anti-AD drugs. Few drugs acting through this mechanism have been approved (Fig. 5). Critical involvement of BChE in amyloid β aggregation makes it an important anti-AD drug target (Greig et al. 2002; Lane et al. 2006), but its inhibitors are associated with inevitable side effects. In a recent manuscript, Mishra et al. (2019) have reviewed various anticholinesterase hybrids of tacrine, donepezil, rivastigmine, resveratrol, galanthamine, huperzine, ferulic acid, indole, curcumin, lipoic acid, acridine, coumarin, ciproxifan, chalcone, etc., having anti-AD properties (Fig. 4). Some of the important categories studied under anti-AD MTDL category targeting AChE along with other related targets are described here.

3.1.1 Dual AChEIs Acting on ACh Hydrolysis Sites (Catalytic and Peripheral Anionic Sites)

AChE and BChE active sites are surrounded by numerous subsites which can be differentiated based on the residues. These structural features govern their potency and selectivity toward both enzymes (Dias and Viegas 2014). Studies have explained

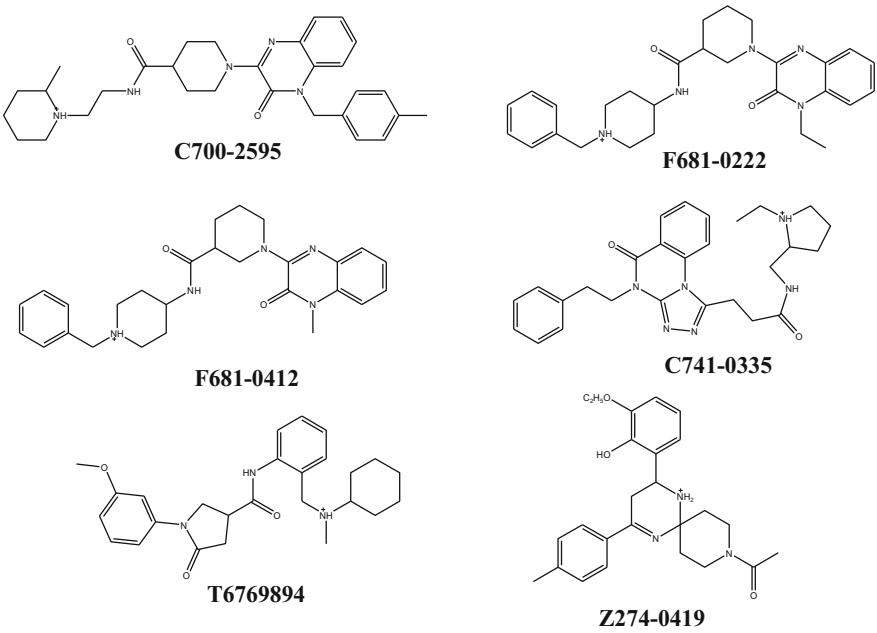


Fig. 5 Chemical structures of AChE and BACE1 inhibitory MTDLs

the role of peripheral catalytic site for reducing the cognitive deficit and lowering AChE-induced Aß aggregation. It leads to disease-modifying effect and thus helps to overcome cognitive deficit (Hosea et al. 1996; Mallender et al. 2000; Radic et al. 1991; De Ferrari et al. 2001; Inestrosa et al. 1996; Small et al. 1999; Bartolini et al. 2003; Hoyer et al. 2008).

3.1.2 AChE and BACE1 Inhibitors

For the last 2½ decades, amyloid hypothesis is the conventional approach for Alzheimer's research. The full-length amyloid precursor protein is split into fragments by ß-secretase 1 (BACE1) and initiates Aβ formation and deposition (Dias and Viegas 2014). Aβ deposition has been correlated with tau protein, inflammation, oxidative stress, etc., and thus specifies its role in anti-Alzheimer's MTDL discovery. In addition to rational approaches (discussed in the later part of this chapter), computational methods like ligand-based screening and scaffold hopping were performed to identify a few dual inhibitors (Fig. 5) from a dataset of approximately three million compounds and were further validated using in vitro (AChE $IC_{50} = 4–7$-μM and BACE-1 $IC_{50} = 50–65$ μM) and in vivo analysis (Stern et al. 2022).

3.1.3 AChEIs and Antioxidant

Oxidative stress is an important contributor for initiating Aß aggregation, tau protein hyperphosphorylation, acute inflammation, and neuronal apoptosis in Alzheimer's disease. Simultaneously inhibiting ROS formation has a conducive role (Dias and Viegas 2014; Nesi et al. 2017; Pohanka 2018). The extract of *Carpolobia lutea* has shown concentration-dependent dual activity and has promising potential as MTDLs for the management of neurodegenerative disorders (Nwidu et al. 2017). The well-reported AChEIs, i.e., donepezil and rivastigmine, have shown reduced antioxidant properties when evaluated for fluoride-induced oxidative stress models (Ferreira-Vieira et al. 2016; Goschorska et al. 2018). Thus, MTDLs from this category can be considered as potential Alzheimer's therapy.

3.1.4 AChEIs and Voltage-Dependent Ca^{2+} Channel Blockers

In Alzheimer's pathogenesis, Ca^{2+} influx stimulates γ-secretase pathway through lowered Aß production and tau hyperphosphorylation. Raised Ca^{2+} levels cause mitochondrial disruption and activate apoptotic cascade followed by cell death (Tan et al. 2012; Dias and Viegas 2014). Blockage of Ca^{2+} channels shows their mechanism by protecting against Aß oligomer (Wareski et al. 2009). Specifically, the L subtype of Ca^{2+} channel blockers are verapamil, diltiazem, isradipine, and nimodipine found to have contributing effect, and hence, it is a good strategy to prevent neuronal cell death (Mattson and Chan 2001; Qin et al. 2009).

3.1.5 AChEIs and Glutaminergic Receptor Inhibitors

Altered cerebral glucose and glutamate concentrations cause Aß plaque deposition, and $>$ 40% of neuronal synapses are glutaminergic. Earlier studies have described the effect of impaired glucose metabolism on glutamate receptor-mediated signaling pathways which cause impaired cognition among Alzheimer's patients (Hoyer 2004). A broad range of inhibitors of glutaminergic receptors (NMDA, AMPA, mGluR5, mGluR2/3, EAAT2) have shown promising preclinical and/or clinical results in improving cognitive functions (Bukke et al. 2020). AChE inhibitor bis (7)-tacrine has shown NMDA inhibitory role (Li et al. 2005). It can slow AD pathogenesis and improve associated cognition. Thus it is a promising approach for the development of anti-AD MTDLs.

3.1.6 AChEIs and CB1 Receptor Antagonists

Certain cannabinoids have exhibited neuroprotection against Aß leading to memory improvement. Additionally, the role in tau hyperphosphorylation, oxidative stress, and inflammation has been reported (Aso and Ferrer 2014). CB1 receptor

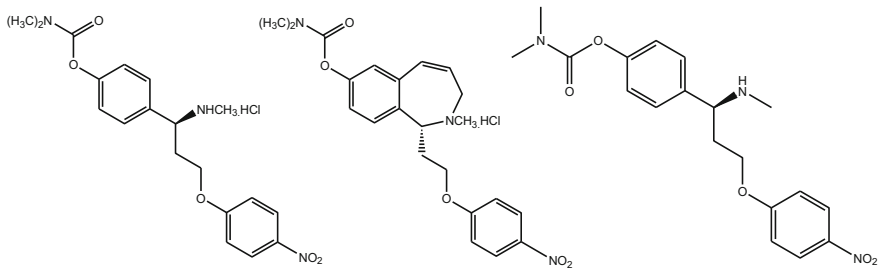
antagonists (increase ACh level in cortical and hippocampal neurons) have also been reported (Huang et al. 2011; Lange et al. 2010). Cannabinoid-based anti-Alzheimer's agents offer advantages like broader coverage of properties by selecting suitable combinations, and during the early phase of dementia, it has the potential to control the progression of neurodegeneration (Aso and Ferrer 2014).

3.1.7 AChEIs and NMDA Receptor Inhibitors

AChEIs have the potential to recover cognition and can act as disease-modifying agents, while NMDAR antagonists can contrast neurodegeneration (Rosini et al. 2015) (Glynn-Servedio and Ranola 2017). A combination formulation of donepezil and memantine has been put forward for clinical evaluation (http://www.adamaspharma.com). Herein, we focused on some multi-targeted ligands having symptomatic relief by blocking AChE and neuroprotection by NMDAR antagonism. During design, AChE and/or NMDAR inhibitory fragments were integrated into a single molecule. Some of the compounds considered for designing MTDLs under this category are carvedilol and tacrine, galantamine, and memantine for Carbacrine and Memagal, respectively (Rosini et al. 2015).

3.1.8 AChEIs and Serotonin Transporter (SERT) Inhibitors

Limitations associated with AD therapeutics can be addressed by the use of multi-targeted approach involving AChE and SERT, where the later can resolve the dose-dependent side effects of AChEIs. Literature reports highlight the preclinical evaluation of dual inhibitors against these potential targets as anti-AD therapeutics (Kogen et al. 2002; Toda et al. 2003, 2010; Rodriguez-Lavado et al. 2020). Few drugs have exhibited potent activity such as (*S*)-*A*, (*R*)-*B* (Lyketsos et al. 2000; Kogen et al. 2002), and RS-1259 (Fig. 6) (Abe et al. 2003, Toda et al. 2010). RS-1259 has shown simultaneous inhibition of AChE and SERT in the brain using in vivo models after oral administration and using in vitro models.



(*S*)-A **(*R*)-B** **RS-1259**

Fig. 6 Chemical structures of AChE and SERT inhibitory MTDLs

3.2 Phosphodiesterase (PDE) Inhibition-Based MTDLs

AChE inhibitors have demonstrated limited efficacy and development of tolerance after prolonged use, and it encouraged to use them in combination with other drugs. When compared with other reported targets, phosphodiesterases (PDEs) are emerging as promising targets for developing inhibitors to contrast neurodegeneration (Ribaudo et al. 2020; Sheng et al. 2022). In particular, selective small molecules targeting PDE4, PDE5, and PDE9 isoforms are being studied to explore alternative strategies against AD in light of their brain localization and of their role, to different extents, in cognitive processes (Zuccarello et al. 2020). Recently, many strategies have been tried to design and synthesize dual inhibitors of PDE subtypes and AChE to combat the multifactorial aspect of AD.

3.2.1 Tadalafil Analogs

In an attempt to synthesize first-generation dual-target inhibitors of AChE and PDE5, using drug repositioning and redeveloping strategy, Ni et al. synthesized a series of tadalafil derivatives (19 compounds). Inhibition of these tadalafil derivatives against AChE and BuChE was determined by the modified Ellman's method. The compounds exhibited good AChE activity ($IC_{50} < 1$ μM) and moderate BuChE activity. Following an IMAP-FP (immobilized metal ion affinity-based fluorescence polarization) assay, the most potent AChE inhibitors were found to show good or moderate PDE5 inhibitory activity (IC_{50} values of 0.050–3.231 μM). One of the essential features of a successful anti-AD drug is good BBB permeation. A parallel artificial membrane permeation assay (PAMPA) was employed, and the compounds exhibited good BBB permeability. In vivo studies on the mouse model showed an effect comparable to that of donepezil. These compounds proved to be potential selective dual-target AChE/PDE5 inhibitors and will be an excellent lead compound for further research. Figure 7 shows the structure of the active compound (Ni et al. 2018).

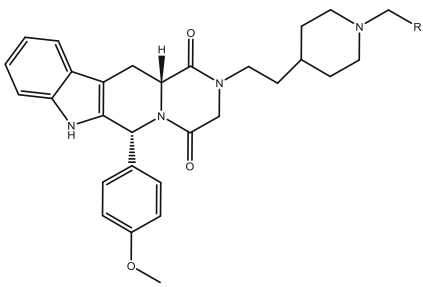


Fig. 7 Representative structure of tadalafil derivatives

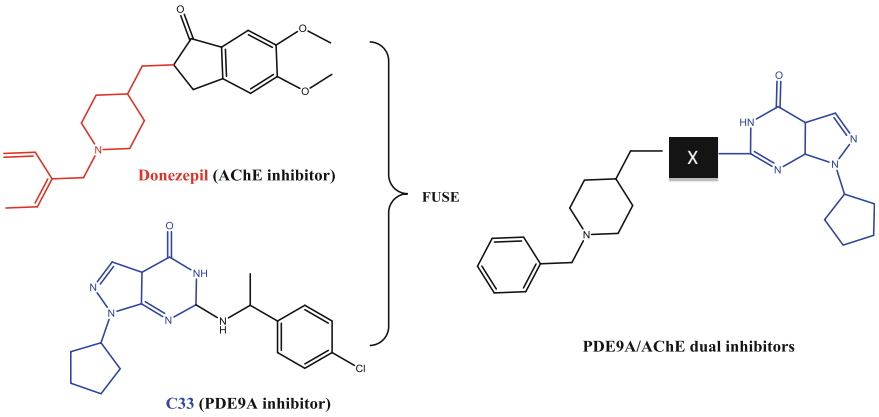


Fig. 8 Rational design of PDE9A and AChE dual inhibitors

3.2.2 Donepezil and Pyrazolo[3,4-d]Pyrimidinone (Pharmacophore of PDE)

In another work performed by Hu et al., dual inhibition of PDE and AChE was achieved by combining the pharmacophore of donepezil and pyrazolo[3,4-d] pyrimidinone (pharmacophore of PDE) using different linkages. A series of dual-target AChE/PDE9A inhibitor compounds Fig. 8 were designed, synthesized, and evaluated as anti-Alzheimer's disease (AD) agents. Among these targets, two compounds exhibited excellent and balanced dual-target AChE/PDE9A inhibitory activities (AChE: IC_{50} = 0.048 μM; PDE9A: IC_{50} = 0.530 μM and AChE: IC_{50} = 0.223 μM; PDE9A: IC_{50} = 0.285 μM). Moreover, these two compounds also possess good BBB penetrability and low neurotoxicity. It was found that they could ameliorate learning deficits induced by scopolamine and improve cognitive and spatial memory in Aβ25–35-induced cognitive deficit mice in the Morris water-maze test. This work produced promising candidates that possess potential inhibition of PDE/AChE (Hu et al. 2019).

3.3 Monoamine Oxidase-Based MTDLs

The oxidative damage is promoted by the increased monoamine oxidase B (MAO-B) level which generates free radicals (Riederer et al. 2004; Tripathi et al. 2013). Selective MAO inhibitors have been demonstrated for metal chelation or AChE inhibition, and therefore, targeting MAO is an important approach to improve cognition- and control-associated symptoms.

Recently Oh et al. (2021) have reported AChE and MAO-B dual inhibitory potential of some ellagic acid analogs which were derived from *Castanopsis*

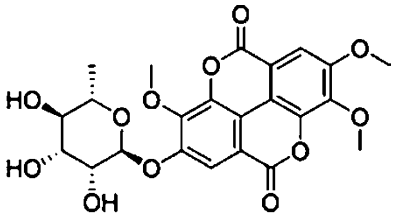


Fig. 9 Chemical structure of 4′-*O*-(α-L-rhamnopyranosyl)-3,3′,4-tri-*O*-methylellagic acid. (AChE: $IC_{50} = 10.1$ μM; binding energy = −8.5 kcal/mol; MAO-B: $IC_{50} = 7.27$ μM)

cuspidata var. sieboldii. In vitro and docking studies have identified 4′-*O*-(α-L-rhamnopyranosyl)-3,3′,4-tri-*O*-methylellagic acid as a potential analog supported with lesser toxicity (Fig. 9).

3.4 Metal Chelation-Based MTDLs

The metal hypothesis of Alzheimer's defines the role of metal ions (Fe^{2+}, Zn^{2+}, Cu^{2+}, Al^{2+}) in cognitive loss and neurodegeneration. It is required to maintain their homeostasis for normal neuronal functioning (Salvador et al. 2010; Bush 2013; Sastre et al. 2015). Higher concentrations of certain bivalent metal ions like Zn^{2+}, Fe^{2+}, and Cu^{2+} are associated with amyloid plaque formation, and Al^{2+} leads to the degradation of some neurotransmitters (ex. MAO) and generation of reactive oxygen species (ROS) (Lovell et al. 1998; Zatta et al. 1999, 2009; Dias and Viegas 2014). Thus, studies are warranted focusing on chelating agents as novel AD therapeutics by incorporating functional moieties which can target other AD pathways (Sharma et al. 2018). Thus metal chelators with AChE/MAO/BACE-1 inhibition and/or antioxidant properties are an important MTDL approach. This category of MTDLs can be subclassified as Aß-aggregation-based, AChE-based, MAO-based, and BACE-1-based metal chelating agents. Studies supporting the beneficiary effect of AChE and metal chelators in the treatment of Alzheimer's disease have been well-reported. Compounds interacting with Aß and capable to chelate Zn^{2+} and Cu^{2+} ions have shown bifunctional properties in Alzheimer's models (Figure) (Choi et al. 2014; Braymer et al. 2010; Jones et al. 2012). Some of the well-documented MTDLs based on inhibition of Aß aggregation are *N*-(pyridin-2-ylmethyl)aniline, *N*1,*N*1-dimethyl-*N*4-(pyridin-2-ylmethyl)benzene-1,4-diamine, pyridine-triazole derivatives, and quinoline–triazole.

A synthetic rhodamine-B-based molecule (Rh-BT, Fig. 10) has exhibited Aß aggregates by capturing redox metal ions and confirms multifunctional nature (Pradhan et al. 2020). It has shown stability in serum along with BBB permeability suggesting its potential for Alzheimer's treatment. Synthetic hybrid derivatives of tacrine with 8-hydroxyquinoline (*MC-AChE1*) and ferulic acid (*MC-AChE 2*) exhibited Cu^{2+} chelation and Aß reduction (Fernández-Bachiller et al. 2010; Xie et al. 2013; Fu et al. 2016). *MC-AChE1* produces AChE and BuChE inhibition (at nano- and subnanomolar concentrations) and *MC-AChE 2* inhibits AChE by

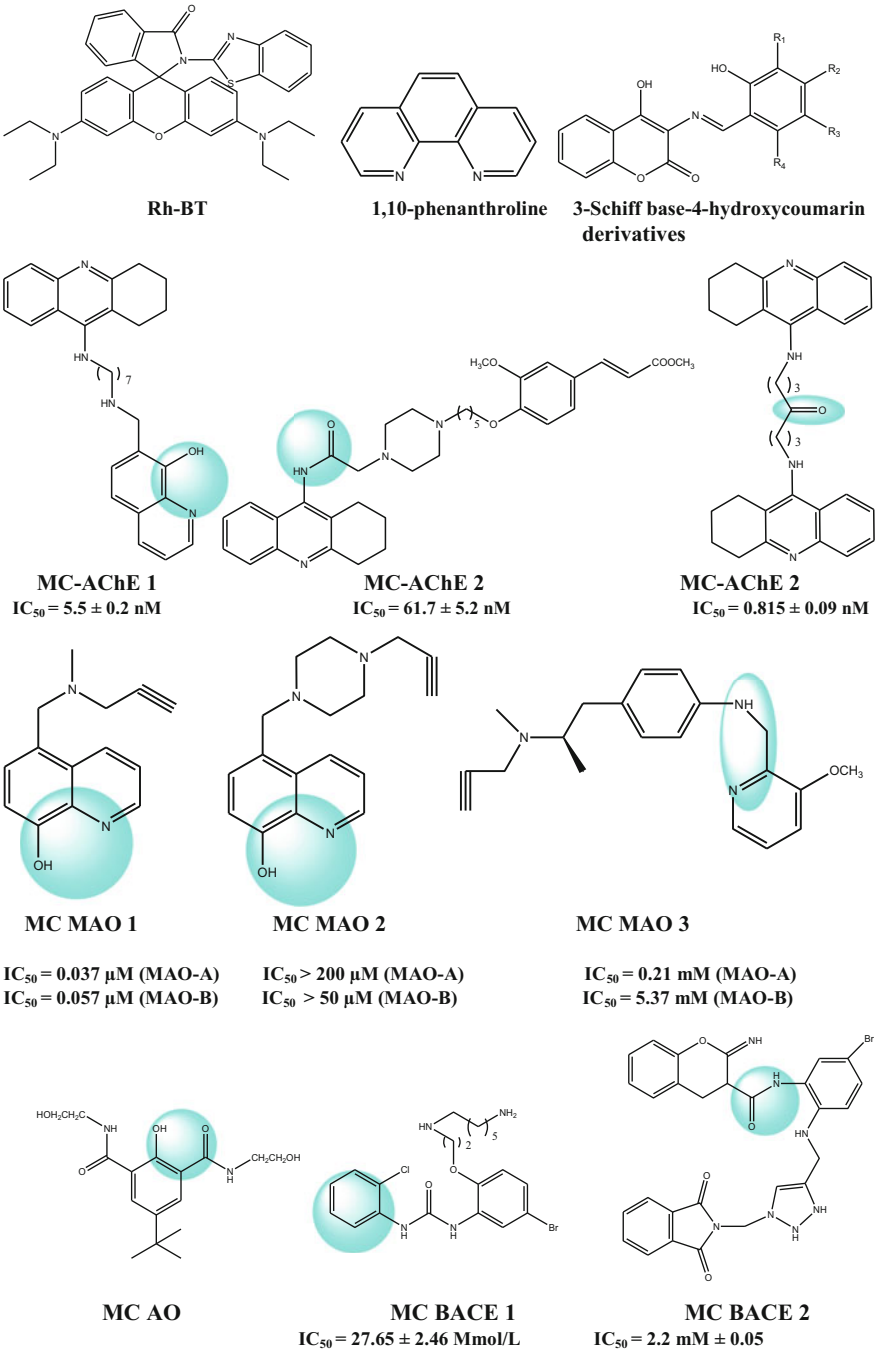


Fig. 10 Metal chelator-based anti-AD MTDLs (blue color indicates binding sites for metal chelation)

binding at the mod-gorge site. The *bis*(7)-tacrine (*MC-AChE 3*) interacts with anionic and catalytic sites to regulate AChE-induced Aß aggregation and shows Cu^{2+} chelation (Bolognesi et al. 2007). A novel chelator of Fe^{2+}, Cu^{2+}, and Zn^{2+} was designed using pharmacophoric features of rivastigmine and donepezil, and *MC MAO 2* has exhibited APP regulation and lowered oxidative stress (Zhang et al. 2013). Indanone metal (Fe^{2+}, Cu^{2+}, and Zn^{2+}) chelating derivative having piperidine moiety through ethylene linkage has blocked AChE at micromolar concentration and 14 times more potency as compared to donepezil (Meng et al. 2012). Similarly, metal chelating 1,10-phenanthroline has been evaluated for its inhibitory effect against AChE, i.e., aryl acylamidase and esterase activity (Chitra et al. 2013). Molecular docking and dynamics simulation have confirmed hydrogen and hydrophobic interactions with Phe295 and residues of the peripheral binding site, respectively, which supports experimental results with inhibition at micromolar concentration.

Among the category of MAO-based metal chelating agents, 8-hydroxyquinoline and propargyl nuclei hybrids (*MC MAO 1, MC MAO 2,* and *MC MAO 3*) were derived based on MAO inhibitory anti-Parkinson drugs (rasagiline and selegiline) (Fig. 10). Among them, the latter is most potent with MAO-B IC_{50} of 0.21 μM supported by docking interactions and can produce antioxidant and chelation properties for Fe^{2+}, Cu^{2+}, and Zn^{2+} (Youdim et al. 2005; Xie et al. 2022). During the evaluation of metal chelation properties of MAO-B inhibitors, 3,5-diaryl-4,5-dihydroisoxazoles have failed to bind with Fe^{2+} and Fe^{3+} (Meleddu et al. 2017).

3-Schiff base-4-hydroxycoumarin derivatives have reported significant potential as anti-AD agents during in vitro studies (Wang et al. 2015). The most potent compound is suggested to act by MAO (A and B) and self- and copper-induced Aß aggregation inhibition, antioxidant, and biometal chelation effects. The anti-AD properties at the micromolar level suggest it as a promising lead molecule.

A prochelator has been proposed showing Cu^{2+} chelating properties on interaction with BACE-1 (Folk and Franz 2010). It has the ability to inhibit Aß aggregation by sequestering the metal ion from Aß. Among this category, some reported BACE-1 inhibitors have been modified to derive metal (Fe^{3+} and Cu^{2+}) chelating agents like 1,3-diphenylurea analogs (*MC BACE1*) (Huang and Mucke 2012) and iminochromene carboxamides with aminomethylene triazole analogs (*MC BACE2*) (Iraji et al. 2017) supported by docking interactions at the active site of the enzyme.

3.5 BACE1 Inhibitor-Based MTDLs

In AD, BACE-1 and GSK-3ß are the important targets involved in the formation of senile plaques and NFTs. Studies suggest that dual inhibition of these targets will show conducive action (Prati et al. 2018). Few series of BACE-1 and GSK-3ß dual inhibitors have exhibited potent inhibition along with neuroprotective and good pharmacokinetic properties in relation to oral bioavailability and BBB penetration (Di Martino et al. 2016; Rampa et al. 2017). The fragment-based approach has been

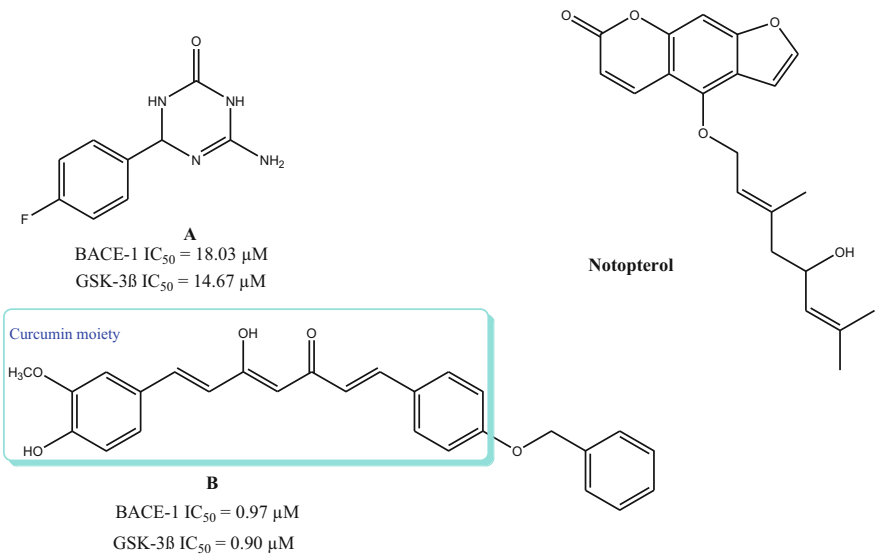


Fig. 11 Details of some BACE-1 and GSK-3ß dual inhibitors

implemented to design and derive dual inhibitors having cyclic amide and guanidine moieties. The most promising compound (Fig. 11a) has shown potent dual inhibition without neurotoxic properties (Rampa et al. 2017). Similarly, curcumin-based inhibitors (Fig. 11b) have exhibited balanced dual inhibition along with neuroprotective properties induced through NAD(P)H quinone oxidoreductase 1 (NQO1) (Di Martino et al. 2016). It has the potential for further evaluation due to BBB permeation.

A natural dual inhibitor notopterol (Fig. 11) has shown a potential to ameliorate AD-associated cognitive deficit in animal models by dual inhibition of BACE-1 and GSK-3ß at micromolar concentration, i.e., IC_{50} of 26.01 µM and 1.0 µM, respectively. The binding profile was further established using docking and dynamics studies showing protein stability in the binding complex (Jiang et al. 2020). Recently, Bajad et al. (2022) utilized both structure and ligand-based approaches such as virtual screening, homology modeling, docking and dynamics studies, drug-likeness screening, and assessment of pharmacokinetic and toxicity properties. It proposed two potential dual inhibitors, i.e., ZINC22551247 and ZINC668197980 (Bajad et al. 2022).

Based on the requirement of agents having multiple effects to comply with the complex pathogenicity of AD, MTDLs targeting toxicity of ROS, serotonergic receptors (5-HT_4 and 5-HT_6 receptors), neuroinflammation, etc., are under evaluation (Lanthier et al. 2019; Benek et al. 2020). Simultaneous targeting of several subpathologies will contribute to derive a better approach to obtain effective anti-AD agents.

4 Rational Design of MTDLs

For the design of MTDLs, it is important to have information about pharmacophores having affinity for diverse disease targets. Such pharmacophores are linked/fused/merged to get a single molecule. In case of linked MTDLs, the linker group may be cleavable or non-cleavable and their large size causes reduced bioavailability. The pharmacophores are partially overlapping each other in fused MTDLs, while the merged ligands have higher overlapping resulting in simple molecules with low molecular weight (Zhou et al. 2019). Some examples of anti-AD MTDLs like memoquin, xanthone-flavonoid derivatives, etc., are discussed here.

AChE has been reported to trigger Aß aggregation, and its peripheral anionic site facilitates fibril formation by interaction with Aß. Thus, for effective inhibition of Aß aggregation, blockage of AChE peripheral anionic site can be considered as an effective strategy (Li et al. 2018).

The first rationally designed compound from this category is memoquin. It is a 1,4-benzoquinone–polyamine hybrid of AChE and muscarinic inhibitor polyamineamide caproctamine with potent antioxidant and neuroprotective 1,4-benzoquinone (Cavalli et al. 2007; Prati et al. 2014). Memoquin is formed by replacing the inner polymethylene chain with benzoquinone nucleus. The structural details are presented in Fig. 12 (Bolognesi et al. 2009). The hydrophobic and planar

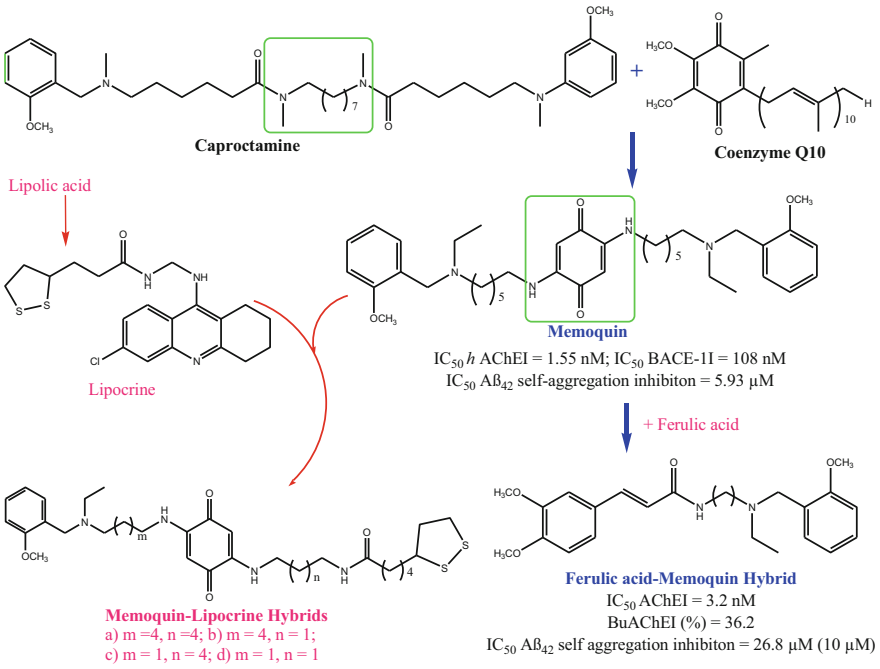


Fig. 12 Design of memoquin and its hybrids with ferulic acid and lipocrine (obtained from lipoic acid)

pi-system contributes toward protein–protein interactions in the Aß fibrillogenesis. It has demonstrated the potential to explore AChE and self-induced Aß aggregation based on the potential observed for ferulic acid–memoquin hybrids (Fig. 12) (Bolognesi et al. 2009; Pan et al. 2016; Ortiz et al. 2019). Multi-targeted profile for memoquin is established through in vitro studies which include inhibition of AChE and Aß aggregation induced by it, BACE-1, and free radical generation. Studies also support its oral bioavailability, BBB permeability, and safety profile. It confirms tolerance on prolog administration and its ability to restore cholinergic deficit, reduced expression, and accumulation of Aß and decreased tau protein phosphorylation (Cavalli et al. 2007; Bolognesi et al. 2009). As a next step to these findings, the mitochondria targeting antioxidant, alpha-lipoic acid, has been used to prepare memoquin hybrid analogs with an aim to prolong the onset/prevent/cure Alzheimer's disease (Bolognesi et al. 2009). Lipocrine, i.e., prepared by conjugating 9-amino-6-Cl-1,2,3,4-tetrahydroacridine with alpha-lipoic acid, has exhibited anti-AChE and antioxidant properties. The newly reported memoquin–lipocrine MTDLs (Fig. 12) has superior potential to prevent and cure AD through multiple antioxidant mechanisms. It involves reduced ROS production and mechanisms mediated through NQO1. These analogs have shown lesser inhibitory properties against AChE and BChE. Studies also confirm the requirement of lipoyl fragment at position 2 of the benzoquinone for receptor interactions.

The next important MTDLs from the AChE inhibitory category (reversible and non-competitive inhibitor) are based on tacrine and donepezil. Such analogs have demonstrated the ability to lessen the neurodegeneration associated with cholinergic damage and participate in other AD-related mechanisms (Fig. 13). The dual binding at AChE peripheral and catalytic sites has been implemented for the tacrine, and donepezil-based AChEIs have additional anti-AD properties against Aß aggregation, MAO, and oxidative stress. MTDLs based on this important scaffold are presented in Figs. 13 and 14 (Zagorska and Jaromin 2020).

In the development of AChE and BACE-1 MTDLs, pharmacophores of inhibitors from both categories are linked to design novel analogs. In this direction, the evaluation of hybrid analogs of donepezil (AChEI) with isophthalamide (Zhu et al. 2009) and 2,4-disubstituted pyrimidine (Mohamed et al. 2011, 2012) led to the identification of dual inhibitors with blockage of $A\beta_{1-40}$ production. In other studies, AChEI tacrine scaffold was fused with BACE-1 inhibitory flavonoid fragment of 4-oxo-4*H*-chromene (Fernández-Bachiller et al. 2012), huperzine A (Camps et al. 2000; Pérez-Areales et al. 2019), and benzofuran (Zha et al. 2016) to get some potent dual inhibitors of AChE and BACE-1, while few of them have exhibited interesting antioxidant activity. Tacrine and donepezil scaffolds are subjected to various structural modifications for AChEIs along with other AD targets to develop potential therapeutics (Ismaili et al. 2017). The potent compounds from such series are presented in Fig. 15.

The potential role of Rho-associated protein kinase (ROCK) for Alzheimer's treatment has been reported (Aguilar et al. 2017), and it helped to design PT109 (Fig. 16), i.e., based on lipoic acid and fasudil. Fasudil scaffold possess well-reported anti-AD contributing properties like blockage of ROCK and kinases,

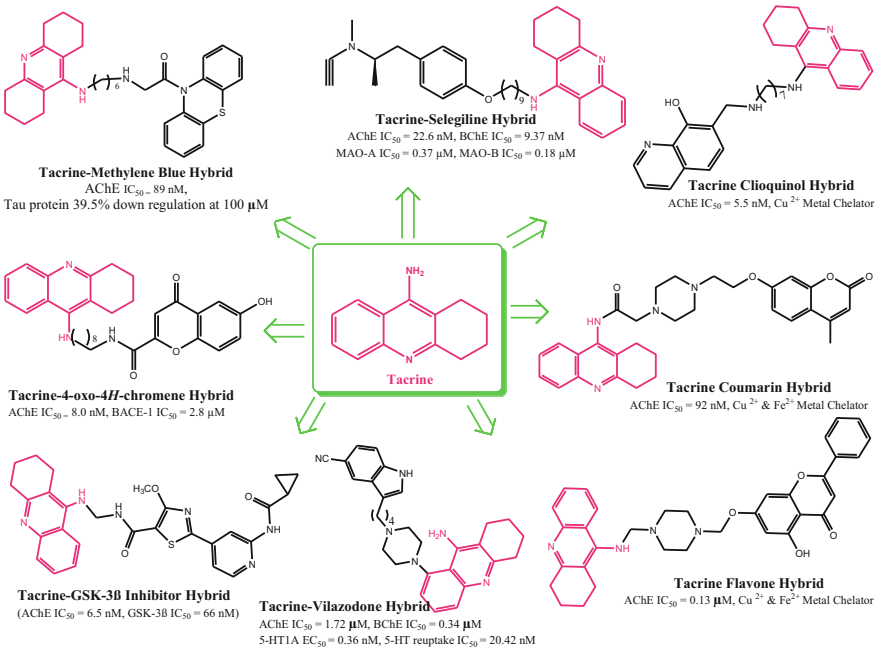


Fig. 13 Structure and activity details of tacrine-based hybrids as MTDLs

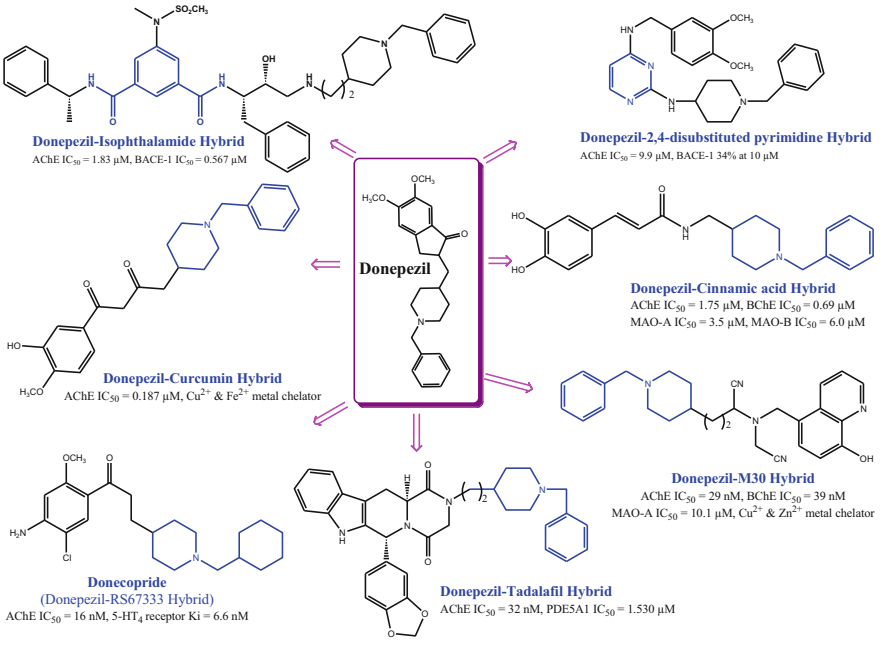


Fig. 14 Structure and activity details of donepezil-based hybrids as MTDLs

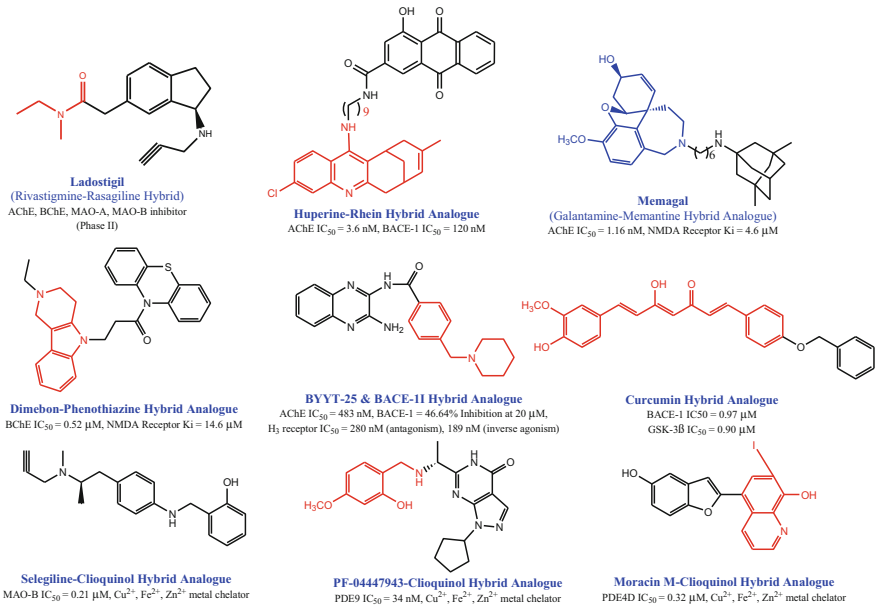
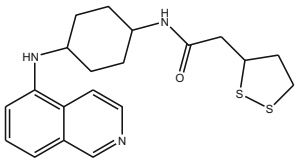


Fig. 15 Structure and activity details of some reported anti-AD MTDLs

Fig. 16 Chemical structure of *PT109*



and anti-inflammatory, antioxidant, and morphological alterations in neural stem cell line (Chen et al. 2017, 2020). It is a multifunctional ligand with broad-spectrum anti-Alzheimer's properties like reduced levels of *p*-Tau, *p*-JNK, etc., which have been demonstrated by in vivo and in vitro methods (Fig. 16).

5 Natural or Nature-Inspired Compounds

Studies have reported a large number of anti-AD natural substances such as huperzine (Serrano et al. 2016), rhein (Li et al. 2019), chelerythrine (Marasco et al. 2021), chalcone (Thapa et al. 2021), curcumin (Mukherjee et al. 2021), berberine (Akbar et al. 2021), resveratrol derivatives (Akbar et al. 2021), and coumarin (Li et al. 2022a). The vast pool of diverse phytoconstituents and their anti-AD potential warrants further studies (Noori et al. 2021). Recently, reported anti-AD drugs include sodium oligomannate; i.e., GV-971 is an oligosaccharide

from marine sources (Wang 2017; Xiao et al. 2021). It highlights a novel strategy for AD management through gut dysbiosis-promoted neuroinflammation (Wang et al. 2019).

Apart from the synthetic strategy used to design the dual-target inhibitors for AD, there are several instances where natural compounds that are inspired from nature are tested for their cholinesterase and PDE inhibition and many of them have shown promising results. Table 2 summarizes the studies on multi-target natural synthetic derivatives, and some reported phytoconstituents are presented in Fig. 17.

Five natural fungal secondary metabolites and one plant metabolite (compounds a to f, Fig. 18) have been selected for anti-AD evaluation based on their structural characteristics like heterocyclic nucleus, molecular weight, and presence of hydroxyl groups. They are evaluated for AChE, BChE, Aß peptide aggregation, and antioxidant properties (Piemontese et al. 2018). The study also aims to provide a possible solution for limitations observed with AChEIs. Additionally, heavy metal (copper (II) and zinc (II)) sequestering properties contribute toward the prevention of ROS production and prevent the formation of amyloid plaques. Aß peptide aggregation properties (at 100 μM) display the role of heterocyclic condensed ring system for disruption of ß-sheet conformation as per documented literature (Hiremathad et al. 2016). The study identified the following MTDLs as potential scaffolds for the development of new anti-AD drugs:

- Antioxidant and interaction with copper (II): tenuazonic acid (A), mycophenolic acid (C).
- AChE and $A\beta_{1-40}$ aggregation inhibitor: *epi*-Radicinol (B).
- AChE and BChE inhibitor: fungerin (F).

Alpha (α)-terpinyl acetate (Fig. 18g), an active phytoconstituent, has shown Alzheimer's disease-modifying activity (Chowdhury and Kumar 2020). It is obtained from *Elettaria cardamomum* L. Maton and exhibited significant interaction with multiple targets. It has demonstrated anticholinesterase, anti-aggregation, and neuroprotective properties and can mitigate symptoms along with disease-modifying activity.

Recently, a review on several anti-AD mechanisms of α-mangostin (α-M, Fig. 18h) which is purified from mangosteen supports its use as a promising molecule for multifactor treatment of Alzheimer's disease (Yang et al. 2021). The safety profile for over 100 years and diverse activity profile (against AChE, BuChE, Aß aggregation, inflammation, metal chelation, and ROS scavenger) has been well-documented through experimental results and clinical trials. MTDL derived from an inexpensive food waste, i.e., cashew nutshell liquid, has been combined with AChE/BChE tacrine nucleus, and it has been achieved by applying sustainable strategies (Fig. 19). The overall sustainability was maintained by adopting principles of green chemistry during synthesis of compounds. The screening was performed based on AChE/BChE selectivity and toxicity observed for hepatic, neuronal, and microglial cells (Rossi et al. 2021). Compound *5* has demonstrated high potency. Its crystal structure in complex with human BChE has been analyzed showing multiple interactions of the two aromatic nuclei at the active site gorge of human BChE.

Table 2 Multi-target natural and nature-inspired compounds

Category	Source/phyto-constituents	MOA	Effects	Ref.
Xanthines	*Coffea arabica* and *C. canephora*/caffeine	Non-competitive AChE inhibitor ($Ki = 175$ μM)	Neuroprotective and anti-inflammatory effects	Pohanka (2015)
		Interfere with intracellular cAMP and cGMP levels by acting as a weak, nonspecific reversible PDE inhibitor ($IC_{50} = 500$–1000 μM)		
Synthetic derivatives of xanthines	Propentofylline	Inhibits AChE ($IC_{50} = 6.40$ μM)	Improve cognition and dementia severity in mild-to-moderate AD	Mohamed et al. (2013)
	Pyrazolopyrimidinones	Inhibits PDE9 in the nM range (IC_{50} values <200 nM)		Singh et al. (2017)
	3-Isobutyl-1-methyl-xanthine (IBMX)	Nonselective inhibitor targeting PDE9 and other isoforms in the μM range ($IC_{50} = 230$ μM for PDE9)		Singh et al. (2017)
	Tacrine–pyrazolopyridine hybrid derivatives	The compounds demonstrated inhibitory activity on cholinesterases ($IC_{50} = 0.125$–0.412 μM for AChE and $IC_{50} = 0.245$–1.283 μM for BuChE) and even better activity on the PDE ($IC_{50} = 0.041$–1.307 μM)	Target AChE, BuChE, another enzyme involved in sustaining cholinergic tone, and PDE4D	Pan et al. (2019)
	Camel artemisia (*Peganum nigellastrum*) Indoline-2,3-dione and quinazoline derivatives	Inhibited AChE with IC_{50} values between 44 and 298 nM, and PDE5 with IC_{50} values between 17 and 746 nM		Zhou et al. (2017)

(continued)

Table 2 (continued)

Category	Source/phyto-constituents	MOA	Effects	Ref.
Flavonoids and coumarins	Rutin and its aglycone quercetin	Efficiently reduce AChE activity in rat tissues (25 and 50 mg/kg) also inhibit PDE5		Adefegha et al. (2018)
Polyphenolic acids	Nigerian plantain (*Musa sapientum*) extracts	Unripe peel aqueous extract showed inhibition of AChE (IC_{50} = 6.30 µg/mL) and PDE5 (IC_{50} = 3.10 µg/mL)		Oboh et al. (2017)
	Alligator pepper (*Aframomum melegueta*)	Inhibit AChE more efficiently (IC_{50} = 5.42 µg/mL)		Adefegha et al. (2017)
	Bastered melegueta (*Aframomum danielli*)	Show inhibition of PDE5 (IC_{50} = 7.24 µg/mL)		
	African walnut (*Tetracarpidium conophorum)*	Efficient in inhibiting AChE (IC_{50} = 0.87 µg/mL) and PDE5 (IC_{50} µg/mL)		Ademiluyi et al. (2019)
	Aqueous extracts of pulverized almond (*Terminalia catappa*) leaf and stem bark	Modulate the activity of AChE and PDE5 in the cardiac tissue of rats (100–200 mg/kg)		Dada et al. (2021)
	Leaves extract (aq.) of *Ocimum gratissimum*	Inhibit AChE (IC_{50} = 43.19–44.67 µg/mL) and PDE5 (IC_{50} = 44.23–53.99 µg/mL)		Ojo et al. (2019)

In silico approaches have been applied to search multi-target AD ligands based on reported information about chemical structures and their biological properties against crucial Alzheimer's targets, namely cyclin-dependent kinase 5, ß-secretase, MAO-B, glycogen synthase kinase 3ß, and acetylcholinesterase (Ambure et al. 2019). Linear discriminant analysis has been applied to derive five classification models and checked for their applicability domain using confidence estimation approach. Further, MTDLs were identified by screening natural database (InterBioScreen) using the derived validated in silico models. Drug-like properties

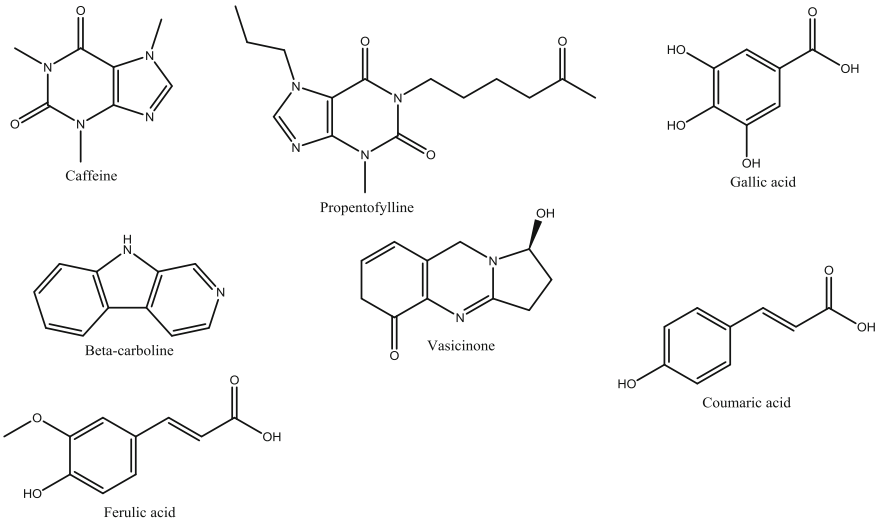


Fig. 17 Chemical structures of phytoconstituents reported in the investigations as MTDLs

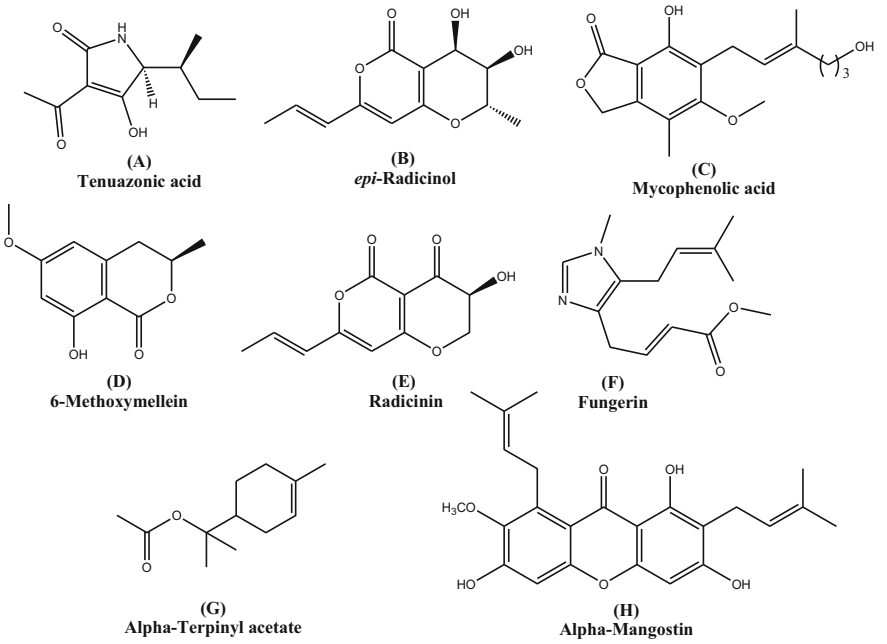


Fig. 18 Chemical structures of anti-AD MTDLs derived from natural origin

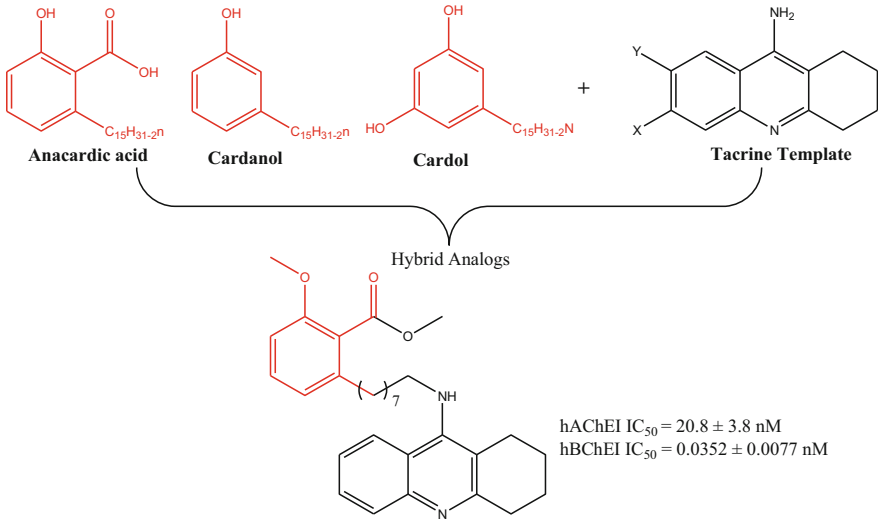


Fig. 19 Structural details of hybrid analogs derived from cashew nutshell liquid combined with tacrine template and the potent analog

Table 3 Details of natural MTDLs and their targets identified by screening InterBioScreen database

	AD targets	Compound
3 targets	CDK5, GSK-3ß, AChE	STOCK1N-31,193
	CDK5, BACE1, AChE	STOCK1N-68,100
	CDK5, BACE1, GSK-3ß	STOCK1N-83,050
2 targets	BACE1, AChE	STOCK1N-68,215, STOCK1N-69,729
	BACE1, GSK-3ß	STOCK1N-03648, STOCK1N-04548
	CDK5, AChE	STOCK1N-71,927, STOCK1N-76,042, STOCK1N-76,267
	CDK5, BACE1	STOCK1N-55,801, STOCK1N-67,973, STOCK1N-68,845
	CDK5, GSK-3ß	STOCK1N-36,270, STOCK1N-36,506, STOCK1N-38,926
	CDK5, MAOB	STOCK1N-50,225
	MAOB, GSK-3ß	STOCK1N-38,066, STOCK1N-38,837, STOCK1N-39,155

and molecular dynamic studies were performed for identified active ligands to analyze their potential as MTDLs against AD. The study outcomes are detailed in Table 3.

6 Conclusions

Alzheimer's disease (AD) is a multifactorial neurodegenerative disease, and a drug that targets a single protein would not provide a cure for this disease. Currently available drugs for AD are all palliative rather than curative. The lack of therapeutic effectiveness of the single-target drugs and multifactorial etiology of AD has led to the design of multi-target directed ligands for AD.

Malfunctioning of cholinergic transmission and glycation, formation of amyloid deposits, and oxidative stress have been proposed to be involved in pathogenesis and progression of the disease (Lane et al. 2018). In this connection, drugs sustaining the cholinergic tone have been developed to contrast the progressive cognitive decline that characterizes AD. In particular, AChE inhibitors such as donepezil are used for the symptomatic treatment of dementia, even if only moderate efficacy is observed in AD patients. Owing to their limited efficacy and problems of the onset of tolerance after long-term use of AChE inhibitors, they are encouraged to be used in combination with other drugs. Various natural and synthetic compounds have been evaluated for their multi-targeted mechanism for AD. The complex pathogenesis of AD is not addressed by available single-target therapeutics and fails to provide complete cure. Recent evidence-based research has focused on the development of MTDLs as anti-AD therapeutics to address the limitations and side effects associated with available therapeutics. MTDLs based on targeting different potential targets involved in Alzheimer's pathogenesis from synthetic or natural sources have exhibited promising results. During clinical use, some of the major limitations like drug-induced hepatotoxicity can be addressed by structural modifications or synthesis of hybrid analogs using hepatoprotective agents. Studies confirm the potential of MTDLs as an ideal pharmacological tool for tackling diseases having complex pathology. Among the various reported pathologies, AChE inhibitor-based multi-targeting has received considerable attention along with other important targets like BACE-1, GSK-3ß, NMDA, and PDE. There is a need for further extension for preclinical and clinical evaluation. Some well-reported anti-Alzheimer's agents like tacrine/donepezil/memoquin have been modified to develop MTDLs to reduce toxicity and side effects and to improve cognition. The success of MTDLs has been evidenced by their neuroprotective, anti-inflammatory, antioxidant, and inhibition of different AD pathogenesis in in vivo and in vitro models.

The Successful implication of MTDLs can eliminate the need to simultaneously administer multiple drugs with potentially different degrees of bioavailability, pharmacokinetics, and metabolism. It will also provide patients a simplified therapeutic regimen. Limitations associated with multi-targeted approach are complex activity profile, unpredictable pharmacokinetics, lack of BBB permeability, adverse effects, etc. In view of the demand for safe and potent AD therapeutics, more efforts are required. In the near future, active immunotherapy against both amyloid pathology and tau pathology in a single bivalent AD vaccine is worth investigating.

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