Review Article

A Review on Tacrine Hybrid; A Multi-Targeting Agent for the Treatment for Alzheimer's Disease

Dhanya.O*, Sujitha P V, Vignesh C, Abitha H, Geethanjaly N S, K V Vismaya, Athira J S.
Associate Professor, Department of Pharmaceutical Chemistry, Nehru College of Pharmacy, Pampady P O, Thrissur(dist)-680588, India.
***Corresponding author's E-mail:** sujithadevidas8009@gmail.com

Received: 11-12-2024; **Revised:** 24-02-2025; **Accepted:** 05-03-2025; **Published online:** 20-03-2025.

ABSTRACT

Alzheimers disease is a progressive neuro degenerative disorder. It is characterised by the beginning by episodic and semantic memory loss and cognitive impairment. As the disease progresses one may experience a decline in language function, depression and anxiety. Later stages psychotic features and personal changes may develop. It is also referred to as late life mental failure in humans. Therefore, the discovery of efficient anti-AD agents is of great importance for drug developers. So far, the mechanism for AD is still not clearly elucidated, but it is well-accepted that AD is a multifactorial syndrome deriving from a complex array of neurochemical factors. Despite many years of this research main cause of this disease is unknown and only symptomatic treatment is used. Pathological changes result in the loss of cholinergic neurons, decreased level of neurotransmitters, the main increased beta amyloid and few proteins deposition and dyshomeostatis of bio-metals and oxidative stresses.

Keywords: Tacrine hybrid, memory loss, neuro degenerative disorder.

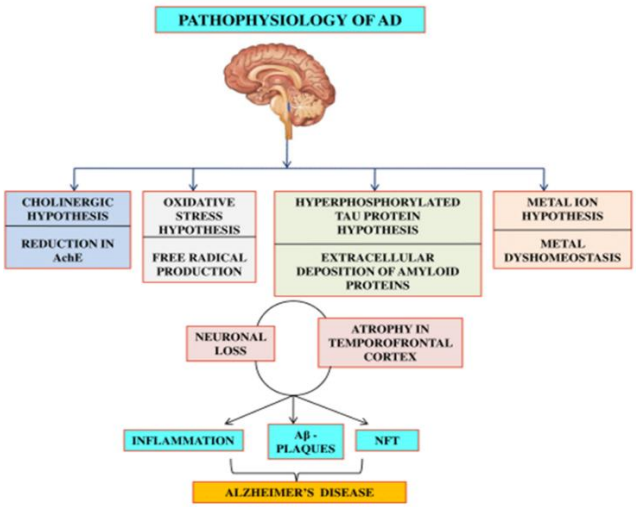
INTRODUCTION

As part of research, an identical approach has been pursued for the development of new multi targeting compounds as potential Anti AD agents, Several hypotheses about AD pathogenesis are presented, such as cholinergic dysfunction, amyloid cascade, hyper phosphorylation of s-protein, cell cycle hypothesis, and brain-derived neurotrophic factor hypothesis, oxidative stress, free radical formation, metal dyshomeostasis, and mitochondrial dysfunction.

These findings not only inspire the design of new anti-AD agents with diverse mechanisms, but also depict a more complex AD scenario. So far, designing drugs targeting the cholinergic system is still the most successful therapeutic strategy against AD. Many studies have shown that the decline of acetylcholine (ACh) level results in the cognitive and memory deficits. Therefore, recovering cholinergic function by inhibiting cholinesterases (ChEs), which are in charge of the hydrolysis of ACh, is beneficial for the treatment of AD.

Pathophysiology

Aβ plaques are one of the main AD hallmarks and are mostly constituted of Aβ peptide. According to the amyloid cascade hypothesis, Aβ is derived from the sequential proteolysis of the amyloid precursor protein (APP) by β –secretase (BACE-1), an enzyme able to cleave APP in two main components: sAPPβ and a C99 fragment. The latter can be further cleaved by β -secretase to form Aβ, which is finally released into extracellular environment. The dominant species is $A\beta_{40}$ peptide, which represents 80 to 90% of all β -peptides. The second major component is the $A\beta_{42}$(5 to 10%) which readily aggregates, forming the seed for larger oligomers and fibrils, and ultimately the amyloid plaques.



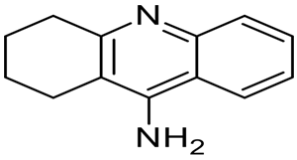
This sequence is structurally accompanied by a protein transition from α-helical conformation to -sheet structures. Aβ plaques, or more probably their soluble oligomers, are neurotoxic, exerting their effects in a variety of ways, including mitochondrial function disruption, apoptosis induction ion channels formation, and stimulation of stress-activated protein kinase pathway.

TACRINE AS LEAD COMPOUND

A centrally active cholinesterase inhibitor that has been used to counter the effects of muscle relaxants, as a respiratory stimulant, and in the treatment of Alzheimer's disease and other central nervous system disorders.

Tacrine possesses a simple structure and strong activity, but despite these features, it was withdrawn from the market due to its side effects. Due to the multifactorial etiology of

Alzheimer's disease, researchers have investigated multitarget- directed ligands based on tacrine structure to achieve better treatment efficacy. To broaden the therapeutic profile of the ligands, tacrine is bound to numerous moieties with various applications.



Mechanism of action

The mechanism of tacrine is not fully known, but it is suggested that the drug is an anticholinesterase agent which reversibly binds with and inactivates cholinesterases. This inhibits the hydrolysis of acetylcholine released from functioning cholinergic neurons, thus leading to an accumulation of acetylcholine at cholinergic synapses. The result is a prolonged effect of acetylcholine.

Pharmacodynamics

Tacrine is a parasympathomimetic- a reversible cholinesterase inhibitor that is indicated for the treatment of mild to moderate dementia of the Alzheimer's type. An early pathophysiological feature of Alzheimer's disease that is associated with memory loss and cognitive deficits is a deficiency of acetylcholine as a result of selective loss of cholinergic neurons in the cerebral cortex, nucleus basalis, and hippocampus.

Tacrine is postulated to exert its therapeutic effect by enhancing cholinergic function. This is accomplished by increasing the concentration of acetylcholine at cholinergic synapses through reversible inhibition of its hydrolysis by acetylcholinesterase. If this proposed mechanism of action is correct, tacrine's effect may lessen as the disease progresses and fewer cholinergic neurons remain functionally intact. There is no evidence that tacrine alters the course of the underlying dementing process.

Indication

For the palliative treatment of mild to moderate dementia of the Alzheimer's type.

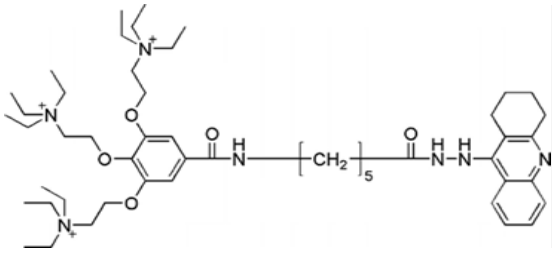
TACRINE HYBRIDS

1) Tacrine-trimethoxy benzene hybrid

Two series of novel hetero bivalent tacrine derivatives were synthesized. A trimethoxy substituted benzene was linked to the tacrine moiety by a hydrazide-based linker. The compounds were evaluated as cholinesterase inhibitors, and trimethoxy benzoic acid derivatives with 11- or 12-atom spacers were the most potent inhibitors of human acetylcholinesterase. The inhibitors showed a surprising selectivity toward human butyrylcholinesterase.[3]

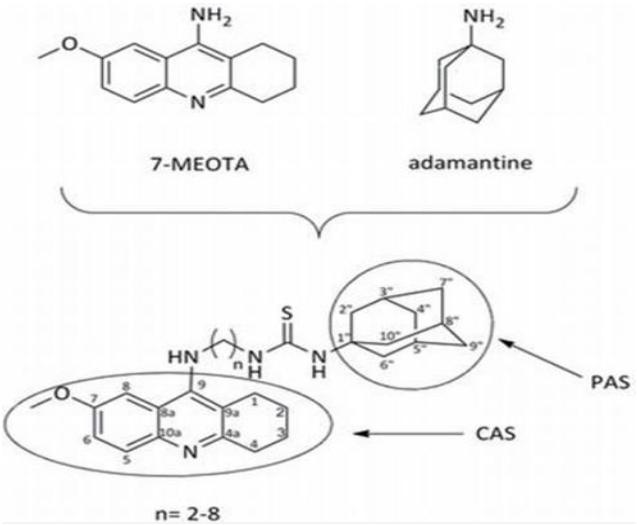
2) Tacrine- Gallamine hybrid

Gallamine and tacrine are allosteric antagonists at muscarinic M2 acetylcholine receptors and inhibitors of acetylcholinesterase. At both acetylcholine-binding proteins, gallamine and tacrine are known to occupy two different binding sites: in M2 receptors within the allosteric binding area and in acetylcholinesterase at its catalytic and its peripheral site. To find new ligands of both targets, we designed a gallamine–tacrine dimer and several derived hybrid compounds to address the two binding sites.[4]



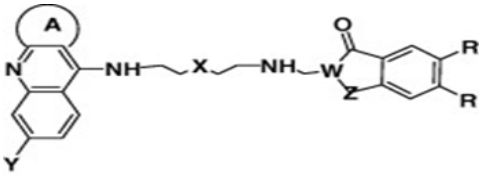
3) 7-Methoxytacrine-adamantylamine hybrid

A structural series of 7-MEOTA-adamantylamine thioureas was designed, synthesized and evaluated as inhibitors of human acetylcholinesterase (hAChE) and human butyrylcholinesterase (hBChE). The compounds were prepared based on the multi-target-directed ligand strategy with different linker lengths (n = 2–8) joining the well-known NMDA antagonist adamantine and the hAChE inhibitor 7-methoxytacrine (7-MEOTA).[5]



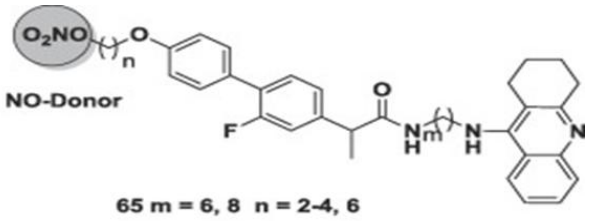
4) Tacrine –donepezil hybrid

A new series of donepezil–tacrine hybrid related derivatives have been synthesised as dual acetylcholinesterase inhibitors that could bind simultaneously to the peripheral and catalytic sites of the enzyme. These new hybrids combined a tacrine, 6-chlorotacrine or acridine unit as catalytic binding site and indanone (the heterocycle present in donepezil) or phthalimide moiety as peripheral binding site of the enzyme, connected through a different linker tether length. One of the synthesised compounds emerged as a potent and selective AChE inhibitor.[6]



5) Tacrine –flubiprofen hybrids

Tacrine–flurbiprofen hybrid compounds were synthesized as multi-target-directed compounds for the treatment of Alzheimer's disease. Compared to tacrine, compounds showed better acetylcholinesterase (AChE) inhibitory activity and better or the same butyrylcholinesterase (BuChE) inhibitory activity. Notably, showed a mixed-type inhibitory action for AChE, indicating a "dual-binding site action" of both toward the catalytic active site (CAS) and the peripheral anionic site (PAS), whereas for BuChE, a competitive inhibitory action was observed.[7]

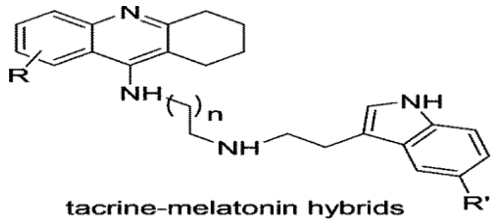


65 m = 6, 8 n = 2-4, 6

6) Tacrine-melatonin hybrid

Tacrine and melatonin are well-known drugs with activities as an acetylcholinesterase (AChE) inhibitor and free radical scavenger, respectively.

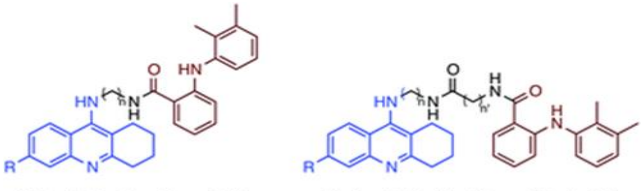
They exhibit a higher oxygen radical absorbance capacity than does melatonin and are predicted to be able to cross the blood−brain barrier to reach their targets in the central nervous system.[8]



tacrine-melatonin hybrids

7) Tacrine-mefenemic acid derivative

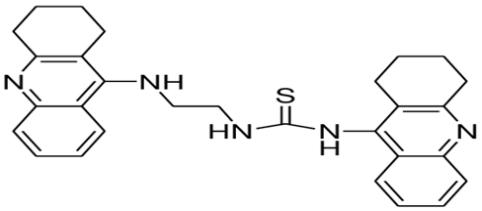
Alzheimer's disease (AD) is a complex syndrome characterized by the degeneration of the brain and central nervous system that may be caused by an assortment of genetic and environmental factors. Consequently, a conjunctive approach targeting multiple affecters of AD could lead to improved drug candidates for the treatment of AD. A convergent chemical synthetic approach yielded a series of tacrine-mefenamic acid hybrids that were evaluated for their ability to inhibit acetylcholinesterase (AChE). [9]



Series A: R = H or Cl; n = 6-12 **Series B:** R = H or Cl; n = 3-8; n' = 1-5

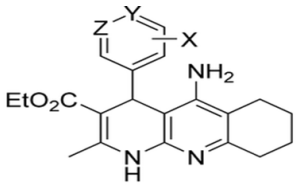
8) Tacrine-1,2,3-triazole hybrids

Tacrine-1,2,3-triazole hybrids were designed, synthesized, and evaluated as potent dual cholinesterase inhibitors. Most of synthesized compounds showed good *in vitro* inhibitory activities toward both acetylcholinesterase (AChE)and butyrylcholinesterase (BChE). Among them,7-chloro-*N*-((1-(4-methoxybenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)-1,2,3,4-tetrahydroacridin-9-amine was found to be the most potent anti-AChE derivative and *N*-((1-(4-methoxybenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)-1,2,3,4-tetrahydroacridin-9-amine demonstrated the best anti-BChE activity.[10]



9) Tacrine–nimodipine hybrid

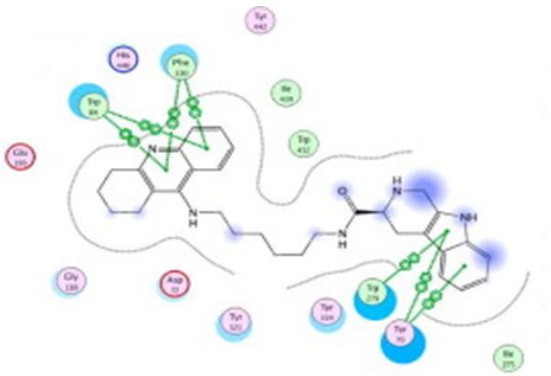
Tacripyrines have been designed by combining an AChE inhibitor (tacrine) with a calcium antagonist such as nimodipine and are targeted to develop a multitarget therapeutic strategy to confront AD. Tacripyrines are selective and potent AChE inhibitors in the nanomolar range.[11]



X= H, 4'-F, 2'-CF_3, 2'-NO_2, 3'-NO_2, 4'-NO_2, 4'-Me, 4'-C_6H_5, 2'-OMe, 3'-OMe, 4'-OMe, 3', 4'-di-OMe
Y= CH, C, N; Z= CH, N

10) Tacrine-beta carbiline hybrid

Tacrine-(β-carboline) hybrids were designed, synthesized and evaluated as multifunctional cholinesterase inhibitors against Alzheimer's disease (AD). In vitro studies showed that most of them exhibited significant potency to inhibit acetylcholinesterase (*ee*AChE and *h*AChE), butyrylcholinesterase (BuChE) and self-induced β-amyloid (Aβ) aggregation, Cu^{2+}-induced Aβ aggregation, and to chelate metal ions. [12]



Toxicity

Overdosage with cholinesterase inhibitors can cause a cholinergic crisis characterized by severe nausea/vomiting,

salivation, sweating, bradycardia, hypotension, collapse, and convulsions. Increasing muscle weakness is a possibility and may result in death if respiratory muscles are involved. The estimated median lethal dose of tacrine following a single oral dose in rats is 40 mg/kg, or approximately 12 times the maximum recommended human dose of 160 mg/day.[13]

Yao Chen et al (2017) studied the synthesis and bioevaluation of new tacrine-cinnamic acid hybrids as Cholinesterase inhibitors against Alzheimers disease.

Small molecule cholinesterase inhibitor provides an effective therapeutic activity to treat AD. New discovery of ChEI with multi target effect with structural activity relationship was seen in tacrine-cinnamic acid hybrids. It has good safety in hepatotoxicity evaluation. Cinnamic acid is a naturally oriented compound with diverse biological activity and several derivatives of cinnamic acid such as ferulic acid, caffeic acid are reported to benefit treatment of AD.[14]

Rangbiao Pi et al (2012) synthesised Tacrine -6-ferulic acid, a novel multifunctional dimer inhibits Amyloid beta mediated Alzheimers disease.

Tacrine -6 ferulic acid which is a dimer that prevent amyloid beta peptide induced Alzheimers disease and it inhibit auto and acetyl cholinesterase induced aggregation of amyloid beta and block cell death induced in PC12 cells.[15]

Barbora Svobodova et al (2016) studied the structure – activity relationship in Tacrine-Squaramide derivatives as potent Cholinesterase inhibitor.

The portfolio of currently approved drugs for AD includes acetyl cholinesterase inhibitors and N-methyl –D-aspartate receptor antagonist. Squaric acid is a versatile structure capable to be easily transformed into amide bearing compounds that having both hydrogen donating and accepting feature to create multiple interactions with complementary sites. Squaramide motif combined with tacrine based derivatives.[16]

Maria Isabel Fernadez Bachiller et al (2014) introduced Tacrine –Melatonin hybrids as multifunctional agent for Alzheimer's disease ,with antioxidant, cholinergic and neuro protective properties.[17]

Tacrine–melatonin hybrids were designed and synthesized as new multifunctional drug candidates for Alzheimer's disease. These compounds may simultaneously palliate intellectual deficits and protect the brain against both b-amyloid (Ab) peptide and oxidative stress. They show improved cholinergic and antioxidant properties, and are more potent and selective inhibitors of human acetylcholinesterase (hAChE) than tacrine. They also capture free radicals better than melatonin. Molecular modeling studies show that these hybrids target both the catalytic active site (CAS) and the peripheral anionic site (PAS) of AChE. At sub-micromolar concentrations they efficiently displace the binding of propidium iodide from the PAS and could thus inhibit Ab peptide aggregation promoted by AChE. Moreover, they also inhibit Ab self-aggregation and display neuroprotective properties in a human neuroblastoma line against cell death induced by various toxic insults, such as Ab25–35, H2O2, and rotenone. Finally, they exhibit low toxicity and may be able to penetrate the central nervous system according to an in vitro parallel artificial membrane permeability assay for the blood–brain barrier (PAMPA-BBB)[18]

Maria Isbel Fernandaz et al (2013) synthesized Tacrine-8-Hydroxyquinoline as multifunctional agent to treat Alzheimer's disease with Neuroprotective, cholinergic, antioxidant and copper complexing properties. Tacrine and PBT2 (an 8-hydroxyquinoline derivative) are well-known drugs that inhibit cholinesterases and decrease β-amyloid (Aβ) levels by complexation of redox-active metals, respectively. In this work, novel tacrine-8-hydroxyquinoline hybrids have been designed, synthesized, and evaluated as potential multifunctional drugs for the treatment of Alzheimer's disease. At nano- and subnanomolar concentrations they inhibit human acetyl- and butyrylcholinesterase (AChE and BuChE), being more potent than tacrine. They also displace propidium iodide from the peripheral anionic site of AChE and thus could be able to inhibit Aβ aggregation promoted by AChE. They show better antioxidant properties than Trolox, the aromatic portion of vitamin E responsible for radical capture, and display neuroprotective properties against mitochondrial free radicals. In addition, they selectively complex Cu(II), show low cell toxicity, and could be able to penetrate the CNS, according to an in vitro blood-brain barrier model.[19]

Maria Isabel Fernandaz-Bachiller et al (2012) synthesized new Tacrine-4-Oxo-4H-Chromene hybrids as multifunctional agent for treat Alzheimer's disease with Cholinergic antioxidant and Beta amyloid reducing properties.

By using fragments endowed with interesting and complementary properties for the treatment of Alzheimer's disease (AD), a new family of tacrine–4-oxo-4H-chromene hybrids has been designed, synthesized, and evaluated biologically. The tacrine fragment was selected for its inhibition of cholinesterases, and the flavonoid scaffold derived from 4-oxo4H -chromene was chosen for its radical capture and β-secretase 1 (BACE-1) inhibitory activities. At nano- and picomolar concentrations, the new tacrine–4-oxo-4H-chromene hybrids inhibit human acetyl- and butyrylcholinesterase (h-AChE and hBuChE), being more potent than the parent inhibitor, tacrine. They are also potent inhibitors of human BACE-1, better than the parent flavonoid, apigenin. They show interesting antioxidant properties and could be able to penetrate into the CNS according to the in vitro PAMPA-BBB assay. Among the hybrids investigated, 6-hydroxy-4-oxo- N-{10-[(1,2,3,4-tetrahydroacridin-9-yl)amino]decyl}-4 H-chromene-2-carboxamide (19) shows potent combined inhibition of human BACE-1 and ChEs, as well as good antioxidant and CNS-permeable properties.[20]

Masood Fereidoonnezhad et al (2017) conducted molecular docking and PLIF studies of Novel Tacrine-Naphtoquine hybrids based on multi-target directed ligand approach for Alzheimer's disease.

Alzheimer's disease (AD), the most typical type of dementia and memory loss, is a complicated and progressive neurodegenerative disorder. Due to the multi-factorial etiology of AD, the multi-target-directed ligand (MTDL) approach can be a potential method in seeking new drug candidates for this disease. : In this study, over 200 tacrine-naphtoquinone hybrids have been designed and their drug-likeness, molecular docking, and descriptor analysis were conducted to find out a drug candidate with less toxicity and better binding affinity than tacrine. The Docking analysis was conducted using human acetylcholineesterase (1ACJ), human butyrylcholineesterase (4BDS), and β-secretase (BACE1) (1w51) enzymes.[21]

Gaia Fancellu et al (2019) covered a research on Novel Tacrine- Benzofuran hybrids as potential multi-target drug for Alzheimer's disease. Tacrine (TAC), by its coupling to benzofuran (BF) derivatives. The BF framework aims to endow the conjugate molecules with ability for inhibition of AChE (bimodal way) and of amyloid-beta peptide aggregation, besides providing metal (Fe, Cu) chelating ability and concomitant extra anti-oxidant activity, for the hybrids with hydroxyl substitution. The new TAC-BF conjugates showed very good activity for AChE inhibition (sub-micromolar range) and good capacity for the inhibition of self- and Cu-mediated Ab aggregation, with dependence on the linker size and substituent groups of each main moiety. Neuroprotective effects were also found for the compounds through viability assays of neuroblastoma cells, after Ab1-42 induced toxicity. Structure-activity relationship analysis provides insights on the best structural parameters, to take in consideration for future studies in view of potential applications in AD therapy.[22]

Jin Shuai Lan et al (2014) designed synthesized and evaluated novel Tacrine (Beta Carbine) hybrids as multifunctional agents for the treatment of Alzheimer's disease. A series of tacrine-(b-carboline) hybrids were designed, synthesized and evaluated as multifunctional cholinesterase inhibitors against Alzheimer's disease (AD). In vitro studies showed that most of them exhibited significant potency to inhibit acetylcholinesterase (eeAChE and hAChE), butyrylcholinesterase (BuChE) and self-induced b-amyloid (Ab) aggregation, Cu2+-induced Ab aggregation, and to chelate metal ions. Especially, the compound presented the greatest ability to inhibit cholinesterase , good inhibition of Ab aggregation and good antioxidant activity (1.57 trolox equivalents). Kinetic and molecular modeling studies indicated that it was a mixed-type inhibitor, binding simultaneously to the catalytic anionic site (CAS) and the peripheral anionic site (PAS) of AChE. In addition, the compound could chelate metal ions, reduce PC12 cells death induced by oxidative stress and penetrate the blood–brain barrier (BBB). These results suggested that might be an excellent multifunctional agent for AD treatment.[23]

Supatra Thiratmatrakul et al (2014) conducted synthesis, biological evaluation and molecular modeling study of novel Tacrine-Carbazole hybrids as potential multifunctional agents for the treatment of Alzheimer's disease. New tacrine-carbazole hybrids were developed as potential multifunctional anti-Alzheimer agents for their cholinesterase inhibitory and radical scavenging activities. The developed compounds showed high inhibitory activity on acetylcholinesterase (AChE) with IC50 values ranging from 0.48 to 1.03 mM and exhibited good inhibition selectivity against AChE over butyrylcholinesterase (BuChE). Molecular modeling studies revealed that these tacrineecarbazole hybrids interacted simultaneously with the catalytic active site (CAS) and the peripheral anionic site (PAS) of AChE. The derivatives containing methoxy group showed potent ABTS radical scavenging activity. Overall, tacrine carbazole derivatives can be considered as a candidate with potential impact for further pharmacological development in Alzheimer's therapy.[24]

Fei Mao et al (2012) worked on the compound O-Hydroxyl-or-O-amino benzylamine-Tacrine hybrids; Multifunctional bio metal chelators, antioxidants and inhibitors of cholinesterase activity and beta amyloid aggregation. In an effort to identify novel multifunctional drug candidates for the treatment of Alzheimer's disease (AD), a series of hybrid molecules were synthesised by reacting N-(aminoalkyl)tacrine with salicylic aldehyde or derivatives of 2-aminobenzaldehyde. These compounds were then evaluated as multifunctional anti-Alzheimer's disease agents. All of the hybrids are potential biometal chelators, and in addition, most of them were better antioxidants and inhibitors of cholinesterases and amyloid-b (Ab) aggregation than the lead compound tacrine.[25]

Yao Chen et al (2013) conducted a study on Tacrine-Flurbiprofen hybrids as multifunctional Drug candidate for Alzheimer's disease. Tacrine–flurbiprofen hybrid compounds were synthesized as multi-target-directed compounds for the treatment of Alzheimer's disease. Compared to tacrine, these compounds showed better acetylcholinesterase (AChE) inhibitory activity and better or the same butyrylcholinesterase (BuChE) inhibitory activity. Notably, it showed a mixed-type inhibitory action for AChE, indicating a "dual-binding site action" of both toward the catalytic active site (CAS) and the peripheral anionic site (PAS), whereas for BuChE, a competitive inhibitory action was observed. Furthermore, a cell-based assay on amyloid-b inhibition demonstrated that the selected target compound 3d effectively inhibits the formation of amyloid-b in vitro.[26]

Huang Tang et al (2011) conducted a study on Hybrids of Oxoisoaporphine-Tacrine cogeners; Novel acetylcholine sterase and acetylcholinesterase Beta amyloid aggregation inhibitors. A series of dual binding site acetylcholinesterase (AChE) inhibitors have been designed, synthesized, and tested for their ability to inhibit AChE, butyrylcholinesterase (BChE), AChE-induced and self-induced bamyloid (Ab)

aggregation. The new hybrids consist of a unit of 1-azabenzanthrone and a tacrine or its congener, connected through an oligomethylene linker containing an amine group at variable position. The hybrid tetrahydroacridine moiety, exhibits a significant in vitro inhibitory activity toward the AChE-induced and self-induced Ab aggregation, which makes them promising anti-Alzheimer drug candidates.[27]

Pelayo camps et al (2009) carried out a work on Pyrano[3,2-c] quinoline-6-Chlorotacrine hybrids as a novel family of acetylcholinesterase and beta amyloid directed anti Alzheimer's disease.

Two isomeric series of dual binding site acetylcholinesterase (AChE) inhibitors have been designed, synthesized, and tested for their ability to inhibit AChE, butyrylcholinesterase, AChE-induced and selfinduced β-amyloid (Aβ) aggregation, and β-secretase (BACE-1) and to cross blood-brain barrier. The new hybrids consist of a unit of 6-chlorotacrine and a multicomponent reaction-derived pyrano[3,2-c]- quinoline scaffold as the active-site and peripheral-site interacting moieties, respectively, connected through an oligomethylene linker containing an amido group at variable position. Indeed, molecular modeling and kinetic studies have confirmed the dual site binding of these compounds. The new hybrids, and particularly 27, retain the potent and selective human AChE inhibitory activity of the parent 6-chlorotacrine while exhibiting a significant in vitro inhibitory activity toward the AChE-induced and self-induced Aβ aggregation and toward BACE-1, as well as ability to enter the central nervous system, which makes them promising anti-Alzheimer lead compounds.[28]

CONCLUSION

One strategy for designing new MTDLs for AD treatment involves incorporating additional pharmacophores in the structure of known anti-AD agents. These additional pharmacophores should be able to hit additional targets relevant to AD. This design strategy should afford new MTDLs with a broader biological profile. Although this approach may appear simple, it requires the most modern investigative techniques for in-depth analysis of the mode of action of the starting lead compound, and the designed derivatives, with the new considered target(s). Furthermore, to define the biological profile of these new MTDLs, new and more accurate biological assays are needed. The additional biological properties demonstrated by tacrine and its derivatives may support this view. In particular, some biological properties of tacrine and its derivatives are related to the modulation of "non classical functions" of AChE, which lie beyond the simple role in terminating synaptic transmission. In other words, the target remains AChE, but other related functions are modulated as well. The design of new hetero/homo-dimers and/or hybrids of tacrine has led to new agents able to hit not only AChE-linked AD biological targets but also a wider number of AD pathological targets. A future perspective in AD treatment may be offered by the design of new MTDLs, starting from a lead compound endowed with the ability to not only inhibit human cholinesterases, but also to interact with the variety of AD targets that have recently been identified.[29]

Source of Support: The author(s) received no financial support for the research, authorship, and/or publication of this article

Conflict of Interest: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

REFERENCES

1. Burns A, Liffe S.Diagnosis and management of Alzheimer's disease:Dialogues in clinical neuroscience. 2009;338:158-163. DOI: 10.31887/DCNS.2000.2.2/aburns; PMID: 22034134
2. Cacabelos R. Pharmacogenomics in Alzheimer's disease: Methods Mol Biol. 2008;448:213-357. DOI:10.1007/978-1-59745-205-2_10.PMID: 18370236.
3. Iqbal K, Grundke-Iqbal I.Alzheimer disease is multifactorial and heterogeneous: Neurobiol. Aging.2000;21:901-902.
4. Hardy J.A hundred years of Alzheimer's disease research: Neuron. 2006;52:s3-13.
5. Terry A V, Buccafusco J J.The cholinergic hypothesis of age and Alzheimer's disease-related cognitive deficits: recent challenges and their implications for novel drug development.J. Pharmacol.sci.2003;306:821-827.
6. Gualtieri F, S Dei, D Manetti, M N Romanelli, S Scapecchi, E Teodori. The medicinal chemistry of Alzheimer's and Alzheimer-like diseases with emphasis on the cholinergic hypothesis. Farmaco. 1995;50:489-503.
7. J Hardy. The amyloid hypothesis for Alzheimer's disease: a critical reappraisal. J. Neurochem. 2009;110:1129-1134.
8. C X Gong, K Iqbal. Hyperphosphorylation of microtubule associated protein tau: a promising therapeutic target for Alzheimer disease. Curr. Med. Chem. 2008;15:2321-2328.
9. K M Webber, A K Raina, M W Marlatt, M.W, L Morelli,G Casadesus, G Perry, M A Smith. The cell cycle in Alzheimer disease: a unique target for neuropharmacology. Mech. Ageing Dev. 2005:126;1019-1025
10. L Tapia-Arancibia, E Aliaga, M Silhol, S Arancibia. New insights into brain BDNF function in normal aging and Alzheimer disease. Brain Res Rev.2008;59(1):201-206. DOI: 10.1016/j.brainresrev.2008.07.007. Epub 2008 Aug 3. PMID:18708092.
11. A Gella, N Durany. Oxidative stress in Alzheimer disease. Cell Adh Migr. 2009;3(1):88-93. DOI: 10.4161/cam.3.1.7402. Epub 2009 Jan 13. PMID:19372765; PMCID: PMC2675154.
12. D A Drachman. Rethinking Alzheimer's disease: the role of age-related changes. Curr Neurol Neurosci Rep. 2007;7(4):265-8. DOI:10.1007/s11910-007-0040-4. PMID:17618530.
13. S He, D L Stankowska, D Z Ellis, R R Krishnamoorthy, T Yorio. Targets of Neuroprotection in Glaucoma. J Ocul Pharmacol Ther. 2018;34(1-2):85-106. DOI: 10.1089/jop.2017.0041. Epub 2017 Aug 18. PMID: 28820649. PMCID: PMC5963639.

14. A J Bruce-Keller,JN Keller. Lessons in the study of Alzheimer's disease: a tribute to Dr. William R. Markesbery. Neuromolecular Med. 2011;13(1):11-14. DOI:10.1007/s12017-010-8127-5. Epub 2010 Jul 17. PMID: 20640533.

15. C G Parsons, A Stöffler, W Danysz. Memantine: a NMDA receptor antagonist that improves memory by restoration of homeostasis in the glutamatergic system. Neuropharmacology. 2007;53(6):699-723. DOI: 10.1016/j.neuropharm.2007.07.013. Epub 2007 Aug 10. PMID: 17904591.

16. D A Butterfield, R William, M D Markesbery. A legacy of excellence in Alzheimer's disease research and a life well-lived. J Alzheimers Dis.2010;20(1):3-4. DOI: 10.3233/JAD-2010-100246. PMID: 20378955.

17. J Avila.Delaying Brain Aging or Decreasing Tau Levels as Strategies to Prevent Alzheimer's Disease. Journal of Alzheimers Dis. 2024;100(1):S265-S270. DOI:10.3233/JAD-240500. PMID: 39058443.

18. H Förstl, A Kurz.Clinical features of Alzheimer's disease. Eur Arch Psychiatry Clin Neuro sci. 1999;249(6):288-90. DOI: 10.1007/s004060050101. PMID: 10653284.

19. M I Fernández-Bachiller, C Perez C, N E Campillo, J A Paez, G C Gonzalez-Munoz, P Usan, E Garcia-Palomero, M G Lopez, M Villarroya, A G Garcia, A Martinez, M I Rodriguez-Franco. Tacrine-melatonin hybrids as multifunctional agents for Alzheimer's disease, with cholinergic, antioxidant, and neuroprotective properties. Chem Med Chem. 2009;4(5):828-41. DOI: 10.1002/cmdc.200800414. PMID: 19308922.

20. S O Bachurin. Medicinal and chemical approaches to focused search of agents for treatment and therapy of Alzheimer disease. Vopr Med Khim.2001;47(2):155-97. Russian. PMID: 11450439.

21. D V Reshetnikov, I D Ivanov, D S Baev. Design, Synthesis and Assay of Novel Methylxanthine-Alkynylmethylamine Derivatives as Acetylcholinesterase Inhibitors. Molecule. 2022;27(24):8787. DOI: 10.3390/molecules27248787. PMID: 36557921.

22. A Cavalli,M L Bolognesi, A Minarini, M Rosini, V Tumiatti, M Recanatini, C Melchiorre. Multi-target-directed ligands to combat neurodegenerative diseases. J Med Chem. 2008:14;51(3):347-72. DOI: 10.1021/jm7009364. PMID: 18181565.

23. J McNulty J, JR Little, J D Brennan, J Bastida. Structure-activity studies on acetylcholinesterase inhibition in the lycorine series of Amaryllidaceae alkaloids. Bio organic & Medicinal Chemistry Letters. 2010;(17):5290-5294. DOI:10.1016/j.bmcl.2010.06.130. PMID: 20655219.

24. A Khalid, Zaheer-ul-Haq, S Anjum S, M R Khan, M I Choudhary. Kinetics and structure-activity relationship studies on pregnane-type steroidal alkaloids that inhibit cholinesterases. Bio org Med Chem. 2004;12(9):1995-2003. DOI: 10.1016/j.bmc.2004.03.002. PMID: 15080903.

25. R B Gibbs, P Aggarwal. Estrogen and basal forebrain cholinergic neurons: implications for brain aging and Alzheimer's disease-related cognitive decline. Horm Behav. 1998;34(2):98-111. DOI: 10.1006/hbeh.1998.1451. PMID: 9799621.

26. R J Obaid, N Naeem,E U Mughal, M M Al-Rooqi, A Sadiq, R S Jassas, Z Moussa, S A Ahmed. Inhibitory potential of nitrogen, oxygen and sulfur containing heterocyclic scaffolds against acetylcholinesterase and butyrylcholinesterase. RSC Adv. 2022;12(31):19764-19855. DOI: 10.1039/d2ra03081k. PMID: 35919585.

27. H Nadri, M Pirali-Hamedani, M Shekarchi, M Abdollahi, V Sheibani, M Amanlou, A Shafiee, A Foroumadi. Design, synthesis and anticholinesterase activity of a novel series of 1-benzyl-4-((6-alkoxy-3-oxobenzofuran-2(3H)-ylidene) methyl) pyridinium derivatives. Bio org Med Chem. 2010;18(17):6360-66. DOI: 10.1016/j.bmc.2010.07.012. PMID: 20673725.

28. P R Carlier, E S Chow, Y Han, J Liu, J Yazal, Y P Pang. Heterodimeric tacrine-based acetylcholinesterase inhibitors: investigating ligand-peripheral site interactions. J Med Chem. 1999;42(20):4225-31. DOI: 10.1021/jm990224w. PMID: 10514292.

29. P R Carlier PR, Y F Han, E S Chow,C P Li, H Wang, T X Lieu, H S Wong,Y P Pang. Evaluation of short-tether bis-THA AChE inhibitors. A further test of the dual binding site hypothesis. Bio org Med Chem.1999;7(2):351-357. DOI: 10.1016/s0968-0896(98)00213-2. PMID: 10218828.