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Review Article

NOVEL HETEROCYCLIC HYBRIDS AS PROMISING SCAFFOLD FOR THE MANAGEMENT OF ALZHEIMER'S DISEASE

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ABSTRACT

A large majority of instances of dementia, which is a chronic neurological disease, are directly associated with Alzheimer's Disease (AD). AD affects cognitive abilities over time and is caused by a variety of mechanisms, but still the cholinergic hypothesis is the most workable approach. This study aims to compile the most recent and interesting scaffolds/scaffold/pharmacophoric combinations to cure AD. In our search for new therapeutic leads for the treatment of AD, some nitrogen and oxygen-containing heterocyclic, including alkaloids, have been highlighted as interesting prospects. The Cholinergic Hypothesis is still the most effective and obvious treatment option for this debilitating and progressive condition and should be used for further study. The outcomes strongly suggest that the hybridization approach is also a successful strategy for identifying novel scaffolds with desirable bioactivities. This article evaluates promising therapeutic compounds and molecules that have recently been introduced as multi-target-directed agents, such as quinoline, quinoxalines, chalcones, coumarins, chromenes, piperazine, carbazoles, tacrine hybrids, donepezil hybrids, rivastigmine hybrids, galantamine hybrids etc. This includes study of workable scaffolds/scaffold/pharmacophoric combinations that may be used as future anti-Alzheimer drugs. We discuss future work that would improve our understanding of this escalating disease.

Keywords: Alzheimer's disease, AD, AChE inhibitor, MTDL, Neuroprotective, Neurodegenerative disorder

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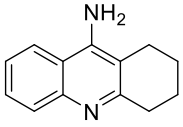
INTRODUCTION

The selections of articles for the current review were searched from specialized databases (Range of years: 1985-2024) such as Elsevier, PubMed, and Cambridge using the keywords Alzheimer's disease, AD, acetylcholinesterase (AChE) inhibitor, Multi-Target Directed Ligand (MTDL), neuroprotective, Neurodegenerative disorder *etc.* Other selections include articles from Springer, information from Internet sources, and online published articles from The Molecules and Bentham Sciences. AD is a progressive, incurable neurological ailment that causes episodic and semantic memory loss as well as cognitive impairment. According to data from the European Prevention of Alzheimer's Dementia, AD already affects more than 40 million individuals globally, and during the next 20 y, its prevalence is predicted to increase. Additionally, AD is presently the fourth most common cause of mortality for persons over 65 y of age worldwide, making it a serious health, social and economic problem for society at large [1]. The main characteristic features of AD are malfunction/abnormality of cholinergic and glutamatergic neurotransmitter systems, built up of aberrant proteins in the brain, for instance, tau protein and beta-amyloid proteins in the form of senile plaques and neuro-fibrillary tangles, and wreckage of some of the mitochondrial functions [2–4]. Significant evidence also points to the possibility that AD causes synaptic disruption early in the course of the disease, altering connectivity within neuronal circuits that are essential for memory and other cognitive functions. The neuronal degeneration found in this puzzling condition has been linked to the accumulation of abnormal proteins both inside and outside of neurons. The most common pathological lesions are plaques and tangles. Extracellular amyloid protein accumulations known as "Senile plaques" are formed of insoluble Amyloid β protein (Aβ). Typically, over the course of their lifespan, neuronal cells release soluble Aβ when the Amyloid Precursor Protein (APP) breaks down. As a result of this breakage, aberrant proteins called Neurofibrillary Tangles (NFT) and senile plaques, which are thick beta sheets, precipitate from Aβ. NFT may result in the death of neurons by obstructing the regular operation of the neuronal axon[5]. Cholinesterase inhibitors, which work to raise the brain's amount of acetylcholine, are only partially effective in reducing behavioural alterations in those who are afflicted. Furthermore, it has been demonstrated that deficiencies in the serotonergic, GABAergic, noradrenergic, dopaminergic, and glutamatergic pathways, among others, are associated with the progression of this neurodegenerative disease [6].

Despite intensive research in this field, a single a fresh drug (for AD) has not entered the market for the last 19 y i.e., since 2003 [7]. Till now, only few drugs are available in the market which are approved and currently used to counteract AD and these drugs also alleviate the symptoms only, giving temporary facilitation to the impaired cognitive and/or behavioural functions. Basically, these drugs include AChE inhibitors *viz* Tacrine (1), Donepezil (2), Galantamine (3) and Rivastigmine (4), as well as *N*-Methyl-D-Aspartate (NMDA) antagonist, Memantine (5)[8]. Tacrine (1) was the first drug introduced in market as anti-Alzheimer agent. The forth with used therapy for AD is symptom based only and basically includes the use of anticholinesterase agents and the NMDA receptor antagonist agents. Several pathogenic pathways to treat AD include targeting AChE, NMDA, Monoamine Oxidase A and B (MAO A AND B), β-site amyloid precursor protein cleaving enzyme (BACE-1) receptors, Ca^{2+}channel blockers, serotonergic antagonists etc.

To solve the problems with the one-target paradigm and address the interconnected aetiology of disease, researchers have developed the MTDLs strategy. The evolving MTDLs strategy is founded on the useful finding that combining various molecules/pharmacophores in a single formulation may improve therapeutic opportunity. Combining two or more well-known chemical scaffolds with the required pharmacological characteristics into a single moiety by pharmacophoric hybridization results in the formation of hybrids [9]. Also, using a single molecule, the recently adopted MTDLs method simultaneously targets several pathogenic pathways of AD. This strategy, which is focused on simultaneous engagement with numerous targets to slow the evolution of the illness, was used due to the complex and multifarious character of AD[10]. Still, the AChE inhibitors are most workable therapeutic option to treat AD and a lot of research is going on in this field.



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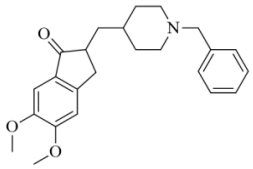

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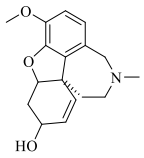

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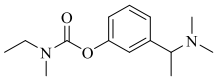

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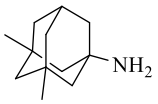

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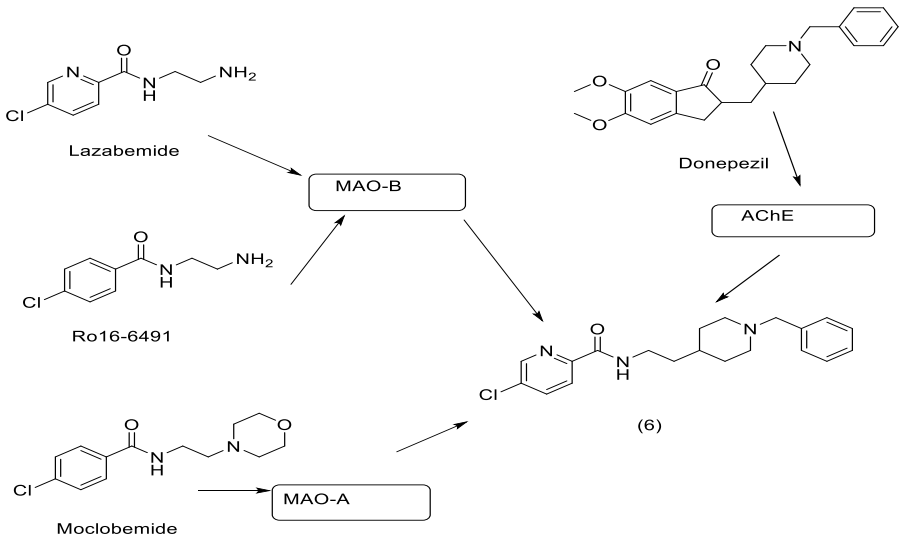
Structural moeities as promising therapeutic scaffolds

The literature survey suggests that the structural moieties (6-81) act as promising therapeutic scaffolds as anti-Alzheimer agents. All the scaffolds are discussed in this review in a systematical manner.

Donepezil hybrids based compounds

Due to its powerful, low toxic, and well-tolerated AChE inhibitory activity, donepezil, the first choice medicine now used to treat AD, is one of the most well-liked pharmacophore inspirations in the design of novel treatment candidates [11]. As a result, other more recent donepezil-other pharmacophore hybrids have been created, produced, and tested as versatile anti-Alzheimer drugs [12].

Fan Li *et al.* synthesized 23 compounds that resemble donepezil that have been discovered to possess potential properties, such as the ability to inhibit both MAOs as well as ChEs [13]. Their plan was to synthesize compounds resembling structure (6) by adding the benzamide component from lazabemide, Ro16-6491, or moclobemide, which have MAOs inhibitory action while retaining the 1-benzylpiperidine fragment from donepezil, which inhibits ChEs [14]. They modified the carbon spacer's length to acquire an alternative conformation that might improve the efficiency of the proposed compounds because the AChE's ability to accommodate the hybrid could be affected by the linker's length [15]. Fan and colleagues synthesized 23 compounds of general formula (7). Out of the synthesized derivatives, compound (8) was found the most potent one.



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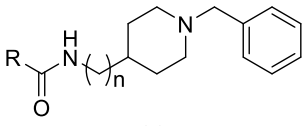

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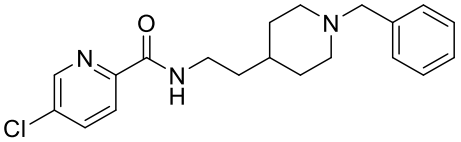

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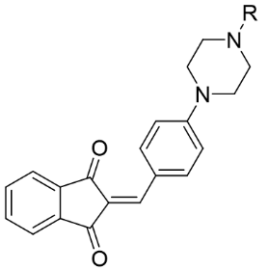
A set of 2-(4-(4-substituted piperazin-1-yl) benzylidene)-1H-indene-1,3(2H)-diones were created by Mezeiova *et al.*, which include an indanone moiety, a curcumin fragment, and a piperazine moiety inside of one framework only. Researchers have found that the indanone moiety is crucial in the inhibition of AChEs. The piperazine moiety is also widely employed to show AChE inhibition, neuroprotection as well as antioxidant properties, and curcumin showed promising Aβ aggregation inhibition activity[16]. Out of the total 11 compounds synthesized (general formula 9), Compounds 10 and 11 demonstrated strong inhibition against AChE and looked to be the most active multifactorial agents among all synthesized compounds (IC_{50}= 0.048 μM: 5; 0.036 μM: 6) [17].



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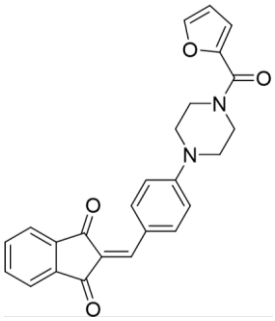

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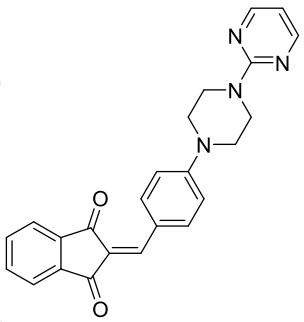

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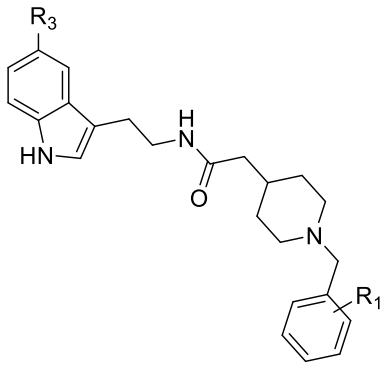
Antioxidants can mitigate AD symptoms and halt the spread of the disease, according to a number of studies. Consequently, pharmaceuticals with a focus on antioxidant activity may be helpful for both the treatment and prevention of AD [17, 18].

Xiao-Bing Wang *et al.* developed a novel class of drugs for the treatment of AD by combining the antioxidant melatonin with the AChE inhibitor donepezil. Wang and colleagues synthesized 21 such hybrid compounds (general structures 12 and 13). Among them compound (14) has shown the maximum inhibition activity (IC50 value of 193 nM for eel AChE). The outcomes strongly suggested that the hybridization approach is a successful strategy for identifying novel scaffolds with desirable bioactivities [19].



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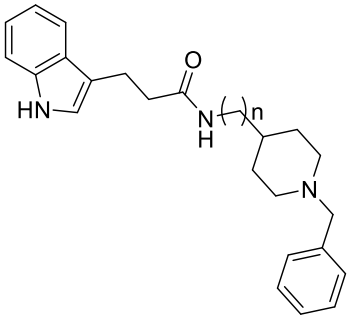

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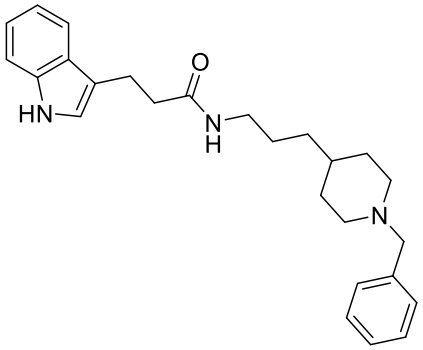

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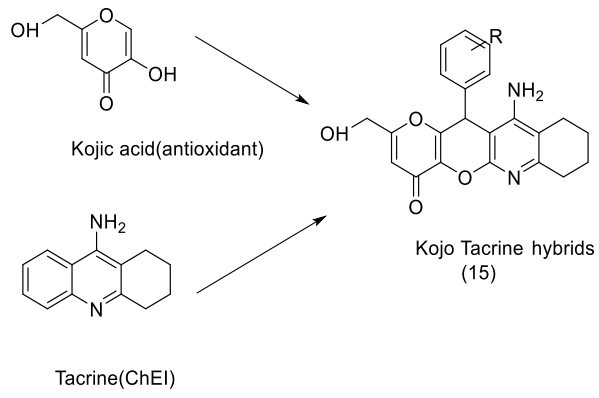
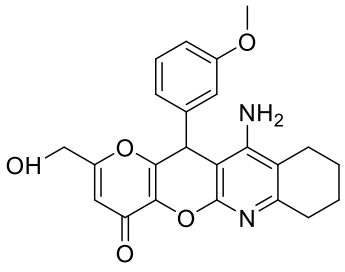
Tacrine based hybrids

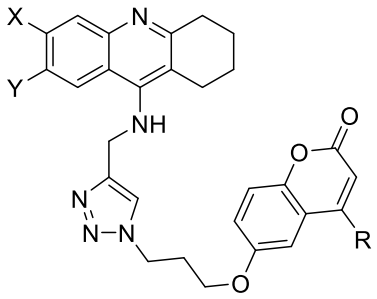
Multitarget small molecules (MTSM) represent the most effective and alluring therapeutic method to develop new therapeutics forthe therapy of AD, in light of the multifunctional nature of disease. Youssef Dgachia *et al.* designed, synthesized and biologically evaluated Kojo Tacrines (KTs) by combining certain pharmacophoric motifs from tacrine and kojic acid. Tacrine was the first AChE Inhibitor (AChEI) for AD therapy to be commercially available and approved, but it was quickly withdrawn due to hepatotoxicity [20, 21]. Despite this, the development of novel non-hepatotoxic analogues for AD has mainly followed the tacrine model. A known antioxidant, KA, is a naturally occurring metabolite of fungi [18]. 12 novel kojotacrines (KTs) having (general structure15) were developed, synthesized, and tested as potential cholinesterase inhibitors (ChEIs) augmented with antioxidant characteristics after taking into account KA's capacity to scavenge reactive oxygen species. The hit agent (16) was found to be less hepatotoxic than tacrine [22].





(16)

Tahmineh Akbarzadeh *et al.* created, synthesized, and evaluated a new class of tacrine-coumarin hybrids (17) connected to 1, 2, 3-triazole as powerful dual binding site cholinesterase inhibitors (ChEIs) for the treatment of AD. The strongest anti-AChE activity was shown by compound 18 (IC50= 0.027 μM). These brand-new tacrine-coumarin hybrids might be useful therapeutically in the treatment of AD in the future [23, 24].



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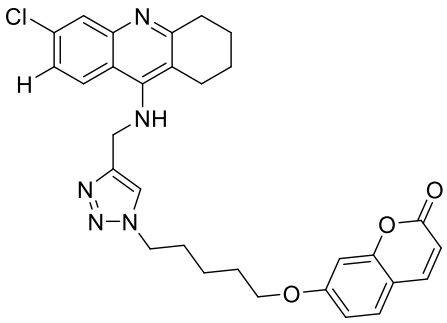
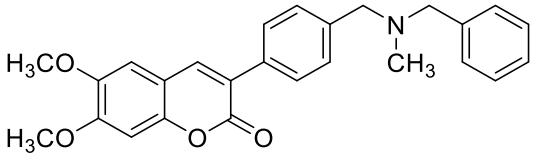


(18)

Coumarin analogs

Natural plant compounds called coumarins have a variety of biological characteristics, including anti-inflammatory, anti-tumor, anti-HIV-1, antiviral and neuroprotective effects *etc*[25]. Additionally, studies have demonstrated that both naturally occurring and chemically synthesized coumarin analogues have strong AChE inhibitory action[26]. The synthesis of novel compounds showing enhanced AChE inhibition effect and other therapeutic activities, such as inhibition of beta secretase (BACE) associated to decreased Aβ deposition and inhibition of MAO, have been made possible by identification of important structural characteristics in the coumarin motif[27]. Additionally, coumarin derivatives shield neurons from oxidative stress and free radicals driven on by Aβ aggregation [28].

In an attempt to develop powerful AChE inhibitors with additional pharmacological properties that are also thought to be crucial for the successful treatment of AD, Piazzi *et al.* synthesized a unique series of coumarin derivatives AP2238 (19)and enasaculine (20) [29].



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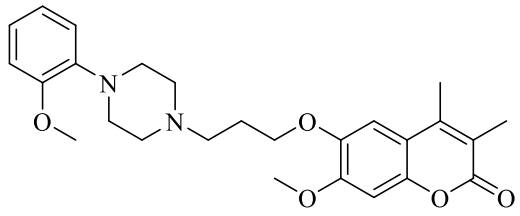

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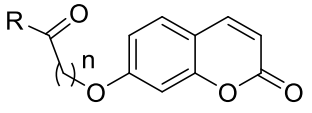
Abbas Shaifee *et al.* synthesized a series of 7-hydroxycoumarins of general formula (21) as potent anti-cholinesterase agents. The Compound **(**22**)** was found to be the most potential agent against AD [30].



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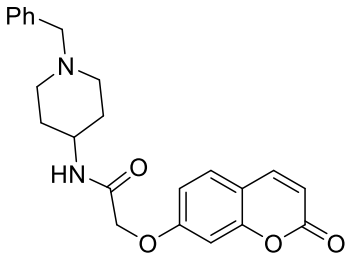

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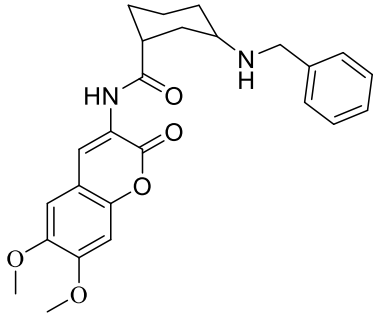
A series of 3-substituted coumarin, most of which were embellished with methoxy groups at positions 6 and 7, were designed, created, and tested as cholinesterase inhibitors by M. Catto *et al.* AChE inhibitory action was somewhat high in 6,7-dimethoxycoumarin derivatives with a benzyl amino group attached to position 3 by appropriate linkers. The spacer's length, shape, and methoxy substituents on the coumarin scaffold all had a significant impact on the inhibitory activity. The compound (23) was found to be the most active molecule (IC50 7.6 nM)[31].



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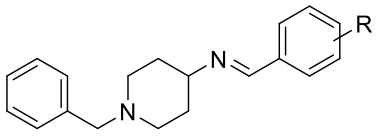
Piperidine analogs

The most effective AChE inhibitor, donepezil, has an N-benzylpiperidine nucleus, which acts as a good AChE inhibitor. The research also argues in favour of altering another terminal component (the indanone nucleus), which would increase BACE-1's inhibitory capability[32]. Researchers suggest that ligands with an N-benzylpiperidine nucleus may have the ability to inhibit AChE and BACE-1 in a variety of ways based on the several findings. Sushant Kumar Shrivastava *et al.* developed and created a pool of N-benzylpiperidine analogs (24, 25) as multifunctional inhibitors of both AChE as well asβ-secretase-1 (BACE-1) with good to exceptional inhibitory activity. Additionally, the two most promising medicines, 26, 27, 28 and 29 improved cognitive impairment in AD rat models [33].



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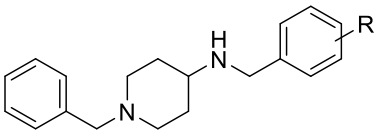

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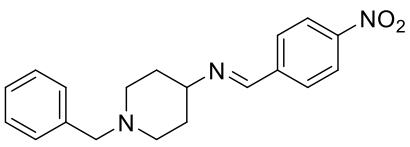

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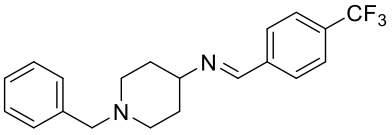

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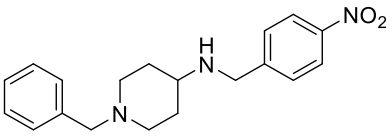

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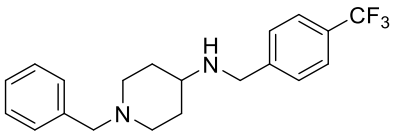

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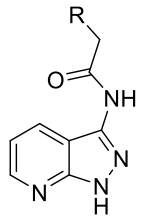
The pyridine moiety is more frequently found in numerous natural goods and pharmaceutically active substances than other heterocyclic compounds [34]. Additionally, efforts have been made to create pyridine scaffolds that can be used to treat AD [35]. The 4-amino-5-carboxylates of pyrazolo pyridines (Etazolate) is an anxiolytic drug that has also been known for its neuroprotective nature. A group of drugs from this scaffold; Tracazolate, Etazolate, LASSBio-872, LASSBio-873, LASSBio-981, and LASSBio-982 have been used to treat anxiety disorder related with GABA induced neuro-inhibition [36]. T. Umar *et al.* developed a series of potent neuroprotective agents against AD derived from pyrazolopyridine and evaluated their biological activities. 2-(piperazin-1-yl)-N-pyrazolo pyridine acetamides (30) are referred to as a new category of powerful AChEI as well as inhibitors of Aβ-aggregation. All compounds were evaluated for their acetylcholinesterase inhibitory activity. Out of 9 synthesized derivatives, compound (31) showed maximum activity. The derivative with the highest anti-AChE activity was the strongest one. (IC50 = 4.8 nM) [37].



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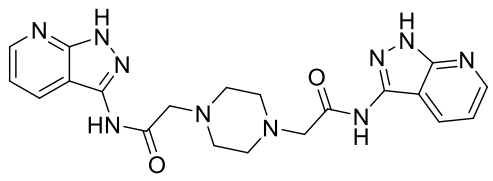

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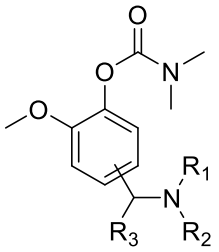
Rivastigmine hybrids

While searching for novel anti –Alzheimer agents, Rong Sheng *et al.* studied newer MTDLs with the natural neuroprotectant curcumin and the AChE/Butyryl Cholinesterase (BuChE) inhibitor rivastigmine [38]. The FDA has recognized rivastigmine as the only carbamate AChEI [39]. A popular natural compound called curcumin has a number of biological activities along with neuroprotective qualities [40]. Rong Sheng *et al.* developed, produced, and assessed a number of newer carbamate compounds (32) which may act as better agents in management of multifactorial AD. The majority of them demonstrated well to exceptional AChE and BuChE inhibitory actions. With an IC50 value of 0.097l μM, compound (33) showed the strongest AChEI among all the substances [41].



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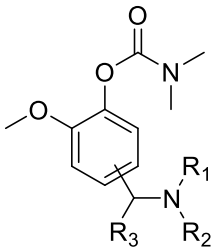
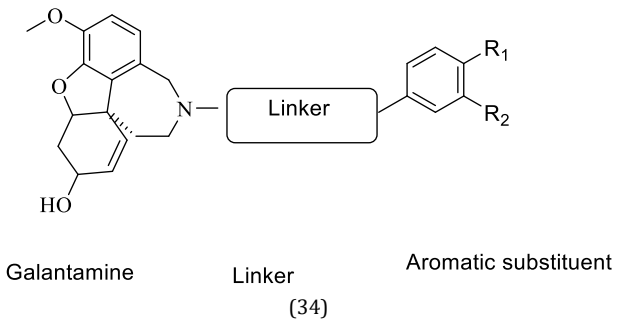


(33)

Galantamine hybrids

An alkaloid called galantamine (GAL) has been found in the bulbs and blooms of Leucojum aestivum L. and Galanthus species. It is one of the approved drugs FDA permitted for the treatment of AD and is an AChE inhibitor. It is also identified as the allosteric nicotinic acetylcholine receptor (nAChR) modulator [42]. Both outcomes enhance the brain's thinking capacity. A naturally occurring polyphenolic substance called curcumin (CU) was discovered in the rhizomes of Curcuma longa L. p. Aβ-oligomers and fibrils are bound by CU, which prevents the production of β-sheets [43]. A series of GAL-CU hybrids (34) with promising anti-amyloid aggregation activity were developed by Georgi Stavrakov *et al.* as dual-site binding AChE inhibitors. The neurotox.icity and anti-AChE activity of the best 10 compounds was produced and assessed *in vitro*. Five of them exhibited activities between 41 and 186 times higher than GAL and were found less harmful than GAL and CU [44].

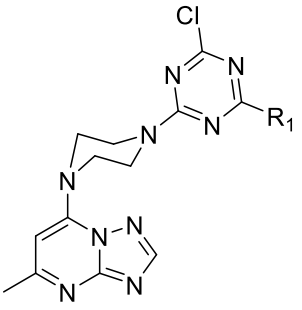


(34)

1, 3, 5Triazines analogues

The manufacturing of antiviral antifungal, antimalarial, antibacterial, and anticancer medicines has a long history with the 1, 3, 5-triazine scaffold. Triazine has a generally planar structure; therefore, it was predicted that it would favour the Aβ disaggregation. Triazolopyrimidine nucleus was anticipated to interact with key residues on AChE's PAS, perhaps improving the capacity of

medicinal molecules to inhibit the enzyme. Triazole scaffold has, in fact, been successfully used in the creation of multifunctional AChEIs [45]. A pool of triazine-triazolopyrimidine hybrids (35) were developed and synthesized in an effort to discover powerful MTDL for the treatment of AD in light of all these findings by Ehtesham Jameela, Poonam Meena, and colleagues [46]. Out of these compounds, (36 and 37) showed good AChE inhibitory activity (IC50 values 0.065 and 0.092μM respectively).



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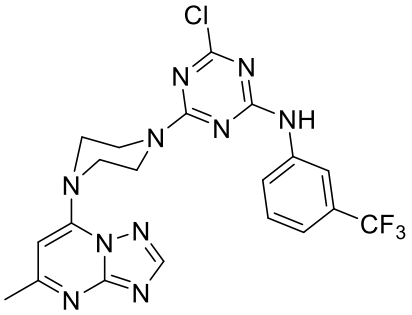

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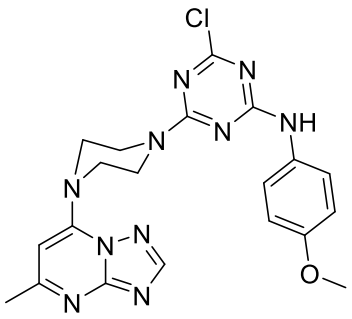
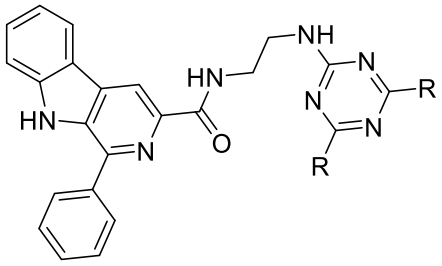


(37)

Potential cholinesterase inhibitors were described across numerous types of heterocyclic compounds, including those with the 1, 3, 5-triazine and β-carboline nuclei. β-Carboline derivatives demonstrated activity in neurological conditions linked to AD, serving as strong AChE and BuChE inhibitors [47]. A series of compounds (38) were created by Helena Sarragiotto and colleagues, who then tested their *in vitro* activity against AChE. The compound with the highest potency (39) showed the (IC50 values 7.6 μM) [48].



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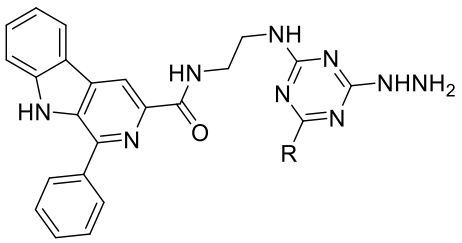
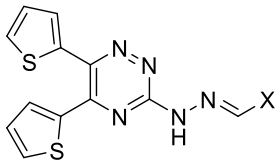


(39)

Numerous tiny hydrazinyl—triazine compoundswere identified as BACE-1 inhibitors in the researcher's investigation. Najmeh Edraki created a triazine-thiophen skeleton with imide linkers and a suitable aryl pendant as the core structure. The biological activities of fifteen compounds (40), including β-Site Amyloid Precursor Protein Cleaving Enzyme 1 (BACE1) inhibition, antioxidant activity, and metal chelating potential, were studied. Using a FRET-based assay, the biological screening findings showed that the majority of our compounds exhibited strong inhibitory effects against (BACE1). Significant BACE-1 inhibitor characteristics were discovered for compounds (41) and (42), with IC50 values of 0.91μM and 0.69μ M, respectively [49].



X=aryl group

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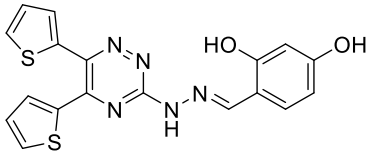

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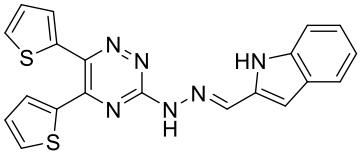
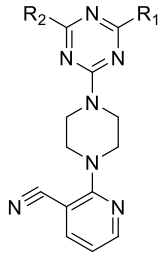


(42)

Triazine scaffold has long been used by medicinal chemists in the creation of pharmaceuticals [50, 51]. Eight novel cyanopyridine-triazine hybrids (43) were created by Manisha Tiwari *et al.* as effective multifunctional AD therapy agents. All of the synthetic compounds were tested for their ability to inhibit cholinesterases and their ability to prevent Aβ from aggregating. Compounds (44 and 45) demonstrated strong inhibitory action against AChE among the produced derivatives, with IC50 values of 0.059 and 0.080 μM, respectively [52].



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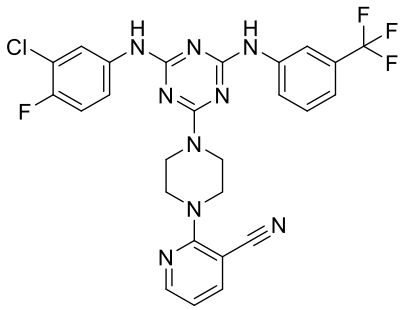

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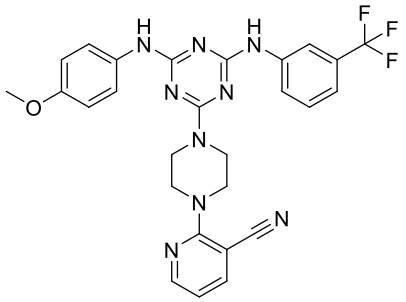
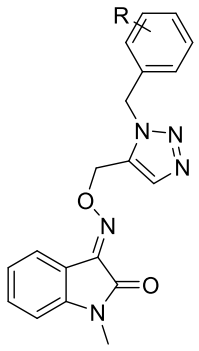


(45)

Triazole analogues

It has recently been demonstrated that 1, 2, 3-triazole isoindoline has potent neuroprotective properties and effective BACE-1 inhibition. The heterocyclic molecule benzoyl 1,2,3-triazole and its derivatives, which have a strong dipole moment and the ability to make hydrogen bond interactions with the active site, are significant [53]. As cholinesterase inhibitors, this primary scaffold is frequently used as a therapeutic possibility for the treatment of AD [54]. Seyedeh Sara Mirfazli *et al.* successfully synthesized and tested a pool of 1, 2, 3-triazole-methylindolinone derivatives (46) for their AChEI efficiency. Compound (47)was shown to have an anti-BuChE IC 50 value of 4.78 μM, making it more powerful than the benchmark medication donepezil (5.19 μM)[55].



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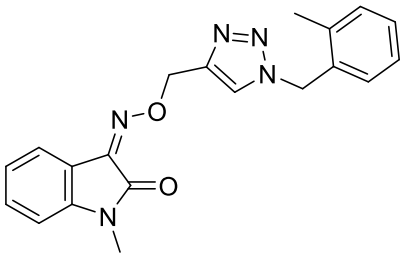
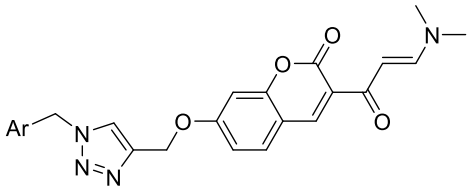


(47)

Recent studies have demonstrated that the triazole moiety exhibits ChE inhibitory action in the micromolar concentration range. Researchers originally discovered an amino methylene triazole fragment as the primary substructure to inhibit BACE-1 using virtual screening of a limited targeted chemical library. Imino chromene ring has recently been identified as a strong neuroprotective agent. To assess the potential neuroprotective activity, the iminochromene group may be bioisosterically substituted with chromenone moiety [56].

On the basis of the multi-target-directed ligands strategy, newer 1, 2, 3-triazolechromenone compounds (48) were produced by Karimi Askarani *et al.* with the goal of discovering novel anti-Alzheimer MTDL agents. Inhibition of AChE and BuChE, aggregation of β-amyloid, and neuroprotective properties were among the *in vitro* biological activities conducted. The findings showed a highly selective BuChE inhibitory action, with compound (49) being the most effective, with an IC50 value of 21.71 Mm [57, 58].



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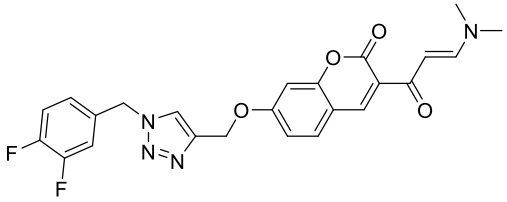
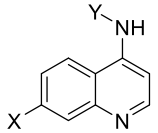


(49)

Quinoline analogues

Numerous investigations have shown that compounds with quinoline structures are powerful inhibitors of both BuChE and AChE, two cholinesterases (BuChE)[59]. These compounds have a tacrine or quinidine moiety as their main structural components [60]. Furthermore, antimalarial medications like chloroquine, hydroxychloroquine, and primaquine have been shown to have anticholinesterase action [61, 62]. These compounds are 4-aminoquinoline derivatives, which have recently been identified as a viable initial structural scaffold for the subsequent development of novel multifunctional AChE inhibitors due to their unwavering structure and strong AChE inhibitory efficacy [63, 64]. The 4-aminoquinoline core's potent AChE inhibition was demonstrated by a number of amino quinolines in which the amino group was replaced at various positions along the quinoline ring.

Anita Bosak *et al.* synthesized some 4-aminoquinoline derivatives (50) with different groups attached to the C (4) and C (7) position. These compounds were evaluated for their activity as human AChE as well as BuChE inhibitors. Out of the 8 Compounds synthesized, two compounds 51 and 52 were found possessing the ability for further modification and the modified compounds may act as workable anti Alzheimer's agents [65].



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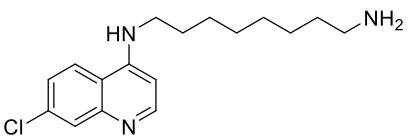

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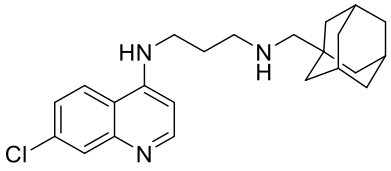
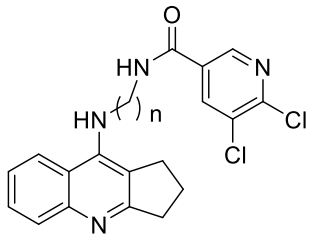


(52)

Kamila Czarnecka *et al.* synthesized some new cyclopentaquinoline hybrids (53) of general formula (4) having effectiveness against AD. The study consists of the synthesis of few quinoline derivatives with substituted nicotinic acid and appropriate linkers. Compound (54) was found to be the most potent acetylcholinesterase inhibitor [66].



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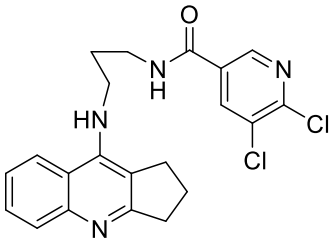
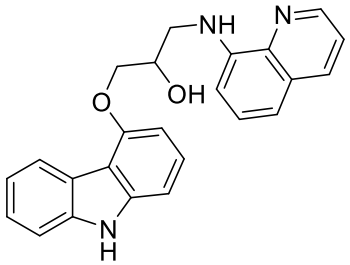


(54)

The compound PZ001(1),carbazole–amino quinoline dimer, was synthesized by Xiao Zhang *et al.* Biological interpretation of the compound indicated that (55) was a multifunctional agent possessing neuro-protection activity [67].

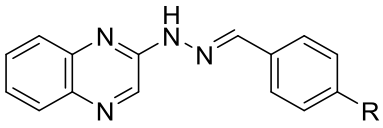


(55)

Quinoxaline analogues

A significant building theme for the creation of novel medications has evolved from quinoxalines [68]. Quinoxaline derivatives in particular exhibit a wide range of pharmacological effects, including MAO and AChE inhibitory characteristics [69]. However, hydrazone derivatives have also been shown to be a viable scaffold for the development of anti-MAO and anti-AChE medicines [70]. Studies have revealed that coupling the hydrazone moiety with quinoxaline ring may create MTDL agents for the possible treatment of AD in an effort to produce novel MAO and AChE inhibitory drugs [71].

Ulviye Acarevik and colleagues created different substituted quinoxaline-hydrazone compounds (56) and looked into their *in vitro* activities, including their ability to inhibit MAOA/B and AChE/BuChE. In accordance with the findings of the experiments, substance (57) had good inhibitory efficacy on AChE (IC50 = 0.028μ M) and monoamine oxidase B (IC50 = 0.046 μM)[72].



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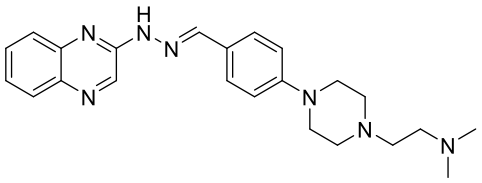
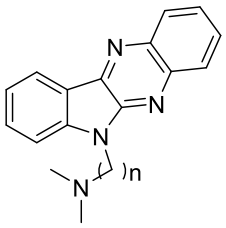


(57)

A. M. Kanhed *et al.* developed a pool of indoloquinoxaline derivatives (58) in the quest to produce multitarget-directed ligands for AD. All of the synthesized derivatives exhibited moderate to good cholinesterase inhibitory activity, according to *in vitro* studies. The most effective and selective BuChE inhibitor was found to be the quinoxaline derivative(59) (IC50 14 0.96 μM) [73].



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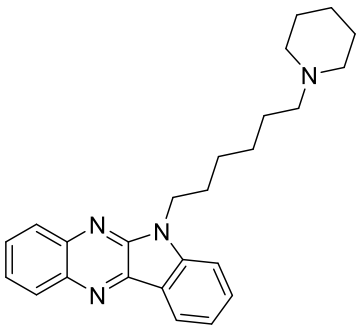
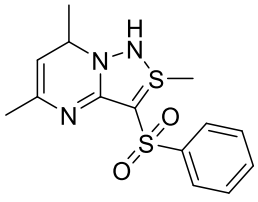


(59)

Phenyl sulfonylpyrazolo pyrimidine

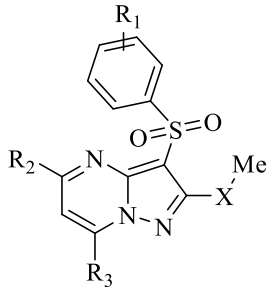
Recently, 5HT6R has been regarded as one of the key biological targets for the treatment of AD[74]. It is reasonable to consider AVN-211(60) to be a unique medication candidate with exceptional therapeutic potency and selectivity against AD. A highly selective 5-HT6 R antagonist is AVN-211, also known as 5,7-dimethyl-2-(methylthio)-3-(phenylsulfonyl)pyrazolo[1,5-a]pyrimidine [75]. In the year 2011, it successfully completed phase IIa trials for schizophrenia and in mid-2013, phase IIb trials started. Avineuropharmaceuticals have also shown intention to start clinical trials of AVN-211 for Alzheimer disease in 2015 [76]. The 5-HT_6 receptor antagonists, SAM-531, Lu-AE-58054 and SB-742457 are currently in phase II clinical trials for multiple mental disorders [77].



(60)

Serotonin 5-HT6 receptor (5-HT6R) has been suggested as a possible pharmacological target for improving cognition in AD in the hunt for novel treatment approaches. The hunt for novel, more powerful, and 5HT6R ligands was sparked by these findings, which led numerous groups to design and test a significant number of variants [76, 78, 79].

Alexandre V. Ivachtchenko and Elena S. Golovina synthesized a series of new 3-sulfonyl-pyrazolo pyrimidine compounds having general structure (61), and studied the structural–activity relationship of thus synthesized compounds. In his research, Researchers looked for highly powerful 5-HT6R antagonists and found that 62,63 and 64are the most potent 5-HT6 receptor antagonists [80].



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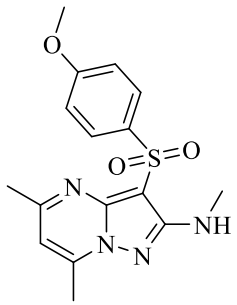

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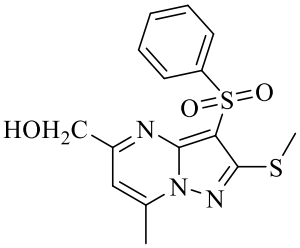

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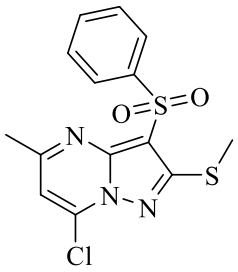
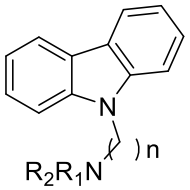


(64)

Carbazole analogs

The naturally occurring alkaloid carbazole is a significant moiety and has demonstrated a wide range of biological functions [81], including anti-Alzheimer activity [82]. As powerful multifunctional drugs, a number of carbazole compounds have been created, and they have proven to have excellent multifunctional activity against AD models [83, 84]. Some carbazoles have also been mentioned as having neuroprotective properties [85, 86]. Tacrine-carbazole hybrids have been described by Thiratmatrakul *et al.* as powerful multifunctional agents with effective antioxidant, anti-Aβ disaggregation, and neuroprotective effects [87]. By fusing into a single molecule two biologically active pharmacophores that operate as cognitive enhancers or modulators of critical stages of neurodegenerative disease pathogenesis, G. F. Makhaeva *et al.* synthesized novel multitarget drugs by linking carbazole with amino adamantane via different spacers [6]. The fundamental pharmacophore pieces were derivatives of carbazoles with γ-carbolines, tetracarbazoles, phenothiazines, and amino adamantanes [88].

Mehdi Khoobi and colleagues created a number of compounds (65), which were then tested as cholinesterase inhibitors. These compounds contained the carbazole backbone connected to benzyl piperazine, benzyl piperidine, pyridine, quinoline, or isoquinoline moiety through an aliphatic linker. The most effective molecule against AChE was compound (66), which also demonstrated good inhibitory effectiveness for self-and AChE-induced Aβ aggregation [89].



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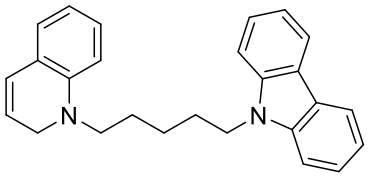
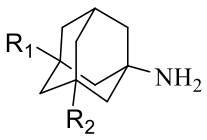
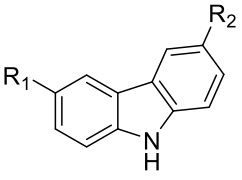


(66)

It is well known that carbazoles and tetrahydro carbazoles exhibit a variety of biological activities. Numerous artificial and naturally occurring physiologically active chemicals share the carbazole skeleton as their primary structural motif. Recent years have seen the discovery of interesting molecules among carbazole derivatives for the design of disease-modifying medicines for the treatment of AD [90]. Sergey O. Bachurin created and studied a new class of substances like amino adamantane (67), carbazole (68), tetrahydro carbazole (69) *etc.* The conjugates of amino adamantane and carbazole derivatives (70) that show promise for the construction of novel multitarget therapeutic medicines for management of neurodegenerative illnesses. First of all, these substances selectively inhibit BuChE and have the ability to prevent nerve cells from dying under conditions of calcium overload. Of all studies, the leading chemical (71) has displayed the most promising results [91].



Amantadine (67)



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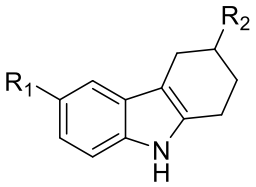

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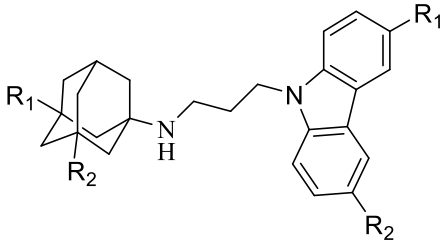

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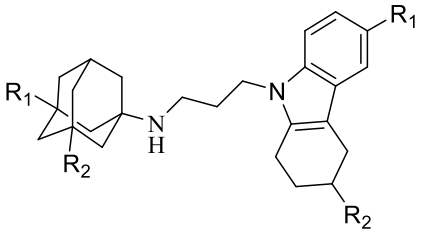
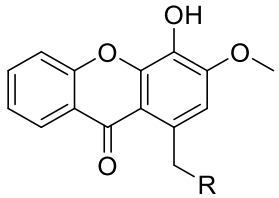


(71)

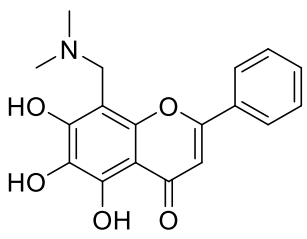
Xanthone analogs

The "privileged structures" that are widely found in nature, xanthones and flavones, exhibit a wide range of biological actions [92]. Numerous studies and investigations have been conducted on natural and synthetic xanthone derivatives that affect the molecular targets of neurodegenerative disorders [93, 94]. These compounds have recently received a lot of interest as possible AD therapy options. AChE, BuChE, MAO, and Aβ peptide aggregation, as well as antioxidant ability, have been demonstrated to be inhibited by certain xanthones. Some xanthones and flavones have been found to act as antioxidants, inhibit AChE and MAO enzymes, and prevent the aggregation of Aβ-peptides [95, 96].

The biological assessment and synthesis of xanthone and flavone derivatives (72) with concurrent antioxidant and AChE inhibitory activity are described by Inês Cruz *et al.* The Mannich base (73) showed the ability to inhibit AChE as well as antioxidant properties, exerting dual action [97].

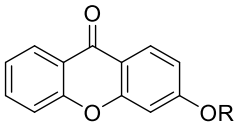


(72)

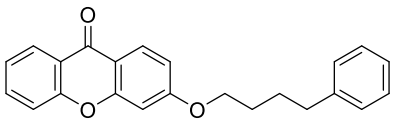


(73)

The type of substituents and their placements on the two phenyl rings that make up the core structure of xanthones, in particular, affect the biological activities of xanthones [98-101]. However, xanthones derived from natural resources are time-consuming to extract and purify and have a restricted range of substituents available on the rings [102]. In order to produce different xanthone derivatives, structural alteration of the xanthone-based skeleton is desirable [103]. Twenty-nine novel xanthone derivatives (74) were synthesized using ether, ester, hydroxyl, alkyl, alkenyl, alkynyl, and five other types of side chains by Z. H. Loh *et al.* The researchers further evaluated the synthesized compounds for their anti-cholinergic activities against both the ChEs. Out of synthesized derivatives, compounds (75 and 76) showed maximum activity [104].



(74)



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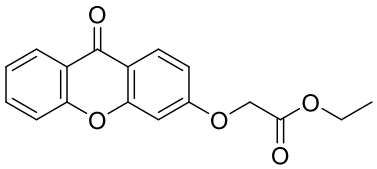
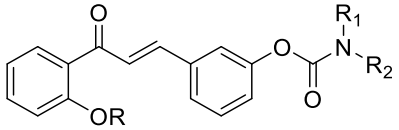


(76)

Chalcone analogs

Small molecule with an unsaturated carbonyl group known as chalcone [(E)-1,3-diphenyl-2-propen-1-one] is a precursor or constituent of numerous naturally occurring flavonoids and isoflavonoids [105, 106]. In medicinal chemistry, it is one of the most privileged structures. Numerous medicinal chemists are studying this scaffold because of its vast spectrum of biological functions and the potential benefits it may have for treating neurodegenerative illnesses like AD [107]. The therapy of AD might benefit from the biological activities of chalcone compounds, which include anti-inflammatory, MAO-B inhibition, radical-scavenging, and neuroprotective effects [108]. Chalcone compounds are important secondary-metabolite precursors of flavonoids and isoflavonoids [109–111]. Using the multitarget-directed ligands approach, a series of chalcone-rivastigmine hybrids or chalcone-O-carbamate derivatives (77) were created with the goal of discovering multifunctional medicines for the treatment of AD. AChE/BuChE inhibition activity was assessed as *in vitro* biological activities. With IC50 values of 3.1 M and 1.2 M, respectively, compounds (78) and (79) demonstrated highly selective BuChE inhibitory action [112].



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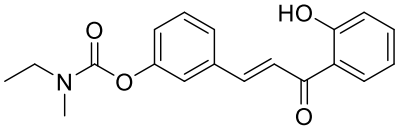

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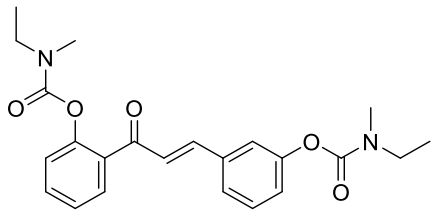
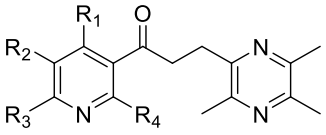
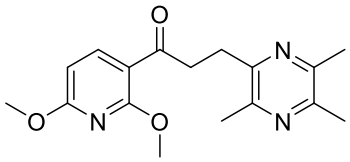


(79)

Syed Nasir Abbas Bukharie and colleagues synthesized a number of novel ligustrazine-based chalcones (80). A novel ligustrazine-based aldehyde was created to introduce tetramethylpyrazine (TMP) into the chemical structure of chalcone. For the incorporation of quinazolin-4-yl and pyrazin-2-yl amino moieties, new ketones were created. For AChE, BuChE, and MAO inhibitory activity, the recently synthesized compounds were tested. Compound (81) demonstrated the greatest activity and efficacy on a number of targets among the synthetic derivatives [113].



(80)



(81)

CONCLUSION

The Cholinergic Hypothesis is still the most effective and obvious treatment option for this debilitating and progressive condition and should be used for further study. AChE and/or dual AChE inhibitors, NMDA inhibitors, and MDTL methods may all be useful in enhancing cognitive and behavioural performance, according to studies. The outcomes strongly suggested that the hybridization approach is also a successful strategy for identifying novel scaffolds with desirable bioactivities. This article evaluates promising therapeutic compounds and molecules that have recently been introduced as multi-target-directed agents, such as quinoline, quinoxalines, chalcones, coumarins, chromenes, piperazine, carbazoles, tacrine hybrids, donepezil hybrids, rivastigmine hybrids, galantamine hybrids etc.

ABBREVIATIONS

Alzheimer's Disease (AD), Acetyl Cholinesterase (AChE), Butyryl Cholinesterase (BuChE), Aβ (Amyloid β), Serotonin 5-HT6 Receptor (5-HT6R), Monoamine Oxidase (MAO), Amyloid Precursor Protein (APP), N-Methyl D-Aspartate (NMDA), Multi Target Directed Ligand (MTDL) β-Site Amyloid Precursor Protein Cleaving Enzyme 1 (BACE1).

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AUTHORS CONTRIBUTIONS

The author has done drafting, designing, writing and all the work related to manuscript.

CONFLICT OF INTERESTS

The author declares no conflict of interest, financial or otherwise.

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