

Therapeutic Agents for Alzheimer's Disease

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Abstract: Currently, a handful of FDA approved drugs are commercially available to treat Alzheimer's disease (AD). Among these, Tacrine (Cognex), Donepezil (Aricept), Rivastigmine (Exelon), Galantamine (Reminyl) and Memantine (Nemenda; Forest) are either acetylcholinesterase or *N*-methyl-D-aspartate antagonists. These are only palliative solutions, however, and side effects remain an important concern. Clearly, the search for more potent and efficacious drugs for the treatment of AD is one of the most pressing pharmacological goals, and many more drugs are either in clinical trials or are being tested in laboratories around the world, both in academia and industry.

In this review, we will compare the aforementioned five drugs with several other molecules that are currently in clinical trials or are ready to go into clinical trials. These will include antioxidants, metal chelators, monoamine oxidase inhibitors, anti-inflammatory drugs, as well as other AChE and NMDA inhibitors. In addition, medicinal chemistry approaches toward designing better pharmaceuticals will be discussed.

Keywords: Alzheimer's disease, therapeutic agents, drugs, pharmaceuticals, X-ray crystal structure, computational chemistry, medicinal chemistry, AD treatment.

INTRODUCTION

Alzheimer's disease [1-3] (AD) was first described by Alois Alzheimer in 1907 and is the most prevalent dementia-related disease, affecting over 20 million people worldwide. Currently, however, only a handful of drugs are available and they are at best only able to offer some relief of symptoms. In this review, we will cover the pharmacological effects and chemical approaches being made to improve activities in the following six classes of molecules: acetylcholinesterase (AChE) inhibitors, antioxidants, metal chelators, monoamine oxidase inhibitors, anti-inflammatory drugs, and NMDA inhibitors. The final two sections will focus on medicinal chemistry approaches toward designing better pharmaceuticals and on the emergence of multi-functional drugs for AD treatment.

ACETYLCHOLINESTERASE (ACHE) INHIBITORS

AChE hydrolyzes neurotransmitters involved with the central and peripheral nervous systems. X-ray structure analysis revealed that AChE contains a narrow gorge about 2 nm in depth lined with hydrophobic (aromatic) side chains. The catalytic triad (acylation and choline-binding sites) is located at the base of the gorge whereas the anionic peripheral site is at the rim [5-12].

The key clinical symptom of AD is the progressive deterioration in learning and memory ability. There are many

lines of evidences suggesting profound losses in the cholinergic system of the brain. This includes the dramatic loss of cholinacetyltransferase level, choline uptake, and ACh level in the neocortex and hippocampus. Also, the reduced number of cholinergic neurons in the basal forebrain and the nucleus basalis of Meynert is closely associated with cognitive deficits observed in the disease [13].

Additionally, pharmacological modulations enhancing or blocking cholinergic neurotransmission produces some improvement or impairment in learning and memory. ACh, a neurotransmitter in the brain plays a critical role in the function of learning and memory. ACh is synthesized from acetyl-CoA and choline by cholineacetyltransferase, and is released into the synaptic cleft which then is hydrolyzed by AChE to become choline and acetic acid. Choline is taken up again into the presynaptic neurons for use in ACh synthesis. AChE, which is widely distributed in the central nervous system (CNS) and the peripheral nervous system, has been the focus of much attention because of the relationship to ACh hydrolysis and cognitive impairment in AD.

Although the overall AChE activity is reduced, it is increased in neuritic plaque and neurofibrillary tangles at the early stages of a AD patient brain. It has also been suggested that AChE may promote aggregation of Abeta (β -amyloid) into a more toxic amyloid form. Thus, inhibiting AChE activity might increase ACh neurotransmission in the synaptic cleft of the brain and diminish the Abeta burden, which will result in improved cognitive function and alleviating the process of amyloid deposition.

Several hypotheses exist to explain the origin of AD; these include the cholinergic, tau, and amyloid theories [1,

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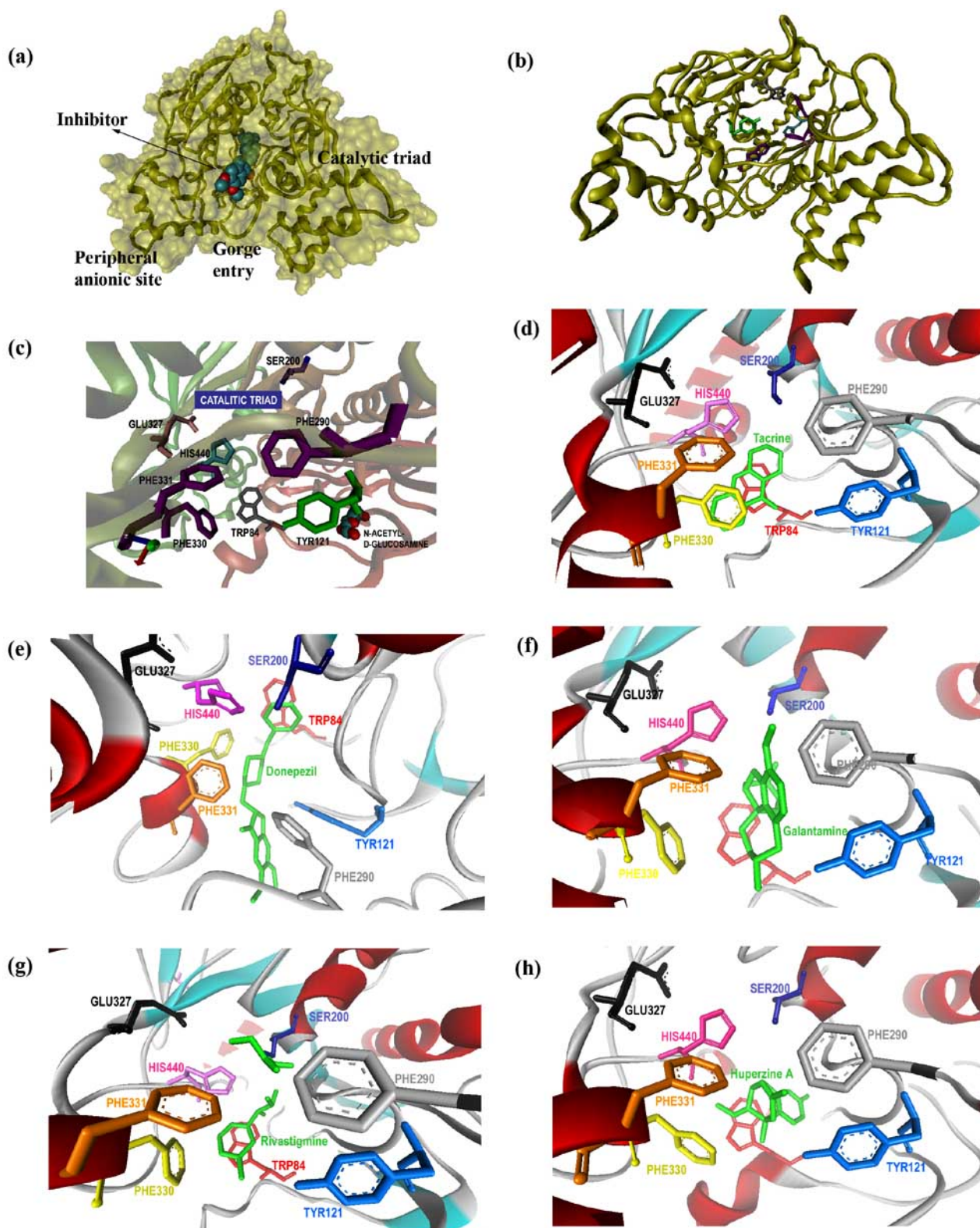


Fig. (1). AChE x-ray structure analysis. (a) AChE showing residues inside the gorge. (b) Close-up inside the gorge pocket. (c) AChE with an inhibitor inside the gorge. (d) AChE with tacrine. (e) AChE with donepezil. (f) AChE with galantamine. (g) AChE with rivastigmine. (h) AChE with huperzine A.

*X-ray structures were downloaded from the Protein Data Bank (www.PDB.org) and then visualized using either VMD [4] (Visual Molecular Dynamics, K. Schulten., Univ. of Illinois at Urbana-Champaign) or WebLab Viewer (MSI). Protein codes for a-h are as follows. a = 1EVE [5]; b,c,e = 1W75 [6]; d = 1ACJ [7]; f = 1QTI [8]; g = 1GQR [9]; h = 1VOT [10].

2]. Among these hypotheses, the cholinergic one is the most studied, and the majority of the drugs on the market are AChE inhibitors. In terms of structural information for the design of new inhibitors, X-ray analysis of AChE has been most helpful, as shown in (Fig. 1); AChE has a hydrophobic gorge or pocket which contains the catalytic triad (GLU327, HIS440, SER200), and it also has a peripheral anionic site on the surface near the gorge. Many inhibitors have been co-crystallized with AChE and the information from these analyses has been important in further development of novel AChE inhibitors [5-12]. This structure-based drug discovery will be dealt with later on in the review.

1. Tacrine (Cognex)

Tacrine (Fig. 2a, Parke-Davis Pharmaceuticals, 1993) was the first FDA-approved AD drug, but is no longer used in practice. This agent inhibits AChE reversibly in a non-competitive manner. Tacrine's severe side effects (hepatotoxicity) and short biological half-life (1.6 h to 3 h), however, limit its clinical use [14]. X-ray analysis revealed that tacrine resides in the gorge, inhibiting the binding of AChE. Recent studies suggests dual inhibition small molecules with tacrine as one of the partners. More on this design concept will be dealt in the latter part of this review paper [7].

2. Donepezil Hydrochloride (Aricept)

Donepezil hydrochloride (Fig. 2b, Eisai Inc., 1999) is a piperidine-based reversible AChE inhibitor which was approved by the FDA and is in use for AD treatment. It is significantly more selective towards AChE compared to butyryl-cholinesterase. The plasma half-life is much longer than tacrine, approximately 70 h. Furthermore, compared to Tacrine, the hepatotoxicity is substantially lower. Daily dosing of 5 and 10 mg/day has proved convenient for most patients. Side effects, which are generally mild and transient, include nausea, diarrhea, vomiting, constipation, headache, dizziness and sleep disturbance [15]. Many studies including X-ray structure analysis have been reported for this compound [6].

3. Galantamine (Reminyl)

Galantamine (Fig. 2c, Janssen Pharmaceutica) is a selective competitive AChE inhibitor 50 times more effective against human AChE than butyrylcholinesterase at therapeutic doses. It has also shown agonistic ability against nicotinic receptors although this action has not been fully investigated yet. The serum half-life is 4 to 6 h, which is slightly longer than tacrine but much shorter than donepezil. Dosing of 16 to 24 mg/day proved beneficial for cognitive and non-cognitive AD symptoms. Adverse effects in the dose-escalation phase include nausea, vomiting, diarrhea, and headache [16-20]. X-ray analysis revealed that the oxygen moiety on the methoxy group on the phenyl ring is in close proximity from SER200 and HIS440. Based on these facts researchers have tried to modify galantamine with different derivatives to design better inhibitors. Recent preliminary studies, however, has found that the rate of progression from mild cognitive impairment to AD showed no significant difference between galantamine and placebo over a two-year period [21].

4. Rivastigmine Tartrate (Exelon)

Rivastigmine tartrate (Fig. 2d, Novartis) is also a reversible AChE inhibitor with high brain selectivity. Its use has been approved in at least 40 countries around the world. Plasma half-life is only 2 h, however. Rivastigmine's adverse effects are gastrointestinal, including nausea, vomiting, anorexia, and weight loss. Thus, patients should take initially 1.5 mg/dose twice a day and then the dosage should be maintained via titration [22-25].

5. Metrifonate (O,O-dimethyl(1-hydroxy-2,2,2-trichloroethyl)-phosphate)

Metrifonate (Fig. 2e) is a precursor to the active pseudo-irreversible AChE inhibitor DDVP (2,2-dichlorovinyl-dimethyl-phosphate). Plasma half-life is longer than donepezil, and it rapidly enters the brain. Most common adverse effects were diarrhea and leg cramps. This compound did not reach the market due to increasing concerns of side effects related to muscular weakness [26, 27].

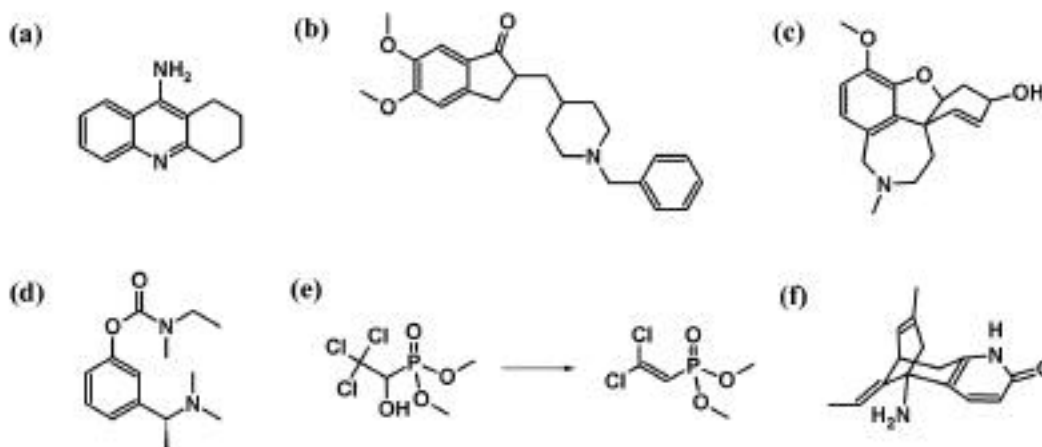


Fig. (2). AChE Inhibitors. (a) Tacrine. (b) Donepezil. (c) Galantamine. (d) Rivastigmine. (e) Metrifonate (to DDVP). (f) Huperzine A.

6. Huperzine A

Huperzine A (Fig. 2f) is an alkaloid isolated from *Huperzia serrata*, a club moss. Currently it is available not as a drug, but as a dietary supplement (US). Its half-life is about 5 h, and mild adverse effects include sleeping, nausea, and vomiting. Recently, in double-blind, placebo-controlled clinical trials with AD patients, significant improvements have been observed both in cognitive function and quality of life. Tests have shown that huperzine A does not have unexpected toxicities. Additionally, huperzine A is claimed to have neuroprotective properties. Several derivatives have also been reported for this molecule [28-30].

N-METHYL-D-ASPARTATE (NMDA) ANTAGONIST

Persistent activation of central nervous system NMDA receptors by the excitatory amino acid glutamate has been hypothesized to contribute to the symptomatology of AD. Thus inhibiting this receptor might improve symptoms in AD patients [31].

Memantine

Memantine (Fig. 3b, 1-amino-3,5-dimethyl-adamantane hydrochloride) is a recently FDA-approved NMDA antagonist. Its half-life is between 3 to 7 h and clinical tests show better outcome from patients compared to placebo. Furthermore, memantine was not associated with harsh adverse effects [32-34].



Fig. (3). (a) NMDA receptor crystal structure with 5,7-dichloro-4-hydroxyquinoline-2-carboxylic acid. (b) Memantine, NMDA antagonist available on the market as a drug.

*Protein structure was downloaded from the Protein Data Bank (www.PDB.org) and then visualized with WebLab Viewer (MSI). Protein code for a is 1PBQ [35].

A -DEPOSIT ANTAGONIST (METAL CHELATORS)

Increasing evidence shows that several metal species including aluminum, iron, zinc, and copper induce ABeta aggregation and neurotoxicity in the AD brain [36]. The aluminum-hypothesis was discredited as an artifact from poor technique in elemental analysis, but recent structural evidence suggests there may be a direct relation between Al and Abeta. *In vitro* studies have been done, and metal binding ligands have also been employed. AD patients often show abnormally high concentrations of iron and zinc thus certain metal chelators like Desferrioxamine and Clioquinol may have the possibility of being used as therapeutic agents for AD treatment.

1. Desferrioxamine (DFO)

DFO (Fig. 4a) is isolated from *Streptomyces pilosus* and this compound was the first to be clinically tested as a metal chelator to treat AD patients. Treated patients showed slowed clinical progression of dementia associated with AD. DFO is presumed to chelate aluminum or other metal ions and reduce the neocortical concentration, leading to behavioral improvements in an unknown manner [37-43].

2. Clioquinol

AD patients have elevated levels of copper and zinc in the neocortex. The transition metals are particularly concentrated in neuritic plaques and potentiate Abeta aggregation and neurotoxicity *in vitro*. Clioquinol (Fig. 4c) [36, 44-46] chelates with copper and zinc in postmortem AD brains and solubilizes Abeta. Thus, Abeta accumulation in the brain may be significantly reduced by treatment with Clioquinol as a therapeutic agent. On the other hand, reports suggest that plaque formation may not be critical pathogenic entities, and soluble Abeta levels are the Abeta correlated to cognitive dysfunction in AD. [47] Crystal structure analysis confirms the coordination chemistry behind clioquinol's possible role as metal chelator [48].

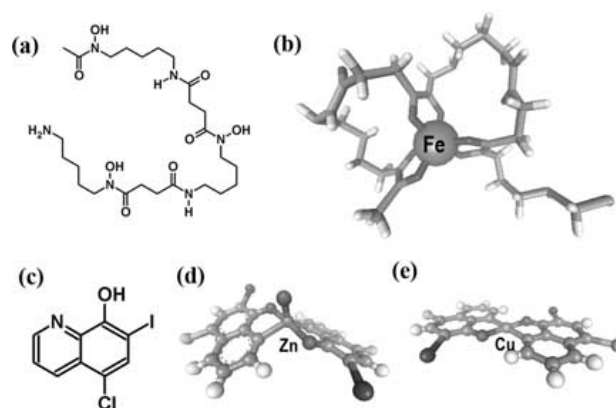


Fig. (4). (a) Desferrioxamine (DFO). (b) Ferrioxamine B. (c) Clioquinol. (d) Clioquinol Zn complex. (e) Clioquinol Cu complex.

*Structure b as received from CCDC (Cambridge Structure Database, 155586, [43]) and d,e were downloaded from ACS ([48], pubs.acs.org) website and visualized using WebLab Viewer.

ANTIOXIDANTS

Accumulating evidence suggests that oxidative damage to neurons plays an important role in the AD pathogenesis [36]. Thus, efforts to reduce oxidative injury may prove beneficial in retarding or preventing the onset and progression of AD in patients. Preclinical studies have been conducted with several potential antioxidant drugs that may have therapeutic uses in the treatment of AD.

1. Ginkgo biloba Extract (Egb761)

Egb761, an extract from *Ginkgo biloba*, was examined to assess efficacy and safety in patients with AD and multi-infarct dementia. Treated patients showed improvement on the Alzheimer's Disease Assessment Scale-Cognitive subscale and the Geriatric Evaluation of Relative's Rating Instrument [50-53].

2. Melatonin

Melatonin (Fig. 5b) can reduce neuronal damage induced by oxygen-based reactive species in experimental models of AD. Melatonin also has anti-amyloidogenic activities [54].

3. Idebenone and Vitamin E

Idebenone (Fig. 5d) is a coenzyme Q10 analog and known to be safe at the clinical stages. Cell culture and animal model studies show that vitamin E (Fig. 5a) and idebenone attenuates A β -induced neurotoxicity and cognitive impairments [55-58]. Recent discoveries, however, rules out the positive role of vitamin E on mild cognitive impairment. This was confirmed by a large, randomized and placebo-controlled clinical trial which also showed that donepezil also had little benefit over a three-year period [21, 59].

4. Dehydroevodiamine Hydrochloride (DHED)

DHED (Fig. 5e) [63] is a compound extracted from *Evodia rutaecarpa*. Recent *in vitro* studies showed that AChE inhibitors like tacrine and Huperzine A may also act as antioxidants attenuating A β -induced oxidative damage and thus may enhance their therapeutic efficacy [60-62]. Results from our studies showed that DHED also protects neurons against hydrogen peroxide and glutamate. DHED decreases reactive oxygen species production and cell death induced by A β and carboxyterminal peptides of APP (amyloid precursor protein) improves cognitive impairments in AD and ischemic animal models, suggesting that DHED might be useful in treatment of AD, vascular dementia and stroke. DHED is currently under clinical studies as well as derivative studies [63-66].

5. Manganese Porphyrin and Salen

Link between mitochondria and aging related diseases has been hypothesized for a while now. However, recent

findings with animal model studies and antioxidant research have allowed researchers to associate the two even closely [67-69]. Manganese complexes of porphyrins (Fig. 5c) increased the mean lifetime of mice and ameliorated dilated cardiomyopathy and hepatic lipid accumulation. Mn-porphyrins also have been found to delay apoptosis of Sod2 deficient neuronal cultures from knockout mice and improve the survival of both heterozygous and wild-type cultures. These results suggest that metalloporphyrin antioxidants can delay neuronal death resulting from increased mitochondrial oxidative stress [70]. An alternative set of inorganic antioxidants was achieved with Mn-salen complexes (Fig. 5f) which showed efficacy in many different oxidative damage models. Recently this SOD/catalase mimic was used to treat lens cataracts developed by A β in transgenic mice [71-73].

MONOAMINE OXIDASE (MAO) INHIBITORS

1. Selegiline

In a 2-year double-blind, controlled, clinical study of patients with moderately advanced AD, progression of the primary outcome of the disease was delayed by treatment with selegiline (Fig. 6b), vitamin E, or both. Although there were no significant effects on cognitive ability, results suggest that the use of these two therapeutics might play some helpful roles in delaying clinical deterioration related to AD [74].

2. Rasagiline and TVP1022 [74-78]

N-propargyl-1(R)-aminoindan, rasagiline (Fig. 6c), and its optical isomer, TVP1022 (Fig. 6d), are selective irreversible inhibitors for MAO. They are structurally very similar to selegiline. Both compounds have similar neuroprotective activities with neuronal cell cultures, which is associated to the propargylamine functionality. However, rasagiline inhibits MAO-B to a much greater extent.

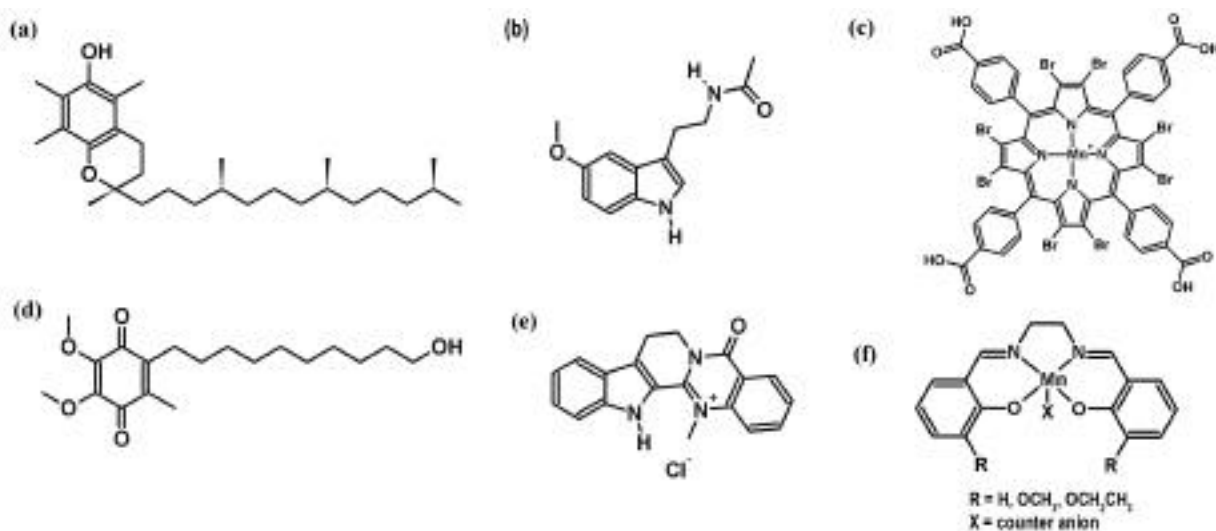


Fig. (5). Antioxidants. (a) α -Tocopherol (component of Vitamin E). (b) Melatonin. (c) Manganese (III) -octabromo-*meso*-tetrakis(4-carboxyphenyl)prophyrin (MnBr₈TBAP). (d) Idebenone. (e) Dehydroevodiamine HCl (DHED). (f) Mn-salen.

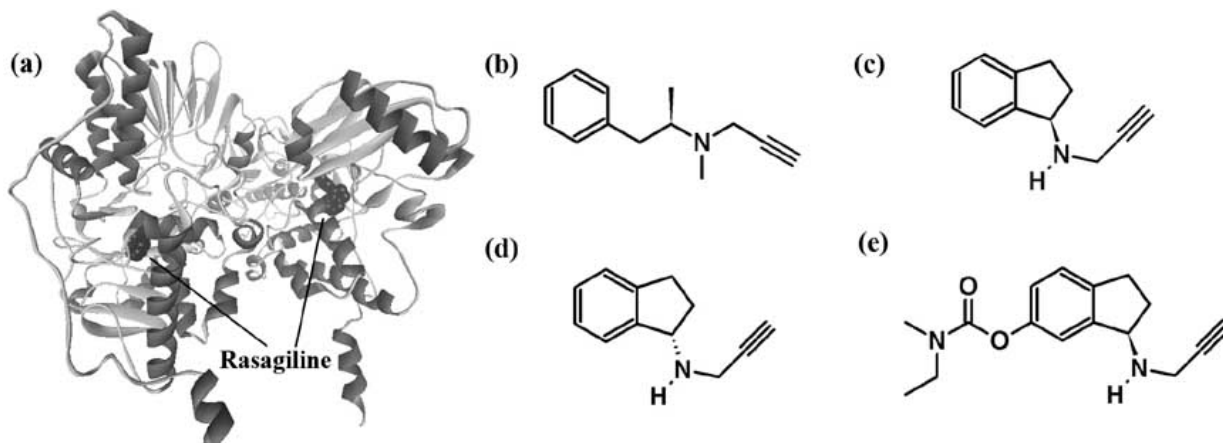


Fig. (6). (a) Monoamine Oxidase B (MAO-B) co-crystallized structure with Rasagiline (N-propargyl-1-(R)-aminodan. (b) Selegiline. (c) Rasagiline. (d) TVP1022. (e) TV3326 (Ladostigil).

*Protein structure was downloaded from Protein Data Bank (www.PDB.org) and visualized using WebLab Viewer. Protein ID is 1S2Q [80].

Furthermore, *in vivo* studies showed that rasagiline is ten times more active in MAO inhibition compared to selegiline. Several *in vitro*, *in vivo*, and cell culture experiments have been conducted for rasagiline [75-79]. X-ray structure analyses are available for complexes of each of these agents bound to MAO [80].

3. Ladostigil (TV3326) and TV3279

Ladostigil (Fig. 6e) also combines AChE/MAO inhibition and neuroprotective ability. This compound is a result of combining active components from rasagline (MAO inhibitor, neuroprotector) and rivastigmine (AChE inhibitor). The optical isomer of ladostigil, TV3279, was also developed but the MAO inhibitory ability was much lower, so ladostigil is the more effective agent. As with rasagline, the propargylamine moiety is responsible for the neuroprotective activity observed in cell cultures. Drugs like ladostigil are highly desirable since multiple therapeutic activities are observed in a single molecule. Future direction towards AD drug development should be identifying active components for specific activities and ultimately combining them together to form a new compound [81, 82].

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS, (NSAIDS)

Destruction of neurons due to inflammation around Abeta plaques is thought to be a major factor in the pathogenesis of AD. [2] NSAIDs, inhibit cyclooxygenase-1 and cyclooxygenase-2 (COX-1 and COX 2), which are responsible for the oxidation of arachidonic acid to prostaglandins. Individuals using conventional NSAIDs (like ibuprofen, Fig. 7a) on a regular basis showed a decreased incidence of AD. This observation suggests that NSAIDs have some neuroprotective effect. The association between AD and NSAIDs remains debatable, however. Like clioquinol many of these over-the-counter drugs are already FDA-approved pharmaceuticals and may be incorporated into clinical use relatively quickly [83-86]. Unfortunately, new evidence regarding some NSAIDs suggests that they may cause cardiovascular problems, which will slow their development for AD treatment [87].

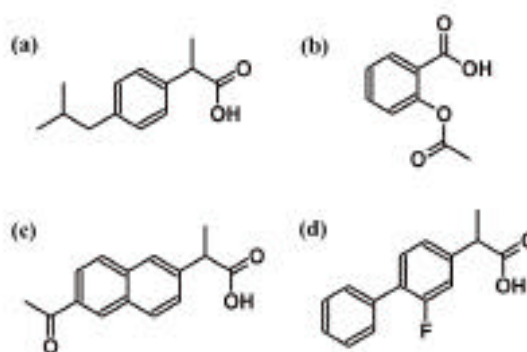


Fig. (7). NSAIDs. (a) Ibuprofen. (b) Aspirin. (c) Naproxen. (d) Flubiprofen.

MEDICINAL CHEMISTRY APPROACHES TOWARD BETTER DRUGS

1. Structure-Based Discovery

Docking experiments between ligands and proteins using X-ray structures and computational methods provides a opportunities to design potent drug compounds in a more systematic way. Structure-based strategies, i.e., QSAR (Quantitative Structure-Activity Relationship), employed to aid in the design of creating potent inhibitors for certain proteins are already well-developed [88, 89]. The usual line of approach is to develop new lead targets based on QSAR and computer modeling of drug-protein interactions. Synthesis of proposed compounds and testing for potencies in the lab make this an iterative process [90]. Among many others, AChE, NMDA and secretase inhibitor designs have also used this approach.

a. AChE

The use of 2D-QSAR has not proved very effective as a predictive tool in the design of novel or potent AChE inhibitors. Nonetheless, taken together, all results combined shows that AChE inhibitors adopt unique binding schemes inside the gorge of the AChE. In recent years, however, the advent of 3D-QSAR analysis utilizing the X-ray crystal

structures has proved much more successful in predicting and generating more potent inhibitors [5-12, 90, 91].

b. NMDA

X-ray structures of NMDA receptor NR1 with agonists, partial agonist, and antagonist were reported recently [35]. The cleft of S1S2 'clamshell' is open in the presence of an antagonist but closed after binding agonists. Also, loop 1 is folded upon agonist binding. The co-crystal structures provide more insight into receptor function mechanism and subunit-subunit associations. Utilizing the structural information may possibly lead to more potent NMDA inhibitors.

X-ray structures of an AMPA (alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) sensitive glutamate receptor and its complexes with different ligands have been solved and this permits the formation of a computational model of NMDA receptor, which will prove important for the design of new ligands [92].

c. BACE (-Secretase)

BACE is one of two proteases that cleave APP (beta-amyloid precursor protein) to produce 40-42 Abeta residues in the brain. Although BACE inhibitor therapeutics are not mentioned elsewhere in the review, it was worth briefly reviewing recent progress in structure-based discovery for such inhibitors.

Using previous X-ray structures [93-95], the active site protonation state of BACE was determined using molecular dynamics simulations and docking experiments [96]. This work suggests an important role for the newly recognized hydrogen bonding acceptor in the active site, and this information should be a key factor in drug discovery. In a different study, molecular docking and 3D-QSAR experiments were conducted to find a more potent peptidomimetic inhibitor compound that would be more successful in crossing the blood-brain barrier [97]. Current statine-based inhibitors like OM99-2 (Fig. 8b) are very hydrophilic, whereas the blood-brain barrier is hydrophobic.

Hydroxyethylamine, a BACE inhibitor, was co-crystallized with human BACE and the apo structure was

solved. (Fig. 8a) Significant movement in the active-site was observed compared to previous data and two additional sites for possible targets for drugs were identified [98].

2. Fragment-Based Lead Discovery and Dual Inhibitors

Fragment-based lead discovery [99, 100] is gaining popularity both in industry and academia. This approach not only reduces time of screening but also allows the generation of molecules with lead-like properties. Individual starting fragments are small molecules and are relatively well understood *via* analytic tools like NMR, X-ray crystallography, and mass spectroscopy. Many good examples exist and AChE inhibitors have also been investigated *via* fragment linking and click chemistry (i.e., the facile generation of chemical libraries based on Huisgen 1,3-dipolar cycloadditions [105]).

a. Bis-Tacrine Analogs

Bis-tacrine compound [101, 102] (Fig. 9a) with an alkylene linker in between was found to be a potent inhibitor for AChE. The results suggest interactions of the tacrine moieties with the two major sites in the AChE, catalytic triad and peripheral anion site. Computational analysis allowed the determination of low-affinity sites for additional design parameters. AChE IC₅₀ was in the sub-nM range, but BChE inhibition was substantially less than tacrine itself.

b. TZ2PA6

Click chemistry has been used to synthesize better inhibitors for AChE. Huisgen 1,3-dipolar cycloaddition [103] (Fig. 9b) of azides and acetylenes offer great advantages over many other chemical modifications, since the reaction itself is water tolerant

and the functional groups involved are generally compatible with biological systems. Also, azides and acetylene units can be readily incorporated into molecules [104, 105].

AChE was selected as a target host system to facilitate the reaction between two molecular fragments which is shown in (Fig. 9c) [106-108]. Inside the narrow gorge (approximately 2nm in depth) site-specific inhibitors based on tacrine and phenanthridinium motifs were linked together

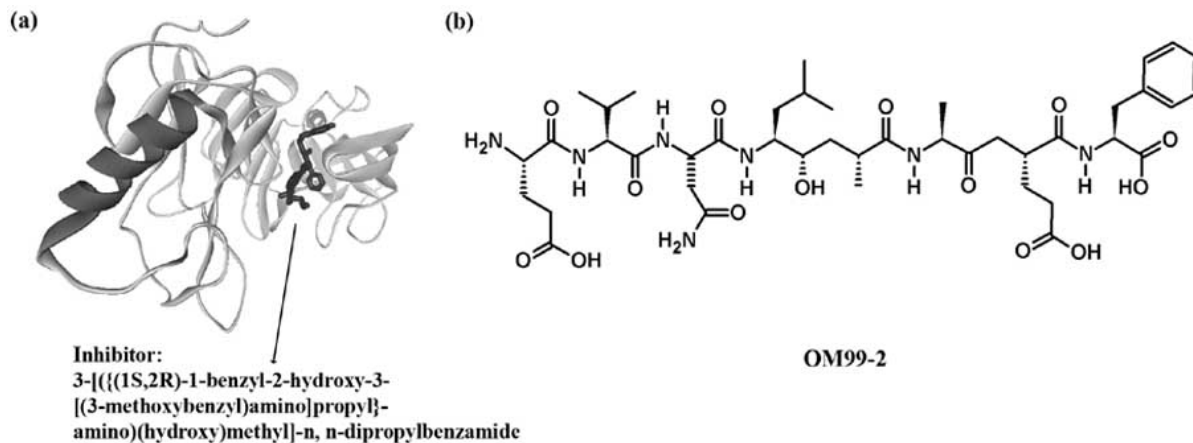


Fig. (8). (a) BACE (-secretase) co-crystal structure with an inhibitor. (b) OM99-2, BACE inhibitor.

*X-ray structures were downloaded from the Protein Data Bank (www.PDB.org) and then visualized using WebLab Viewer (MSI). Protein codes for a is 1W51 [97].

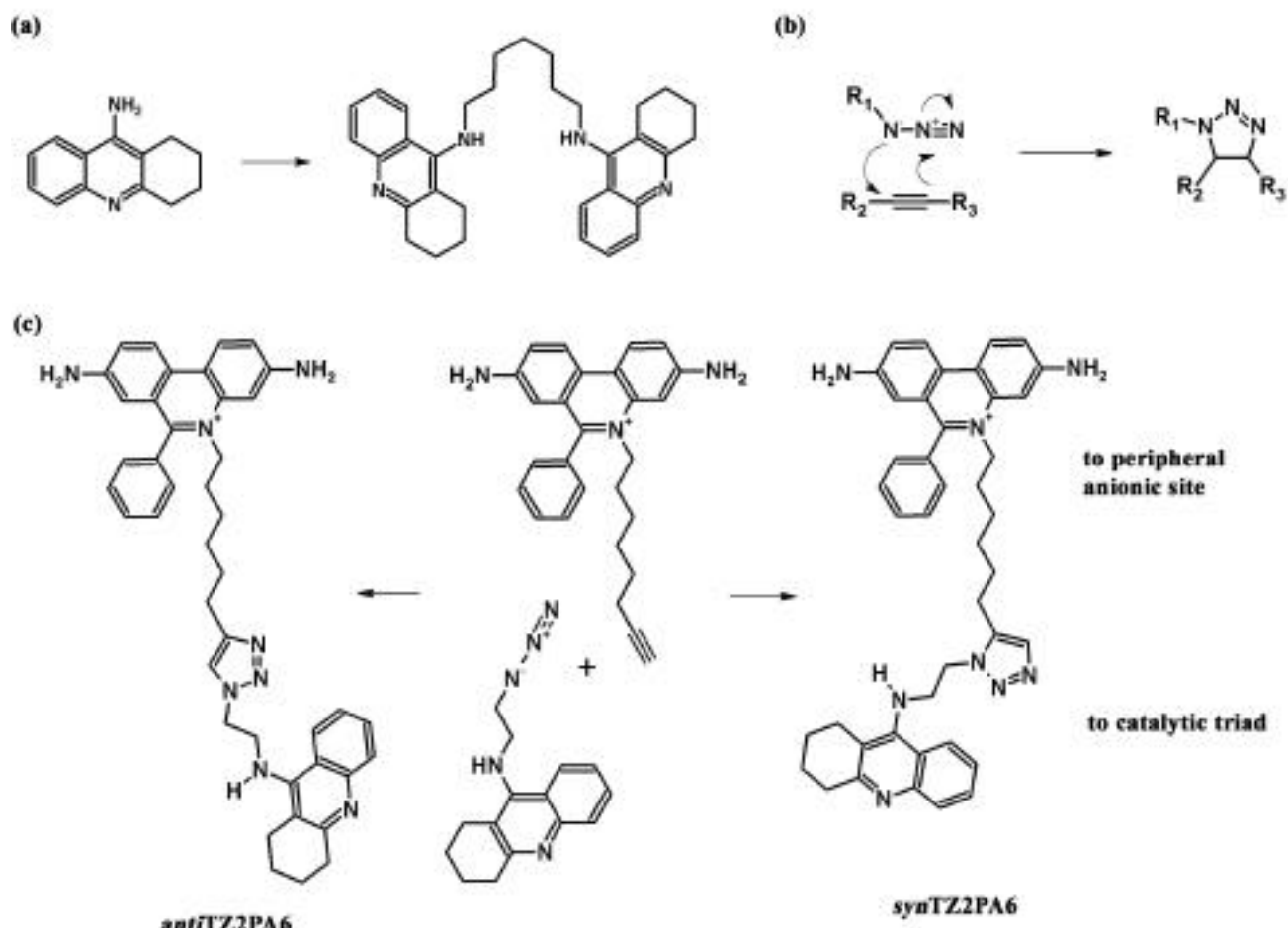


Fig. (9). Fragment-Based Lead Discovery of AChE Inhibitors. (a) Bis-tetrahydroaminacrine (dual tacrine) inhibitor. (b) Huisgen 1,3-dipolar cycloaddition between acetylides and azides; click chemistry. (c) TZ2PA6 inhibitors, the tacrine moiety binds inside the gorge whereas the phenanthridium motif associates with the peripheral anionic site (see Fig. (1) for the x-ray crystal structures).

as a proof of principle. These bivalent inhibitors contain 1,2,3-triazole units that serve as additional binding motifs in the bisfunctional compound. Authors emphasized that the synthesized inhibitors should be handled with care since high-affinity inhibitors could prove to be highly toxic neurotoxic agents. Usually, AChE inhibitors used to treat AD are reversible agents. More recent examples gave more potent noncovalent AChE inhibitors which are 3 times as potent as the phenylphenanthridium-derived compounds [109].

MULTIFUNCTIONAL INHIBITORS

Recent examples show successful attachment of two moieties known for its inhibitory effects to get better pharmacological effects. Another class of molecules in vogue are dual inhibitory drugs to act on two different targets. Ladostigil, which is both MAO and AChE inhibitor, was discussed earlier.

1. Propidium-Tacrine Heterodimer

This heterodimer, shown in (Fig. 10a), is an effective AChE and Abeta aggregation inhibitor. *In vitro* biological

studies revealed the IC_{50} for AChE and Abeta aggregation are in the low nanomolar range. This compound may be a valuable lead for developing a more potent AD drug [110].

2. Huprine-Tacrine Heterodimer

Huprine and tacrine, when linked together with an adequate tether containing hetero atoms, provide a good inhibitory effect for AChE [111]. There might be extra interaction factors between the aromatic residues with the protonated amino groups on the linker. The specific case shown in (Fig. 10b) has IC_{50} in the sub-nanomolar range for human AChE and low nanomolar range for human BChE.

3. Lipocrine

Linkage of tacrine and lipoic acid also leads to a improvement in biological activity [112]. This compound (Fig. 10c) is the first of its kind which inhibits AChE, BChE activity and Abeta aggregation and further protects neuroblast cells (SHSY5Y) from ROS (reactive oxygen species) damage. Further investigation using this compound as a lead might bring about a more potent AD drug.

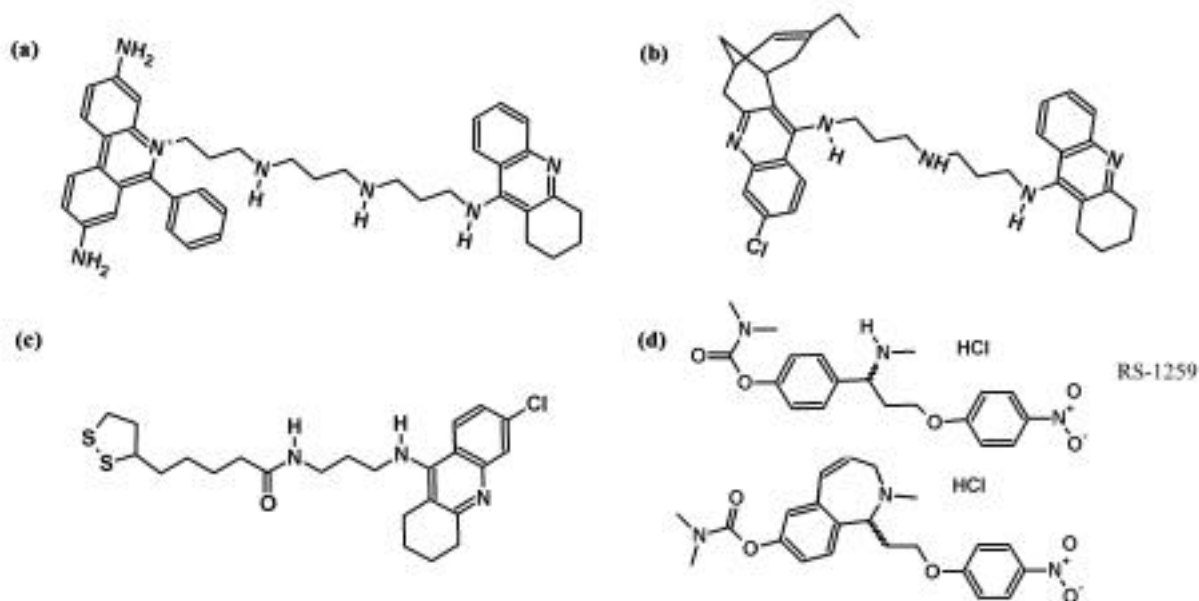


Fig. (10). Multifunctional Inhibitors. (a) Propidium-tacrine heterodimer. (b) Huprine-tacrine heterodimer. (c) Lipocrine. (d) AChE/SERT dual inhibitors.

4. AChE and SERT (Serotonin Transporter) Dual Inhibitors

RS-1259 (Fig. 10d)-top was designed to include the functions of rivastigmine (AChE inhibitor) and fluoxetine (SERT inhibitor). After synthesis, *in vitro* and *ex vivo* experiments were conducted and this compound is an orally active drug tested on rodents. IC_{50} values are sub-150 nM range and *ex vivo* activities are either more or as potent as the parent compound. Further development lead to (Fig. 10d)-bottom compound which has nanomolar IC_{50} values for AChE and SERT activity inhibition [113-116].

CONCLUSIONS

The creation of effective therapeutic agents for AD would be a major medical milestone. From commercially available drugs to experimental compounds in the laboratory, tremendous effort is being put into discovering more potent drugs for AD. Different causation targets are being targeted and medicinal, pharmacological, clinical and pathological research is on going around the world. This review has examined the major drug molecules commercially available, as well as those that are in clinical or experimental trials. Furthermore, new avenues of approaches for AD drug development have been discussed with recent examples. The current focus of research is in developing multifunctional drugs that target multiple components thought to be contributing to AD, in part due to the multiple possible causative sources of AD. In aiding drug development, proper analysis of target and ligand interaction is key. Thus, X-ray and NMR structure analyses, combined with computational methods, become especially effective when combined with both chemical synthesis and biological screening, which is ultimately where the most potent therapeutic agent will be identified, developed, tested, and distributed.

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ABBREVIATIONS

AD	=	Alzheimer's disease
FDA	=	Food and Drug Administration
AChE	=	Acetylcholinesterase
NMDA	=	<i>N</i> -Methyl-D-aspartate
ACh	=	Acetylcholine
CNS	=	Central nervous system
Abeta	=	-Amyloid
PDB	=	Protein Data Bank
VMD	=	Visual Molecular Dynamics
GLU	=	Glutamine
HIS	=	Histidine
SER	=	Serine
DDVP	=	2,2-Dichlorovinyl-dimethyl-phosphate
DFO	=	Desferrioxamine
DHED	=	Dehydroevodiamine HCl
APP	=	Amyloid precursor protein
SOD	=	Superoxide dismutase

MAO	=	Monoamine oxidase
COX	=	Cyclooxygenase
NSAIDs	=	Nonsteroidal anti-inflammatory drugs
QSAR	=	Quantitative Structure-Activity Relationship
AMPA	=	-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
BACE	=	-Secretase
NMR	=	Nuclear magnetic resonance
IC50	=	Inhibition concentration 50
BChE	=	Butyrylcholinesterase
ROS	=	Reactive oxygen species
SERT	=	Serotonin transporter

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