Saudi Pharmaceutical Journal 31 (2023) 998–1018

HOSTED BY

Contents lists available at ScienceDirect

Saudi Pharmaceutical Journal

journal homepage: www.sciencedirect.com

Review

An overview of structure-based activity outcomes of pyran derivatives against Alzheimer's disease

Faisal A. Almalki

Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Umm Al-Qura University, 21955 Makkah, Saudi Arabia

ARTICLE INFO

Article history:
Received 18 February 2023
Accepted 30 April 2023
Available online 8 May 2023

Keywords:
Alzheimer's disease
Pyran
SAR
Flavone
Coumarin
Xanthone

ABSTRACT

Pyran is a heterocyclic group containing oxygen that possesses a variety of pharmacological effects. Pyran is also one of the most prevalent structural subunits in natural products, such as xanthones, coumarins, flavonoids, benzopyrans, etc. Additionally demonstrating the neuroprotective properties of pyrans is the fact that this heterocycle has recently attracted the attention of scientists worldwide. Alzheimer's Disease (AD) treatment and diagnosis are two of the most critical research objectives worldwide. Increased amounts of extracellular senile plaques, intracellular neurofibrillary tangles, and a progressive shutdown of cholinergic basal forebrain neuron transmission are often related with cognitive impairment. This review highlights the various pyran scaffolds of natural and synthetic origin that are effective in the treatment of AD. For better understanding synthetic compounds are categorized as different types of pyran derivatives like chromene, flavone, xanthone, xanthene, etc. The discussion encompasses both the structure–activity correlations of these compounds as well as their activity against AD. Because of the intriguing actions that were uncovered by these pyran-based scaffolds, there is no question that they are at the forefront of the search for potential medication candidates that could treat Alzheimer's disease.

Contents

Abbreviations: μM, Micrometre; AChE, Acetylcholinesterase; AD, Alzheimer's disease; AGEs, Advanced glycation end products; APP, *Amyloid precursor protein*; Aβ, Amyloid β protein; BuChE, Butyrylcholinesterase; CaMKII, Ca^{2+}/calmodulin-dependent protein kinase II; COX-2, Cyclooxygenase-2; *CREB*, *cAMP response element-binding protein*; ERK, Extracellular signal-regulated kinase; FDA, Food and Drug Administration; GFP, Green fluorescent protein; GPx, Glutathione Peroxidase; GTF, Glucose Tolerance Factor; IC50, Half-maximal inhibitory concentration; IL, Interleukin; iNOS, Inducible nitric oxide synthase; LPS, Lipopolysaccharide; MAO, Monoamine oxidase inhibitors; MTDL, Multi-Target-Directed Ligands; NO, Nitric oxide; NRF2, *Nuclear factor erythroid 2-related factor 2*; PAS, Peripheral anionic site; PKA, Protein kinase A; ROS, Reactive oxygen species; SAR, Structure-Activity Relationship; SH-SY5Y, *Neuroblastoma cell line*; SOD, *Superoxide dismutase*; TNF, Tumor necrosis factor.

E-mail address: famalki@uqu.edu.sa
Peer review under responsibility of King Saud University. Production and hosting by Elsevier.

Production and hosting by Elsevier

https://doi.org/10.1016/j.jsps.2023.04.030
1319-0164/

1. Introduction

AD is a slow, age-related neurodegenerative condition that cannot be reversed and is characterised by behavioural abnormalities and cognitive deficits. The progression and development of AD are both influenced by a number of pathogenic pathways, some of which include the cholinergic deficiency, cholinergic deficit, production of plaque, and oxidative stress (Van Cauwenberghe et al., 2015). Approximately a decade passes before the disease has run its course and victims die in a situation of full helplessness. The extended duration and severity of AD impose a tremendous emotional and financial burden on individuals, their families, and society as a whole. There are still no effective treatments for preventing, halting, or reversing AD, but recent research advancements could alter this bleak outlook. AD is characterised by the appearance of extracellular amyloid-beta (Aβ) plaques and neurofibrillary tangles in the intracellular environment, neuronal mortality, and the progressive loss of synapses, which all contribute to cognitive decline. Several hypotheses have been proposed to explain AD. The formation of aberrant neurofibrillary structures may be influenced by abnormal tau phosphorylation. The reticular formation, the nuclei in the brain stem (e.g., the raphe nucleus), the thalamus, the hypothalamus, the locus ceruleus, the amygdala, the substantia nigra, the striatum, and the claustrum are all susceptible to AD. Continuous, low-level activation of N-methyl-D-aspartate (NMDA) receptors results in excitotoxicity. AD progression is associated with premature synaptotoxicity, alterations in neurotransmitter expression, neurophils loss, accumulation of amyloid -protein deposits (amyloid/senile plaques), and neuronal loss and brain atrophy. Recent investigations have investigated the connection between Aβ and NMDA receptors. Aβ -induced spine loss is associated with a decrease in glutamate receptors and is dependent on the calcium-dependent phosphatase calcineurin, which is also associated with chronic depression (Fig. 1).

Only a few drugs, like Galantamine, Rivastigmine, Memantine, and Donepezil, are approved by the FDA to treat AD. According to the reports, the AD death rate has doubled in the past couple of years (Park, 2015; Hassan et al., 2022; Ghai et al., 2020). So, the development of effective treatment is the need of the hour.

Pyran is a six-membered heterocyclic compound consisting of five carbon atoms and one oxygen atom in the ring. The discovery of pyran dates back to the 20th century, when it was first isolated and characterized in 1962 via pyrolysis of 2-acetoxy-3,4-dihydro-2H-pyran (Masamune and Castellucci, 1962). It was found to be very unstable, particularly in the presence of air. 4H-pyran easily decomposed to the corresponding dihydropyran and the pyrylium ion, which is easily hydrolyzed in aqueous medium.

Pyran derivatives have also been found to possess antibacterial, antiviral, and anti-inflammatory activities (Nazari et al. 2017; McCord et al. 1976; Chen et al. 2017). Some pyran derivatives have been used to treat HIV, hepatitis C, and herpes infections (Defant et al. 2015; Konreddy et al. 2014; Karampuri et al. 2014). In addition to their therapeutic applications, pyran derivatives have also been used as agrochemicals, such as insecticides and herbicides (Ali and Venugopalan, 2021; Lei et al. 2019). Finally, the discovery of pyran and its derivatives has had a profound impact on medicine, agriculture, and other disciplines. Pyran derivatives continue to be an important area of research, with scientists exploring their potential for treating a variety of diseases and conditions.

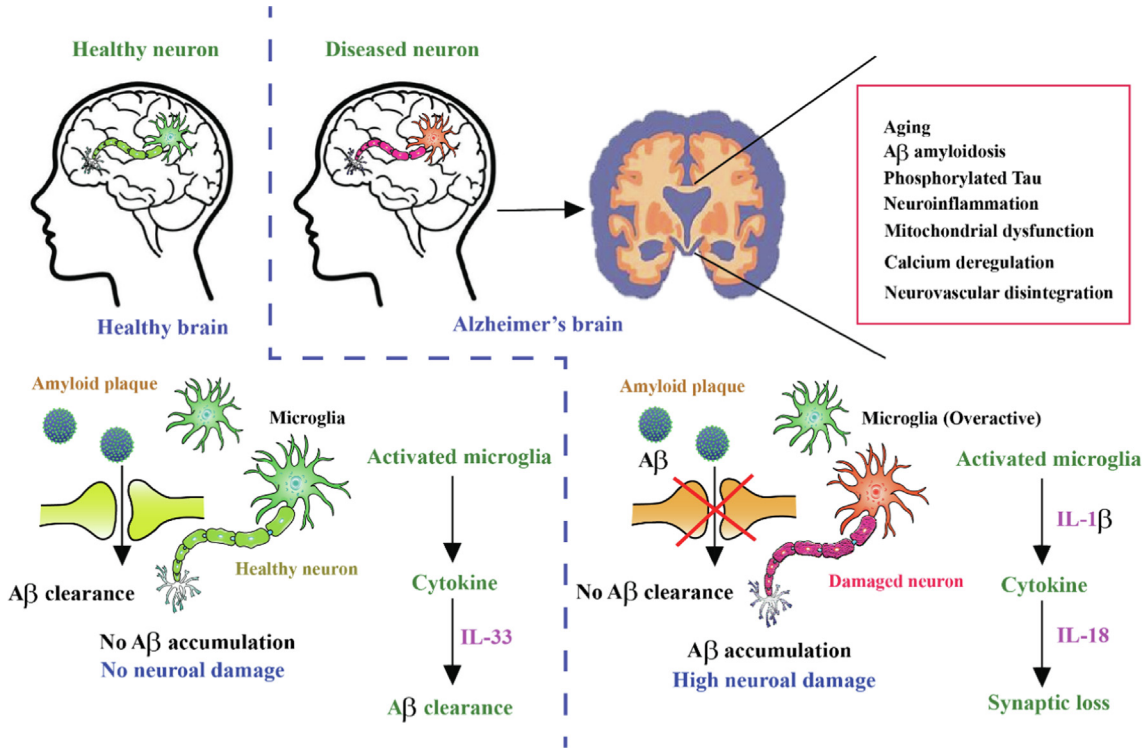


Fig. 1. Mechanism of action of AD.

Pyran and pyran-based heterocycles are continuously being investigated by many researchers to develop new drugs that are effective for the treatment of AD (Kumar et al., 2017; Martins et al., 2015). Pyran scaffolds can be found in a vast array of natural substances, medicines, and bioactive compounds. The various pyran-based heterocycles including Coumarin, Xanthene, Benzopyran, Chromene, Xanthone, 2H-Naptho[1,2-b]pyran, etc are shown in Fig. 2.

Apart from its use in AD and neuroprotective disorders, pyran based drugs are found to have diverse pharmacological activity. The pyran nucleus in Fig. 3, which shows various drugs that are marketed with wide-ranging pharmacological activities, possesses pyran as the key scaffold (Hassan et al., 2016; Johnson and Dietz, 1968; Garkavtsev et al., 2011; Miean and Mohamed, 2001; Zhang et al., 2019; Grover et al., 2021). Alpha-Lapachone has antibacterial potential, Beta-Lapachone has anticancer activity whereas Lanimavir and Zanamivir has antiviral activity.

The search for clinical trials revealed that some new pyran-based drugs are being studied for safety and efficacy, as well as some clinically used drugs that are considered to be repurposed for the treatment of mild to moderate Alzheimer's disease. A list of pyran-based drugs for the treatment of AD in clinical trials is summarized in Table 1 below:

Studies of the structure-based activity relationships (SAR) of pyran and its derivatives may offer a number of advantages. For instance, SAR investigations can be used to pinpoint the pyran derivatives' structural characteristics that are crucial to their biological activity. Designing more potent molecules with increased activity and selectivity is possible using this information. By eliminating the need for extensive experimental testing, SAR analyses can be used to predict the activity of novel pyran derivatives, which can save time and resources. Additionally, pyran-based lead compounds might be improved to increase activity or decrease toxicity with the aid of SAR investigations. Overall, the structure-based activity studies of pyran and its derivatives have the potential to lower the cost of medication research, increase the efficacy and safety of novel molecules, and speed up the drug discovery process.

A survey of the scientific literature reveals that numerous commercially available therapeutic agents contain the pyran unit. Due to their vast array of biological activities, pyran based compounds are an essential structural motif for a large number of natural and

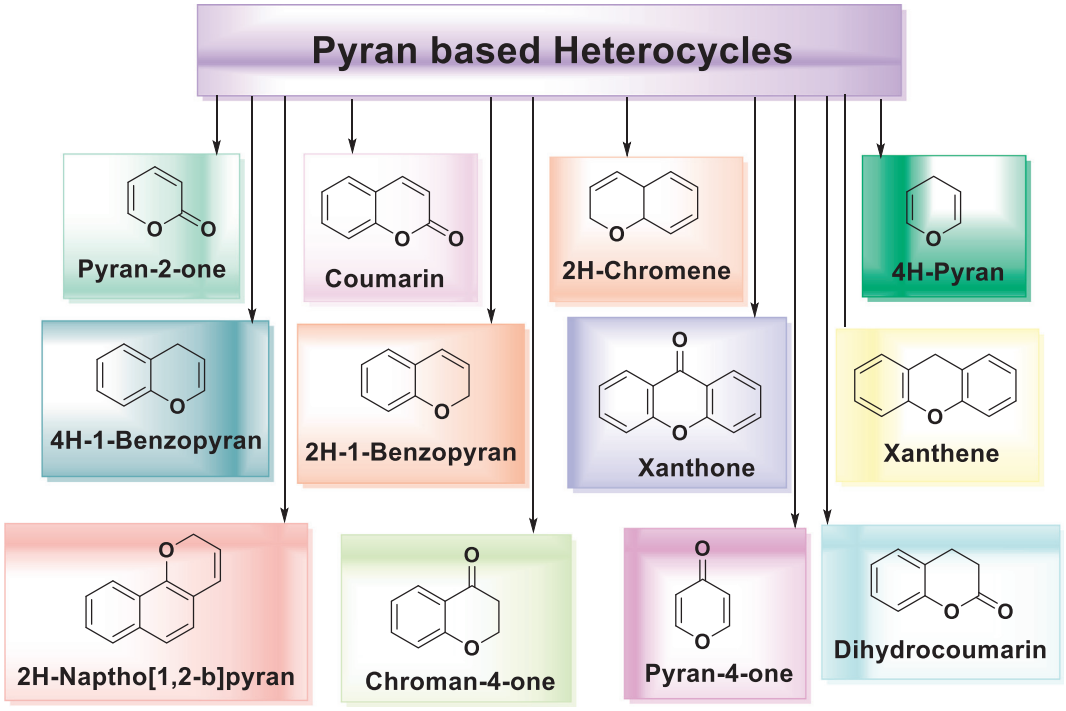


Fig. 2. Pyran based heterocycles.

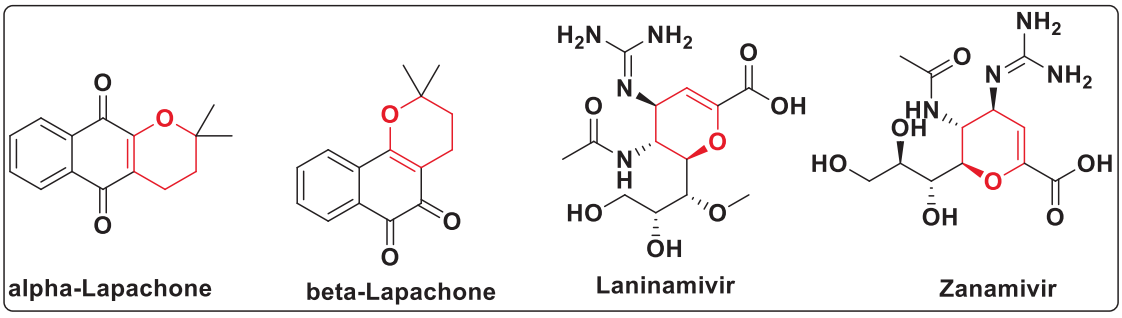
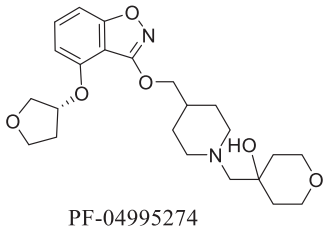
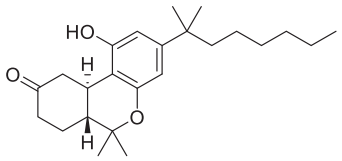
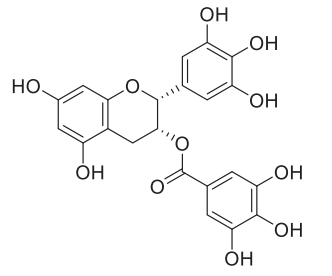
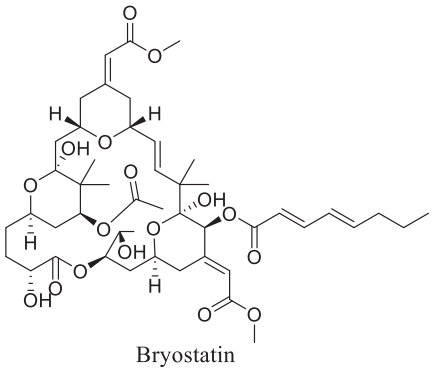
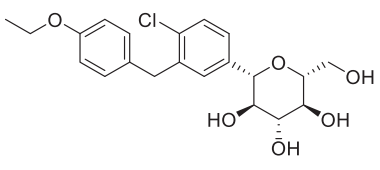


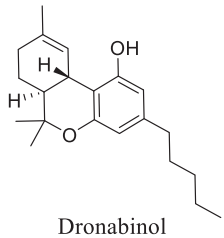
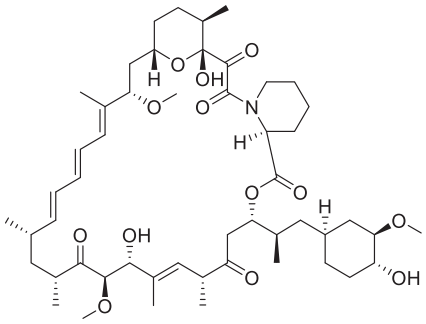
Fig. 3. Some pyran-containing marketed drugs in preclinical/clinical trials.

Table 1
Clinical trials of pyran-based repurposed/new molecules for treatment of AD.

Drug/Compound	Mechanism	Intervention	CT Number
 PF-04995274	Serotonin 4 receptor (5-HT4R)	PF-04995274 is a brain penetrant that can be used to treat cognitive disorders associated with Alzheimer's disease.	NCT03515733
 Nabilone	Agonists at cannabinoid receptors 1 and 2	Nabilone is a novel medication that may be a safe and effective treatment for agitation in Alzheimer's disease, with additional benefits for appetite and pain.	NCT02351882
 Epigallocatechin-Gallate (EGCG)	EGCG seems to cause the induction of alpha-secretase and the endothelin-converting-enzyme, as well as prevent the aggregation of beta-amyloid into toxic oligomers through its direct binding to the unfolded peptide.	EGCG is a promising compound that has proven efficacious in AD.	NCT00951834
 Bryostatin	Bryostatin-1 has the ability to activate protein kinase C (PKC) and thus induce the activity of α-secretase, resulting in an increase in sAPP release.	Bryostatin: Treatment of Moderately Severe Alzheimer's Disease	NCT03560245 NCT04538066
 Dapagliflozin	Several reports indicated that dapagliflozin restored mitochondrial dysfunction, therefore slowing down Alzheimer's progression.	The drug is under clinical trials for its efficacy in treating moderate to severe Alzheimer's disease.	NCT03801642

(*continued on next page*)

Table 1 (*continued*)

Drug/Compound	Mechanism	Intervention	CT Number
 Dronabinol	At the Type 1 and Type 2 endocannabinoid receptors, dronabinol acts as a partial agonist.	The drug is investigated for adjunctive treatment of agitation in Alzheimer's Disease	NCT02792257
 Rapamycin	Rapamycin promotes the elimination of toxic proteins, primarily via the autophagy-lysosomal pathway, in the treatment of neurodegenerative diseases such as Alzheimer's disease.	This trial study evaluates the safety and efficacy of rapamycin in older adults with mild cognitive impairment (MCI) or early-stage AD.	NCT04629495

synthetic molecules with high activity. The main objective of the present review is to assess and afford an in-depth knowledge of pyran-based compounds which exhibited promising action against AD. A thorough study of the available data from various search engines including Google Scholar, Science Direct, SciFinder and PUBMED has been carried out to gather the data. This review attempts to spotlight the active compounds and SAR of various pyran-based scaffolds for the treatment of AD. The compilation will broaden the potentiality of pyran in AD and will be helpful for researchers working in the area of drug development for AD to make more potential molecules.

2. Pyran based derivatives of natural origin for treatment of AD

The flavonoid known as quercetin can be found in a wide variety of medicinal plants, including apples, onions, berries and green tea. Quercetin has high antioxidant capabilities and can scavenge reactive oxygen species (ROS) (Ossola et al., 2009). In addition to its anticancer, antiviral, antiinflammatory, and antiamyloidogenic effects, (Russo et al., 2012; Bischoff, 2008) it also possesses additional therapeutic qualities. Quercetin at a concentration of 10 μM inhibits the accumulation of -amyloids, demonstrating anti-amyloidogenic action (Jiménez-Aliaga et al., 2011). It is also found to inhibit A-induced neuronal cell death. Nevertheless, at greater concentrations (40 μM), quercetin can elicit cytotoxicity (Ansari et al., 2009). Recent studies have shown that senescence-accelerated P8 mice can have their cognitive and memory deficiencies efficiently restored by administering nano-encapsulated quercetin contained in zein nanoparticles. There is a possibility that this mechanism is connected to the reduced expression of the astrocyte marker GFAP in the hippocampus (Moreno et al., 2017).

Camellia sinensis contains the flavonoid-type catechin epigallocatechin-3-gallate. Numerous studies (Ahmad et al., 1997) have studied the impact of epigallocatechin-3-gallate on a variety of disorders, including cancer, cardiovascular disease, and neurological disease. In mice with streptozotocin-induced dementia, it has been shown that epigallocatechin-3-gallate increases the activity of glutathione peroxidase, decreases the activity of acetylcholinesterase, and prevents the generation of ROS and NO metabolites (Biasibetti et al., 2013). Epigallocatechin-3-gallate boosted memory formation and reduced the activity of the -secretase enzyme in Alzheimer's mutant PS2 mice (Lee et al., 2009). Epigallocatechin-3-gallate attenuated LPS-caused memory loss and mortality by reducing amyloid precursor protein production, blocking beta-site APP cleaving enzyme 1, and reducing -amyloid buildup. It prevents astrocyte activation in neuronal cells and lowers inflammatory factors such as tumour necrosis factor-(TNF), IL-6, interleukin 1-alpha (IL-1), cyclooxygenase-2 (COX-2), inducible nitric oxide synthase (iNOS), and soluble intracellular adhesion and molecule-1 macrophage colony-stimulating factor. Epigallocatechin-3-gallate increased neprilysin enzyme expression in senescence-accelerated P8 mice. Enzyme Neprilysin limits A degradation (Li et al., 2004; Lee et al., 2013; Chang et al., 2015).

Luteolin is a flavonoid present in numerous medicinal plants, such as Bryophyta, Magnoliophyta, Pteridophyta, and Pinophyta (Lopez-Lazaro, 2008). Numerous biological actions, including antibacterial, anti-inflammatory, antioxidant, anticancer, and neuroprotective properties, have been attributed to luteolin (Seelinger et al., 2008). It is possible that the antioxidant activity of luteolin and its ability to control the tau phosphatase/kinase system (Zhou et al., 2012) are responsible for the ability of luteolin to reduce the zinc-induced hyperphosphorylation of the tau protein. In addition, research has shown that luteolin has the ability to prevent the formation of amyloid precursor protein and -amyloid (Liu et al., 2011). In addition to this, luteolin is capable of suppressing apoptosis by preventing the creation of intracellular ROS, bolstering the body's natural antioxidant defences by elevating the levels of SOD, CAT, and GPx activities, and stimulating the NRF2 pathway (Hwang et al., 2013). In rats with prolonged cerebral

hypoperfusion, luteolin can ameliorate cognitive impairment, boost the antioxidant system, and reduce lipid peroxide production (Fu et al., 2014). In a rat model of Alzheimer's disease that had been streptozotocin-induced, luteolin was found to improve both cognitive performance and memory (Wang et al., 2016). Despite the results of these studies, further data from clinical trials are necessary to demonstrate that luteolin protects against Alzheimer's disease (Bui and Nguyen, 2017).

In vivo studies have demonstrated that vitamin E, which is present in a wide variety of fruits and vegetables, can reduce the amount of amyloid beta (A) in the body (Sung et al., 2004). Cotherapy of many medications with vitamin E was also explored and tested within the context of clinical trials. Sano et al. (1997) conducted research to investigate the effects of simultaneously ingesting vitamin E and selegiline (Ary Ano et al., 1997). It has been demonstrated that cotherapy can effectively slow the progression of an illness. The relationship between donepezil and vitamin E was also analysed in this study. In the treatment of Alzheimer's disease (AD), the medicine donepezil is used to manage symptoms. Petersen et al. (2005) (Petersen et al., 2005) conducted a clinical investigation in which they compared the effects of this medication to those of vitamin E on the outcomes of people who had mild cognitive impairment. The experiment was designed to be double-blind, and it was controlled by a placebo. Unfortunately, vitamin E was not effective in preventing the worsening of the illness. Dysken et al. (2014) conducted research into the interactions that can occur between vitamin E and memantine (Dysken et al., 2014). When compared to a placebo, treatment with vitamin E alone proved to be more beneficial in slowing the progression of cognitive decline in patients suffering from illness. However, there was no discernible difference found between the memantine treatment alone and the co-therapy combination. Kryscio et al. (2017) wanted to find out if consuming vitamin E and selenium could help prevent dementia in men over the age of 60 who were in good health (Kryscio et al., 2017). Even though there is no evidence to back the use of selenium in the treatment of Alzheimer's disease (AD), a number of studies (Youdim et al., 2006; Varikasuvu et al., 2019; Andrade et al., 2019) show that this substance may have the ability to act as a preventative measure. Fig. 4 depicts the structural make-up of a variety of naturally occurring pyran-based derivatives in their various forms.

3. Various pyran based scaffolds active against AD and their SAR

3.1. Coumarin based scaffolds

The inhibitory activity of a group of biscoumarin derivatives was tested to study novel candidates which would act as AChE inhibitors. The results displayed that some of the tested compounds indicated acceptable activity against AChE. Besides, the **(1)** demonstrated substantial activity, having an IC_{50} value of 2.0 μM. Moreover, the binding state of coumarin derivatives was rationalized using intra-silica studies regarding stability analysis, IC_{50} values, binding interactions, and binding score (Zare-Akbari et al., 2022).

Chiu and colleagues made the discovery that compound 2 offers neuroprotective advantages to cells by altering the PKA, CaMKII, and ERK signalling pathways. These pathways all encourage CREB phosphorylation and neurite outgrowth. Compound 2 may be particularly promising for the advancement of drugs for the medication of Alzheimer's disease since it targets numerous pathways to give neuroprotection. This is because multiple pathways are thought to be involved in the genesis of Alzheimer's disease. The fact that compound 2 was shown to have neuroprotective effects in a model consisting of tau cells further suggests that this medication is promising for the treatment of other neurodegenerative tauopathies (Chiu et al., 2021).

In this study, the possible neuroprotective effects of a first series of 3,7-substituted coumarin derivatives were investigated. The findings suggest that the chemicals in question are moderate inhibitors of cholinesterase. The propargylamine functional group found in compounds three and four, which have IC50 values of 0.029 and 0.101 M respectively, showed the most potential as MTDLs. This can be attributed to the fact that these compounds demonstrated the greatest potential. According to the findings, the propargylamine substitution at the 3-position had the most MAO-B selectivity as well as the most neuroprotective effects. In general, the findings demonstrated that the phenylethyloxy moiety being substituted at the 7-position conferred greater overall activity to the derivatives (Mzezewa et al., 2021).Three novel pyrazoles containing derivatives of brominated 4-methyl 7-hydroxycoumarin were developed. The affinity of compound **(5)** for the crystallographic structure (4EY7) of the acetylcholine

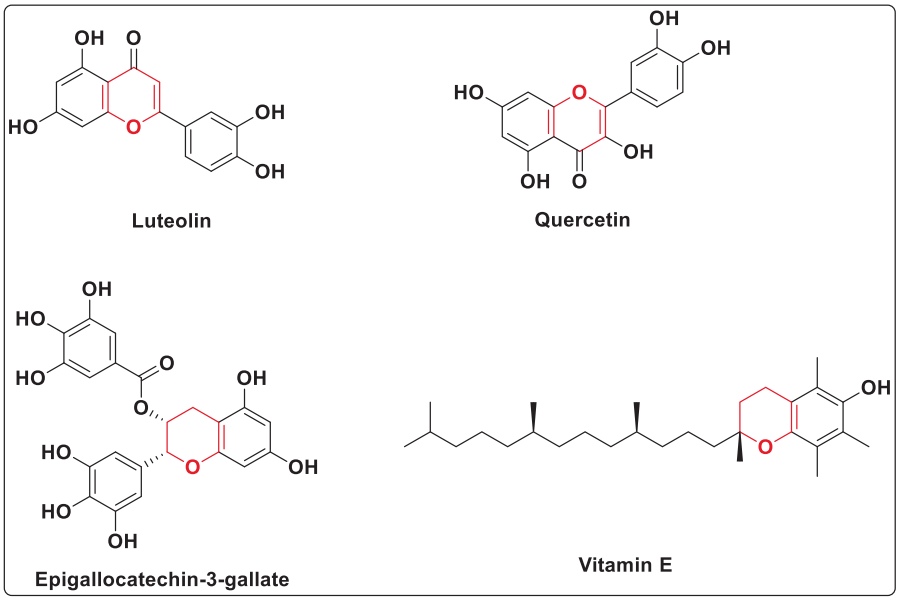


Fig. 4. Pyran-Based Derivatives from Natural origin for treatment of AD.

esterase enzyme was high. Investigations using the molecular docking technique revealed that the chemical (**5**) has the potential to attach to both the active sites of the acetylcholine esterase enzyme as well as the amino acid concurrently. In the experiment designed to block acetylcholine esterase, the chemical shows a significant increase in the amount of acetylcholine esterase activity it can produce. MAO inhibitory activity was found in the nanomole range (the IC50 value for human MAO-A was 3.9, while the IC50 value for human MAO-B was 4.4) (Narayanan et al., 2021).

In SH-SY5Y neuroblastoma cell models of Alzheimer's disease, Huang et al. made a discovery about the potential of two unique synthetic coumarin derivatives, numbers **(6)** and **(7)**, to inhibit A and provide neuroprotection. In SH-SY5Y cells that were expressing a GFP-tagged A-folding reporter, both medications were able to reduce A aggregation as well as oxidative stress, activity levels of caspase-1 and AChE, and they were able to stimulate neurite outgrowth. Compounds **(6)** and **(7)** were shown to minimise A neurotoxicity via pleiotropic processes. The results recommended the compounds as novel treatment possibilities for AD and indicated that compounds **(6)** and **(7)** reduced A neurotoxicity (Huang et al., 2021).

Kumar et al. successfully synthesised fifteen different coumarin derivatives. It was discovered that a 4 methylthiocoumarin derivative **(8)** was a robust acetylcholinesterase (AChE) inhibitor, while **(9),** on the other hand, demonstrated potent butyrylcholinesterase (BuChE) inhibition. Compound **(8)** was also capable of inhibiting MAO B enzymes to a marginal degree, as well as BACE1 to a moderate degree.The action of the compounds against cholinesterase enzyme, BACE1, A, and oxidative stress appears promising. The IC_{50} (μM) at 80 μM concentration for **(8)** against AChE is 5.63 ± 1.68 and for **(9)** against BuChE is 3.40 ± 0.20 respectively (Kumar et al., 2020).

Using multi-target-directed ligands, a new series of 1,2,3-triazolechromenone products was designed and synthesised. *In vitro* biological activity included anti-Aβ aggregation, AChE and BuChE inhibition, neuroprotective effects, and metal chelation properties. According to the findings, compound **(10)** had the strongest BuChE inhibitory action, having an IC_{50} value of 21.71 M. This was determined by analysing the data. In addition, compound 10 was able to suppress the self-induced aggregation of Aβ1–42 as well as the AChE-induced aggregation of A, with respective inhibition values of 32.6% and 29.4%. As shown by the Lineweaver–Burk plot and the investigations that involved molecular modelling, compound (10) targeted both the catalytic active site (CAS) and the peripheral anionic site (PAS) of BuChE. Compound 10 was notable in that it possessed the potential to bind biometals. Therefore, it is possible to consider this molecule to be a multifunctional agent when it comes to the search for AD medications (Karimi Askarani et al., 2020).

In the search for potential novel AChE and BChE inhibitors, the in vitro inhibitory activity of a set of coumarin derivatives was evaluated. The IC_{50} for compound **(11)** was determined to be 2.0 nM based on the results (Abu-Aisheh et al., 2019).

Another group of 3–(4-aminophenyl)-coumarin derivatives was conceptualised, designed, manufactured, exhaustively documented, and put through a battery of tests in vitro and *in vivo*. Experiments using biological assays revealed that certain compounds selectively block the enzymes AChE and BuChE. Compound **12** demonstrated the highest level of AChE inhibition with an IC50 value of 0.011 mM, whereas compound **13** demonstrated the highest degree of BuChE inhibition with an IC50 value of 0.017 mM (Hu et al., 2019).

A total of twelve different conjugated coumarin-benzofuran hybrids were designed, fabricated, and evaluated in this study by Hiremathad et al. The synthesised hybrids were then examined for their ability to inhibit AChE and Aβ self-aggregation. The compounds containing methoxy substitutions and longer chain linkers had the strongest AChE inhibitory activity among all hybrids. Compounds **14, 15, 16, and 17**, which include a methoxy group either on the benzofuran or coumarin ring, were found to have a superior AChE inhibitory capacity compared to hybrids (Hiremathad et al., 2018); their respective values were 0.27, 0.32, 0.18, and 0.224 μM.

Dibromoalkanes were used to conjugate several 7-hydroxycoumarin derivatives (8-hydroxyquinoline, 2-mercaptobenzoxazole, and 2-mercaptobenzimidazol) with various benzoheterocycles (8-hydroxyquinoline, 2-mercaptobenzoxazole, and 2-mercaptobenzimidazol). Using Ellman's technique, final derivatives were screened against AChE and BuChE. Compound **(18)** containing a quinoline group had the highest activity against AChE, with an IC_{50} value of 8.80 μM (Hirbod et al., 2017).

The monocoumarin derivatives **19** and **20**, each of which contains a benzyl pyridinium group, displayed excellent acetylcholinesterase inhibiting effect (IC_{50} values of 0.11 and 0.20 nM, respectively). Bis-coumarin ligands displayed significant levels of inhibitory activity and selectivity towards MAO-A (Hamulakova et al., 2017).

A series of 7-hydroxycoumarin derivatives with amide connections to a variety of different amines was devised and manufactured with the purpose of acting as cholinesterase inhibitors. The overwhelming majority of compounds exhibited significant inhibitory action against both AChE and BuChE. According to the findings of certain studies, the most effective treatment for AChE is the medication known as N-(1- benzylpiperidin-4-yl)acetamide derivative **21**, which has an IC_{50} value of 1.6 mM (Alipour et al., 2014).

Fig. 5 provides an overview of the structural makeup of every coumarin-based drug currently in development for the treatment of AD.

3.2. Xanthone and Xanthene-based scaffolds

Four kinds of mangostin-based derivatives. Further research studied the anti-AD effects of these substances on fibrillogenesis, microglial absorption and degradation, anti-neurotoxicity of Aβ and LPS-induced neuroinflammation. An instance of fibrillogenesis was discovered by the utilisation of a fluorometric test using thioflavin T. The enzyme-linked immunosorbent assay was used to determine the levels of Aβ1-42 and inflammatory cytokines in the sample. The CCK-8 test was utilised in order to determine the neuronal viability. In the vast majority of impacts, compound (**22**) acted as if it were α-M. According to the findings of the structure–activity study, the 3-methyl-2-butenyl group that is located at the C-8 position is necessary for the bioactivity of α-M, whereas modifying the double hydroxylation that is located at the C-2 position has the potential to improve the multifunctional anti-AD capabilities (Hu et al., 2022).

Anti-cholinergic effects of series of 3-O-substituted xanthone derivatives were tested against AChE and BuChE after they were produced in a laboratory setting. According to the findings, the xanthone derivatives had good AChE inhibitory activity, with compounds **23** and **24** exhibiting the highest levels of activity (IC_{50} values of 0.88 ± 0.04 μM and 0.88 ± 0.15 μM respectively, respectively) (Loh et al., 2021).

In this study, an additional series of hydroxyxanthone derivatives were produced and tested for their ability to inhibit AChE. Compounds **25** and **26** were determined to have the highest IC50 values for their ability to inhibit AChE, coming in at 20.8 and 21.5 μM respectively (Vanessa et al., 2022).

This study discusses the design, synthesis, and biological evaluation of chromeno[3,4-b]xanthones and their (E)-2-[2-(propargyloxy)styryl]chromone precursors as first-in-class AChE and beta-amyloid (A) aggregation dual-inhibitors. Compounds **27** and **28**

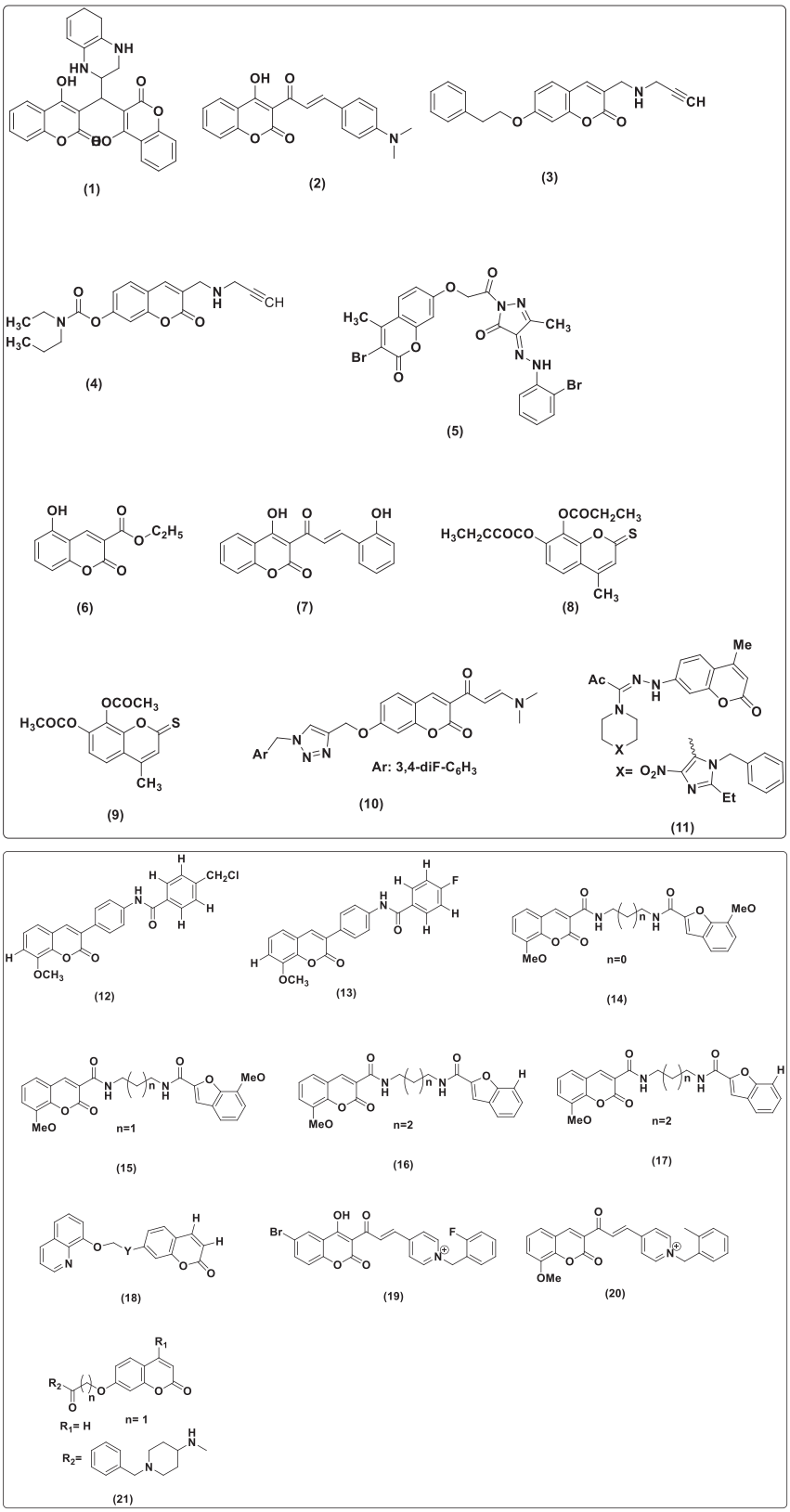


Fig. 5. Coumarin-based compounds for the treatment of AD.

were found to be effective dual-target inhibitors, which is a rare combination to find. Their IC50 values for AChE were 3.9 and 2.9 mM, whereas their percentages of inhibition for A aggregates were 66% and 70%, respectively (Malafaia et al., 2021).

Conjugation of the pharmacophores of xanthone and alkylbenzylamine through an alkyl linker resulted in the design and synthesis of a number of multifunctional hybrids with anti-AD activity. These hybrids were designed to have a number of different

functions. The biological activity data for compound **29** demonstrated that it was the most effective and well-balanced dual ChEs inhibitor. It had IC_{50} values of 0.85 mM for the inhibition of AChE and 0.59 mM for the inhibition of BuChE. These values were calculated using the data on the biological activity of the chemical (Zhang et al., 2021).

Through onepot condensation of different substituted aromatic aldehydes, 2hydroxy1,4naphthoquinone, and dimedone in the presence of Bi(OTf)3 as an eco-friendly and reusable catalyst, 3,4dihydro12aryl1Hbenzo[b]xanthene1,6,11(2H,12H) trione compounds were produced. Their inhibitory actions against BuChE) and AChE was investigated. Compound **(30)** was found to be active AChE, with IC_{50} 28.16 ± 3.46 mM, and compound **31** is found active for BuChE with IC_{50} 36.24 ± 3.19 mM. These chemicals interacted with either the catalytic active site or a site linked to the catalytic active site of the AChE and BChE enzymes, respectively, in order to directly block the catalytic activity (Turhan et al., 2020).

The ability of four xanthone derivatives to chelate metals and exhibit antioxidant action against Alzheimer's disease was investigated after they were synthesised and tested as acetylcholinesterase inhibitors, also known as AChEIs. The compound with the formula 3-(2-(pyrrolidinyl)ethoxy)-1- hydroxy-9H-xanthen-9-one (32) demonstrated the best capacity to inhibit AChE and exhibited good selectivity for AChE (IC_{50} = 2.403 ± 0.002 μM for AChE and IC_{50} = 31.221 ± 0.002 μM for BuChE) (Yang et al., 2020).

Using the Ellman approach, a different set of xanthone derivatives was produced and tested to see if they had the ability to act as multifunctional ligands against AD. According to the findings, compound **33** exhibited the strongest inhibitory action against AChE. Furthermore, the IC_{50} value for this compound was (0.328 ± 0.001) μM, which was on par with the typical medication tacrine (Kou et al., 2020).

Menendez et al., synthesized and characterized Xanthone derivatives. The compounds were evaluated as potential anti-Alzheimer agents using Ellman's method. The results showed that compound **(34)** was the most active with piperidine in the structure and had a linker length of 5 carbons. The IC_{50} value was found to be 0.46 ± 0.02 μM (Menéndez et al., 2017).

In a separate line of research, xanthenedione derivatives were produced, and the Ellman microplate assay method was used to investigate the efficacy of these compounds to inhibit the AChE enzyme. According to the findings, the xanthenedione derivative **(35)**, which contained a catechol unit, functioned as a powerful AChEI (IC_{50} = 31.0 0.09 μM) (Seca et al., 2014).

Using the Ellman methodology, a number of novel 1, 3-dihydroxyxanthone Mannich bases derivatives were created, their structures were uncovered, and their anti-cholinesterase activity was evaluated. Diakylamine methyl types at position 2 of xanthone altered cholinesterase activities and AChE/BuChE selectivity. Alkoxy or alkenoxy substituents in position 3 of xanthone increased inhibitory potency. Xanthones having alkoxy or alkenoxy at position 3 led to these findings. 2-((diethylamino)methyl)-1-hydroxy-3-carboxylate (3-methylbut-2-enyloxy). The half-maximal inhibitory concentration (IC50) for 9H-xanthen-9-one **(36)** was determined to be 2.61 ± 0.13 μM for acetylcholinesterase (AChE), and it was found to be 0.51 ± 0.01 μM for butyrylcholinesterase (BuChE). The results of this study (Qin et al., 2013). indicate that 1,3-dihydroxyxanthone Mannich base derivatives have the capacity to inhibit both AChE and BuChE.

Cruz et al. conducted a study in which they examined and collated the SAR of a number of different xanthone derivatives. In their findings, they discovered that the number of substituents and their positions have an effect on the AchE inhibiting activity of xanthones. Antiacetylcholinesterase action appears to be increased by the presence of a N-alkyl-N-(3-alkylcarbamoyloxyphenyl)-methyl]aminoalkoxy group at position 3, as well as a 3,4-fused pyran ring on the xanthone nucleus (Cruz et al., 2017).

The structures of all xanthone and xanthene-based compounds for the treatment of AD are given in Fig. 6.

3.3. Flavone and isoflavone-based scaffolds

Using the Williamson approach, four flavonoid derivatives were synthesised in a study. The Ellman method for evaluating AChE inhibitory activity revealed two compounds (37 and 38) with rather good biological activities and these biological activities were superior to those of naringenin, which was used as the standard flavonoid (Tran et al., 2021).

Shi et al. developed and synthesised hybrids of 7-O-galloyltricetiflavan (GTF). GTF is a naturally occurring flavonoid renowned for its neuroprotective properties. The chemicals were then tested to determine whether or not they could treat AD. Compound (39), among them, demonstrated the most effective suppression of AChE aggregation (78.81% at 20 M), the most powerful AChE inhibitory potencies (IC_{50}, 0.56 M), and the greatest ability to inhibit BuChE (IC_{50}, 5.8 M). All of these properties were measured at 20 microMolar concentrations. Compounds 39 and 40 exhibited high levels of neuroprotective activity against H2O2-induced damage to human neuroblastoma SH-SY5Y cells and almost no toxicity toward SH-SY5Y cells. These results suggest that compounds **39** and **40** may be useful therapeutic agents. Additionally, these compounds displayed virtually minimal toxicity toward SH-SY5Y cells when tested (Shi et al., 2020).

As potential anti-AD drugs with several functionalities, nineteen different compounds have been created and are now being researched. These compounds all include flavone and cyanoacetamide groups. Compounds **41**, **42**, **43**, **44**, and **45** all exhibited high inhibitory efficacy (AChE, IC50, ranging from 0.271 ± 0.012 to 1.006 ± 0.075 μM) and selectivity against acetylcholinesterase. In addition to this, these compounds demonstrated a large amount of antioxidant activity, good regulation effects on self-induced A aggregation, minimal cytotoxicity (Basha et al., 2018).

In this study, several novel isoflavones were synthesised, and in vitro AChE and BuChE bioassays were used to investigate the activities of these compounds. The majority of isoflavone derivatives showed just a little inhibition of AChE and BuChE. Compound (**46**) was found to be an effective AChE/BuChE inhibitor (Feng et al., 2017), with IC50 values of 4.60 μM for AChE; 5.92 μM for BuChE (Feng et al., 2017).

The structures of flavone and isoflavone-based scaffolds for the treatment of AD are given in Fig. 7.

3.4. Other scaffolds

In this study, the anti-AD potential of a variety of recently found isochroman-4-one derivatives that were synthesised from naturally occurring (±)-7,8-dihydroxy-3-methyl-isochroman-4-one was analysed. Compound **47**, also known as (Z)-3-acetyl-1-ben zyl-4-((6,7-dimethoxy-4-oxoisochroman-3-ylidene)methyl)pyridin-1-ium bromide, was shown to have considerable anti-AChE activity as well as minor antioxidant activity. Compound 10a is a dual-binding inhibitor, as was discovered by more molecular modelling and kinetic testing. [Citation needed] This indicates that it is capable of binding to both the catalytic anionic site (CAS) and the peripheral anionic site (PAS) of the acetylcholinesterase enzyme (Li et al., 2022).

In order to determine whether or not a variety of 1,2,3-triazole-chromenone carboxamides were capable of inhibiting cholinesterase, the researchers conceived of a number of novel carboxamides, synthesised them, and tested them. N- (1-benzylpiperidin-4-yl) −7-(1-(3,4-dimethylbenzyl) −1H-1,2,3-triazol-4-yl)methoxy) −2-

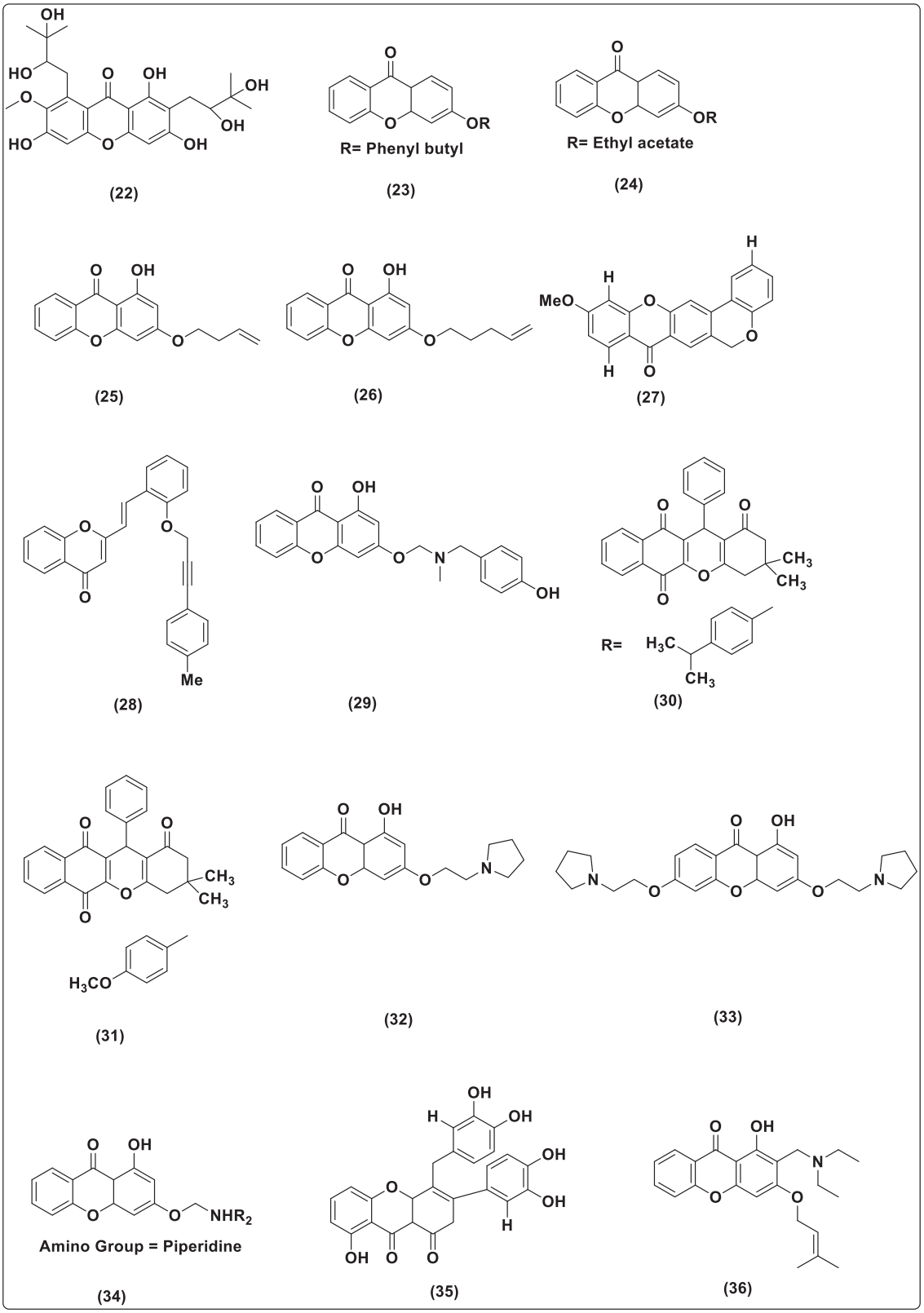


Fig. 6. Xanthone and Xanthene based compounds for treatment of AD.

oxo-2H-chromene-3-carboxamide (48) has demonstrated the maximum inhibitory action of acetylcholinesterase among these (IC50 = 1.80 M), however it had no effect on butyrylcholinesterase Notably, the inhibitory effect of BACE1 was investigated using compound (**48**), and the obtained IC50 value of 21.13 μM supported the expected inhibitory action. In addition, when tested at a concentration of 50 M, this compound demonstrated metal chelating activity toward Fe2+, Cu2+, and Zn2 + ions as well as a

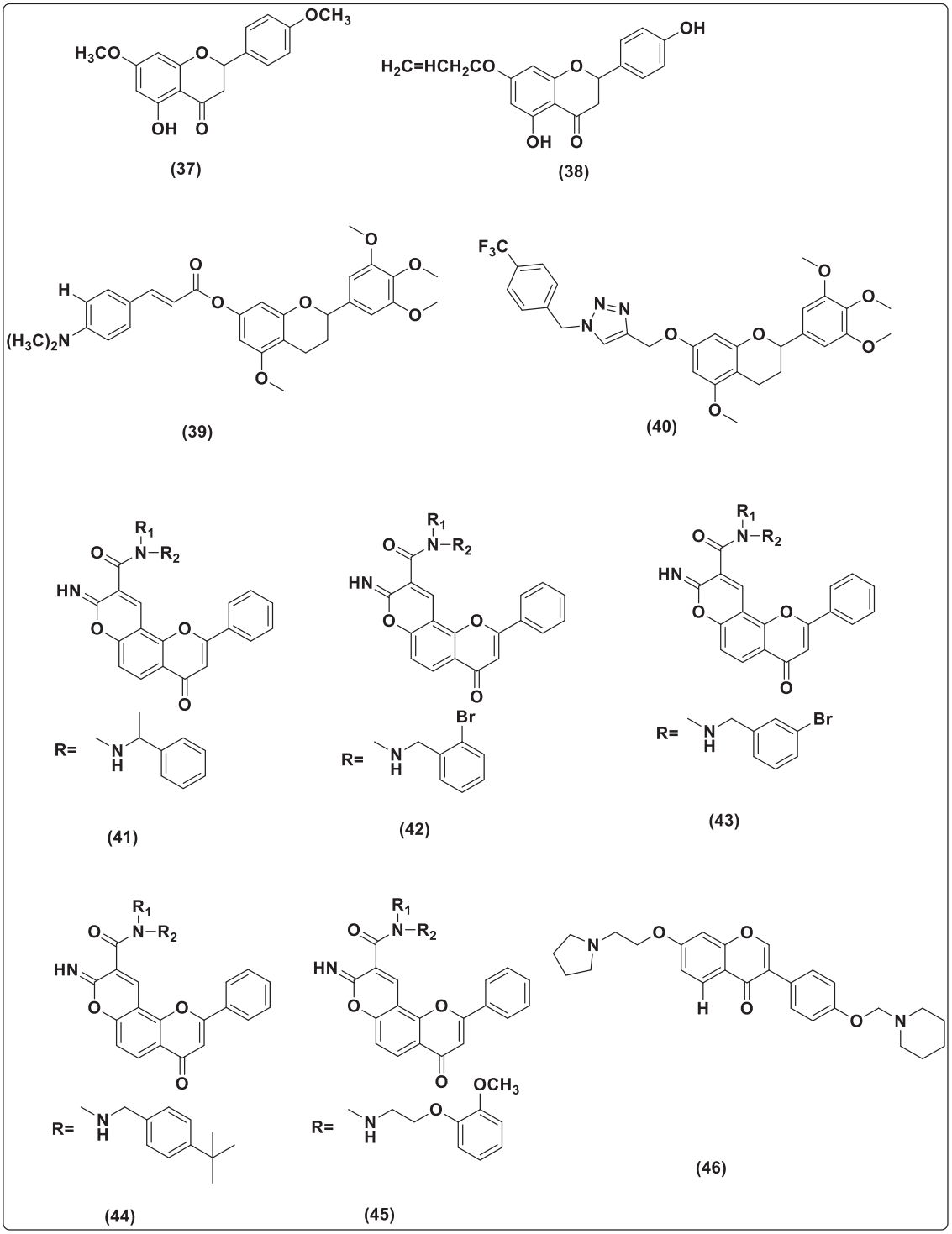


Fig. 7. Flavone and Isoflavone-based compounds for the treatment of AD.

neuroprotective effect that was plausible against H2O2-induced cell death in PC12 neurons (Rastegari et al., 2019).

A variety of 2-phenyl-4H-chromen-4-one and its derivatives were developed, synthesised, and tested for their polyfunctionality as acetylcholinesterase (AChE) and advanced glycation end products (AGEs) production inhibitors against Alzheimer's disease in this work. The findings of the screening revealed that the majority of them possess a high capacity to suppress the synthesis of AChE AGEs in conjunction with radical scavenging activity. This was discovered after the results of the screening were analysed. The IC50 values for inhibitory activity against AChE were 8, 8, and 11.8 nM, respectively, for compounds **49, 50**, and **51**, while the IC50 values for AGE formation were 55, 79, and 54 nM, respectively (Singh et al., 2018).

The structures of above-mentioned compounds for the treatment of AD are given in Fig. 8.

The structure–activity relationship (SAR) analysis of pyran derivatives involves studying the relationship between the

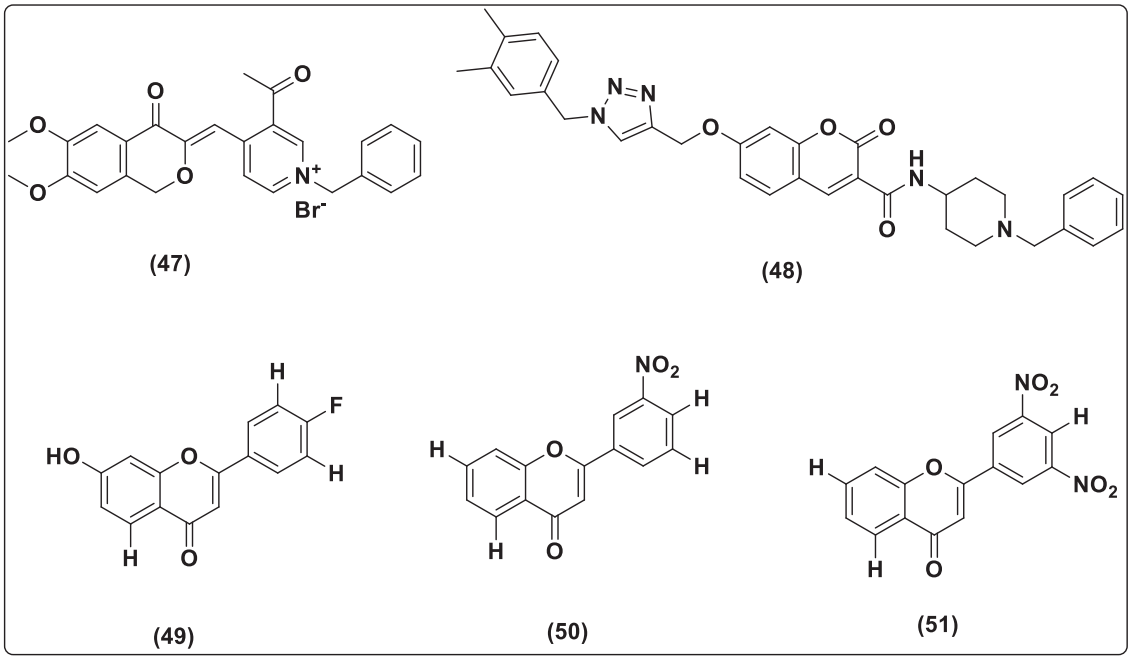
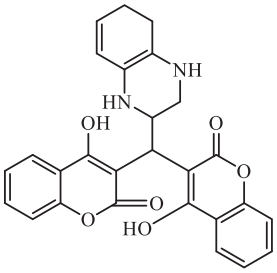
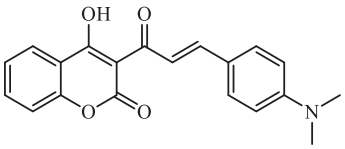
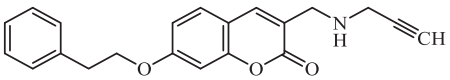
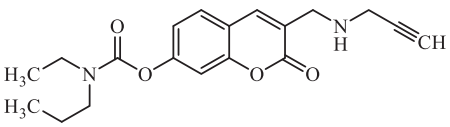


Fig. 8. Compounds for treatment of AD.

chemical structure of these compounds and their biological activity against Alzheimer's disease. The SAR and IC_{50}/EC_{50} values of all pyran derivatives stated above are summarized in Table 2 below. This will help readers a comparison of activities and structures of pyran-based compounds that are potential for the treatment of AD. Also, general SAR studies of various pyran derivatives have been summarized below in Fig. 9, which gives an insight into the structural features essential for anti-Alzheimer's disease activity.

Table 2
SAR and cholinesterase inhibition activity of pyran-based derivatives.

Compound Number	Structure	IC_{50}/EC_{50}; Method	SAR Remarks/Essential Groups with pyran that affects activity against Alzheimer's disease	Reference
Coumarin Based Scaffolds				
1		IC_{50}: 2 μM (Ellman assay)	1,2,3,4-Tetrahydroquinoxaline moiety with bis coumarin increases activity.	(Zare-Akbari et al., 2022)
2		EC_{50}: 14 μM (Aβ aggregation inhibition in Tau cell model)	Diethyl amino phenyl separated by 2 carbons from coumarin and a carbonyl group increased activity	(Chiu et al., 2021)
3		0.029 μM (Ellman assay)	Substitution of phenylethyloxy at the 7-position and propargylamine at the 3-position increased activity.	(Mzezewa et al., 2021)
4		0.101 μM (Ellman assay)	Potential activity observed due to the inclusion of the propargylamine functional group	(Mzezewa et al., 2021)

(*continued on next page*)

Table 2 (*continued*)

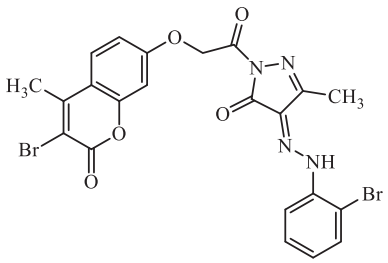
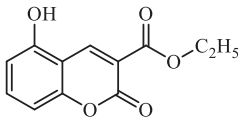
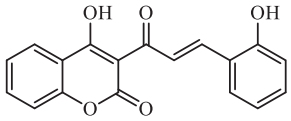
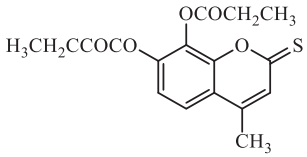
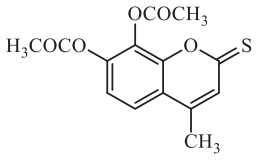
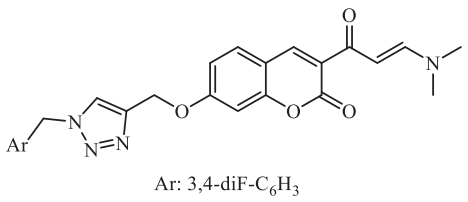
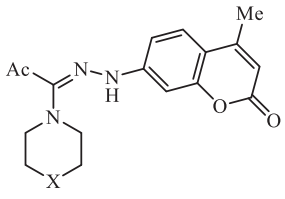
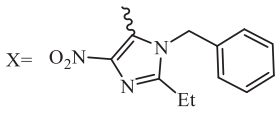
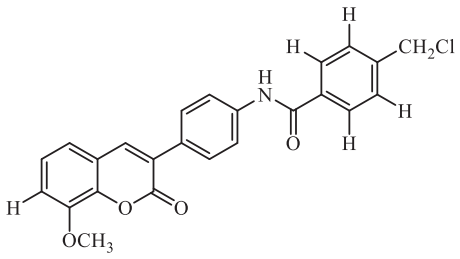
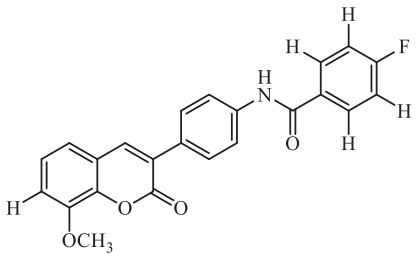
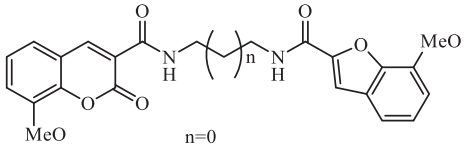
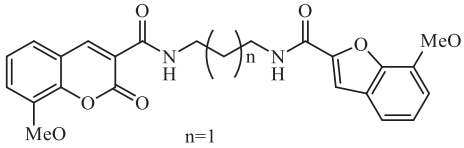
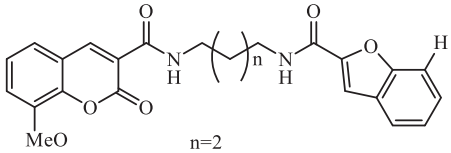
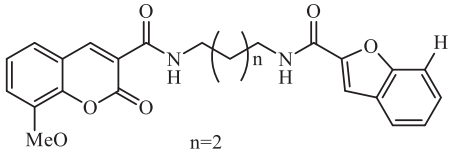
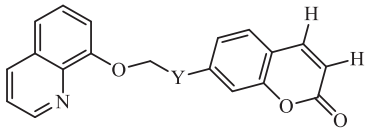
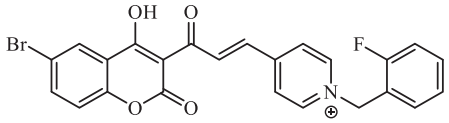
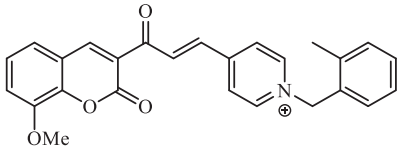
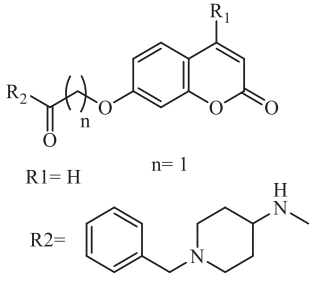
Compound Number	Structure	IC_{50}/EC_{50}; Method	SAR Remarks/Essential Groups with pyran that affects activity against Alzheimer's disease	Reference
5		human MAO-B IC_{50} = 3.9 nM human MAO-B IC_{50} = 4.4 nM (acetylcholine esterase inhibition assay)	Substitution of pyrazole on coumarins may show an increase in anti-Alzheimer's activity	(Narayanan et al., 2021)
6		SH-SY5Y cell model	The ethoxycarbonyl group increases activity	(Huang et al., 2021)
7			Phenyl separated from coumarin by ethylcarbonyl group imparts increased activity	(Huang et al., 2021)
8		Ellman assay, FRET assay)	The thioxo group and ether linkage increase activity.	(Kumar et al., 2020)
9		Ellman assay, FRET assay		(Kumar et al., 2020)
10	 Ar: 3,4-diF-C_6H_3	21.71 μM (Ellman assay)	Difluorobenzyl and triazole dimethylamino groups increased activity	(Karimi Askarani et al., 2020)
11	 	2.0 nM (Ellman assay)	The choline-binding site was comprised of the phenyl ring, which was coupled to the piperazine ring.	(Abu-Aisheh et al., 2019)
12		0.091 ± 0.011 mM (Ellman assay)	Benzoylamino-phenyl group results in increased activity	(Hu et al., 2019)
13		0.559 ± 0.017 mM		

Table 2 (*continued*)

Compound Number	Structure	IC_{50}/EC_{50}; Method	SAR Remarks/Essential Groups with pyran that affects activity against Alzheimer's disease	Reference
		(Ellman assay)		
14		0.27 μM	Derivatives with a methoxy substitution and a longer chain linker performed best activity.	(Hiremathad et al., 2018)
15		0.32 μM		
16		0.18 μM		
17		0.224 μM		
18		8.80 μM	Compound containing quinoline demonstrated the most action.	(Hirbod et al., 2017)
19		0.11 nM	Benzyl pyridinium group showed excellent acetylcholinesterase inhibition.	(Hamulakova et al., 2017)
20		0.16 nM		
21		1.6 mM	The phenyl ring coupled with the piperidine ring showed maximum activity.	(Alipour et al., 2014)

(*continued on next page*)

Table 2 (*continued*)

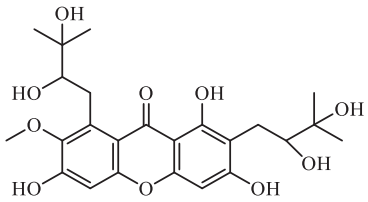
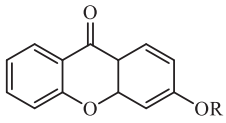
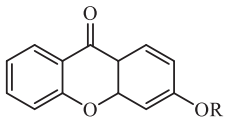
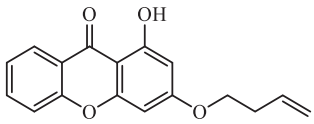
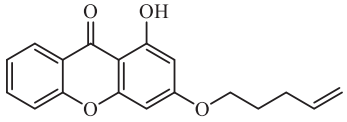
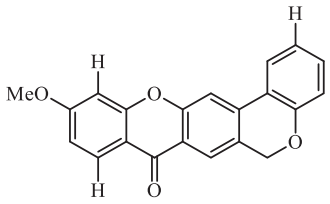
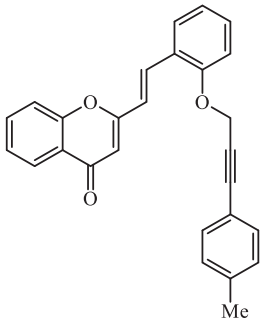
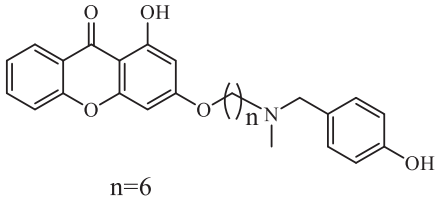
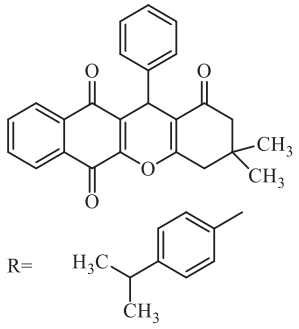
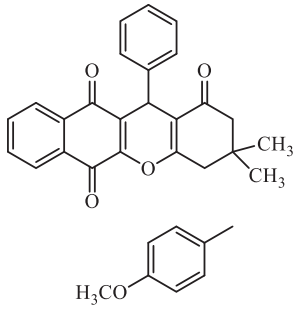
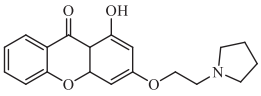
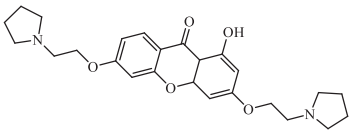
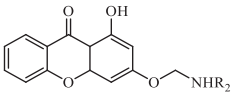
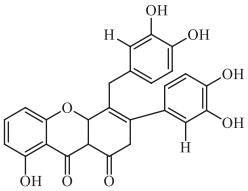
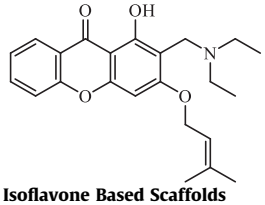
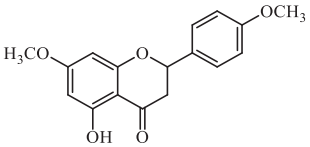
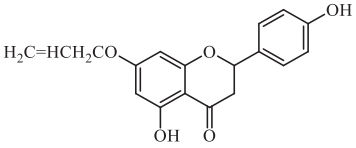
Compound Number	Structure	IC_{50}/EC_{50}; Method	SAR Remarks/Essential Groups with pyran that affects activity against Alzheimer's disease	Reference
Xanthone and Xanthene Based Scaffolds				
22		Thioflavin T fluorometric assay CCK-8 assay	The 3-methyl-2-butenyl group that is located at position C-8 is absolutely necessary for the bioactivity, whilst modifying the double hydroxylation that is located at position C-2 has the potential to improve the multifunctional anti-AD capabilities.	(Hu et al., 2022)
23	 R= Phenyl butyl	0.88 ± 0.04 μM (Ellman assay)	Amongst different hydrocarbon substituents, phenyl butyl and ethyl acetate on xanthone showed maximum activity	(Loh et al., 2021)
24	 R= Ethyl acetate	0.88 ± 0.15 μM (Ellman assay)		(Loh et al., 2021)
25		20.8 μM (Ellman assay)	Both the chain length and the linearity of the hydrocarbon side chain at the C-3 position played a role in determining the inhibitory effects.	(Vanessa et al., 2022)
26		21.5 μM (Ellman assay)	Throughout the entirety of the alkenyl series, the xanthone derivatives that have a substituent group that is composed of a linear chain of four carbon atoms exhibit a higher level of AChE inhibitory activity.	(Vanessa et al., 2022)
27		3.9 μM (Thioflavin T fluorometric assay)	The structures of chromeno[3,4-b]xanthones are significantly potent AChE inhibitors	(Malafaia et al., 2021)
28		2.9 μM (Thioflavin T fluorometric assay)	The (E)-2-styrylchromone exhibited intriguing AChE-inhibitory activity, suggesting that the inclusion of the D-ring may be favourable for anti-AChE activity	(Malafaia et al., 2021)
29	 n=6	0.85 mM AChE inhibition 0.59 mM BuChE inhibition (Ellman assay)	• The ideal linker length was from four to seven carbon atoms, although compounds with an even number of carbon atoms appeared to be preferable (AChE inhibitory activity). • Typically, a hydroxyl substituent at the 4-position of the benzene ring exhibited more activity. • Compound, which possesses both a hydroxyl group at the 4-position of the terminal benzene ring as well as a six-methylene linker, demonstrated the most effective and well-balanced ChE inhibitory action.	(Zhang et al., 2021)

Table 2 (*continued*)

Compound Number	Structure	IC_{50}/EC_{50}; Method	SAR Remarks/Essential Groups with pyran that affects activity against Alzheimer's disease	Reference
30		28.16 ± 3.46 mM	Isopropylphenyl group may cause an enhanced activity	(Turhan et al., 2020)
31		36.24 ± 3.19 mM	Methoxyphenyl and trione along with pyran may produce an enhanced activity.	(Turhan et al., 2020)
32		2.403 ± 0.002 μM for AChE and 31.221 ± 0.002 μM for BuChE	Pyrrolidine ethoxy moiety may cause an increased activity.	(Yang et al., 2020)
33		0.328 ± 0.001 (Ellman method)	1) The xanthone scaffold's 1-hydroxy and carbonyl groups can chelate metal ions. 2) Molecular simulations show the alkylamine side chain and xanthone ring interact with cholinesterase.	(Kou et al., 2020)
34	 Amino Group = Piperidine	0.46 ± 0.02 μM (Ellman's method)	The most active compound contains piperidine in its structure	(Menéndez et al., 2017)
35		31.0 ± 0.09 μM (Ellman's method)	Xanthenedione derivative bearing a catechol unit showed to be a potent AChEI	(Seca et al., 2014)
36		2.61 ± 0.13 μM against AChE and 0.51 ± 0.01 μM against BuChE	1) Alkoxy or alkenoxy substituents in position 3 of xanthone have a beneficial effect on inhibitory potency, 2) dialkylamine methyl types in position 2 of xanthone alter cholinesterase activities and AChE/ BuChE selectivity	(Qin et al., 2013)
Flavone and Isoflavone Based Scaffolds				
37		75.0 ± 4.8 μM (Ellman method)	A hydroxy group at position 5 and dimethoxy at position 4 and 7 enhances activity.	(Tran et al., 2021)
38		48.4 ± 2.9 μM (Ellman method)	Dihydroxy at position 4 and 5 and allyloxy at position 7 enhances activity.	(Tran et al., 2021)

(*continued on next page*)

Table 2 (*continued*)

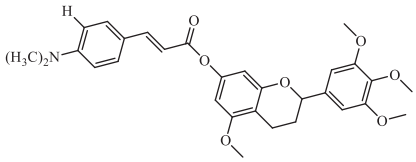
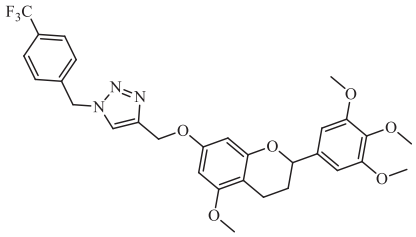
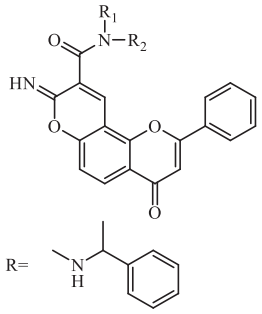
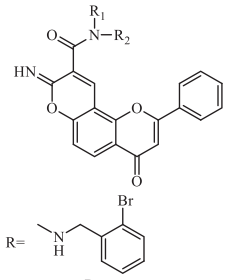
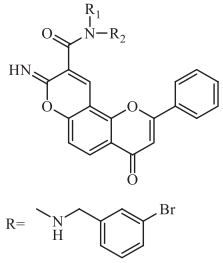
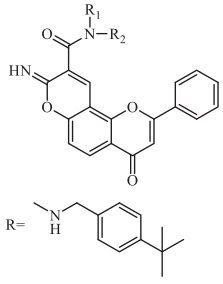
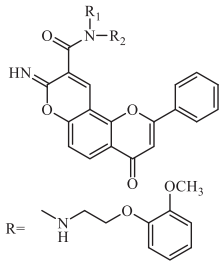
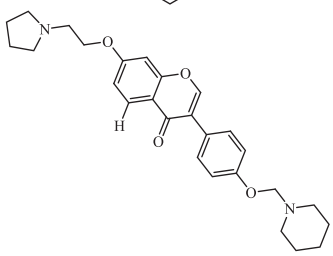
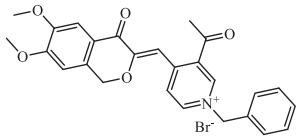
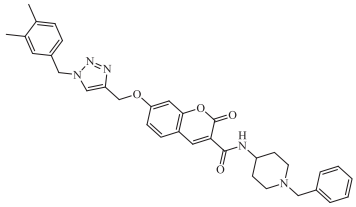
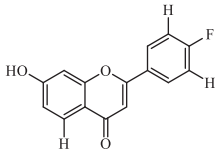
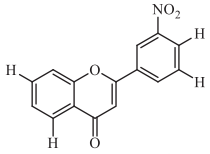
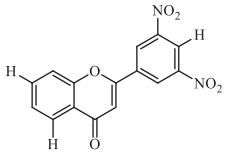
Compound Number	Structure	IC_{50}/EC_{50}; Method	SAR Remarks/Essential Groups with pyran that affects activity against Alzheimer's disease	Reference
39		0.56 μM (Ellman method)	The 4 methoxy group results in an increased activity.	(Shi et al., 2020)
40		5.77 μM (Ellman method)	The presence of a triazole ring results in an increased activity	(Shi et al., 2020)
41		0.273 ± 0.002 (Ellman method)		(Basha et al., 2018)
42		0.286 ± 0.010 (Ellman method)	The carboxamide group increases AChEI activity without affecting the side chain.	(Basha et al., 2018)
43		0.280 ± 0.003 (Ellman method)		(Basha et al., 2018)
44		0.291 ± 0.007 (Ellman method)		(Basha et al., 2018)

Table 2 (*continued*)

Compound Number	Structure	IC_{50}/EC_{50}; Method	SAR Remarks/Essential Groups with pyran that affects activity against Alzheimer's disease	Reference
45		0.271 ± 0.012 (Ellman method)		(Basha et al., 2018)
46		4.60 μM for AChE; 5.92 μM for BuChE (Modified Ellman's Method)	It would appear that a length of two is ideal for the linker that connects the amino group and the isoflavone core structure.	(Feng et al., 2017)
Other Scaffolds				
47		1.61 nM (Ellman method)	The acetyl substitution on the pyridine ring is preferable to the carbamoyl substitution, and the carbonyl moiety has the potential to serve as an important part of a number of different skeleton configurations.	(Li et al., 2022)
48		1.80 μM (Ellman method)	1,2,3-triazole-linked compounds have high AChEI activity. The addition of a 1,2,3-triazole moiety to the iminochromene-2H-carboxamide derivative, on the other hand, resulted in beta-secretase (BACE1) inhibitory action.	(Rastegari et al., 2019)
49		8.0 nM	Fluorophenyl substitution at position 2 and 7-hydroxy substitution gives enhanced activity	(Singh et al., 2018)
50		8.2 nM	2-(3-Nitrophenyl) on chromene results in potential activity.	(Singh et al., 2018)
51		11.8 nM	2-(3,5-Dinitrophenyl)-chromene derivatives are also potential compounds but less active than monosubstituted.	(Singh et al., 2018)

4. Conclusion

The pyran scaffold has received much attention from researchers both from the pharmaceutical industry and academic organizations in the recent past. As evident from numerous cited papers, the pyran scaffold is the building block of various coumarins, xanthones, and flavonoids present in various natural plants. There is abundant evidence that the utilization of diversely substituted pyran analogues has provided the platform for the identification of new chemical entities that could be drug candidates with diverse biological properties. There are now just a handful of medications that have been given approval by the FDA for the treatment of AD, and the rate at which the disease is progressing is only growing. Therefore, there is a demand for the discovery of an anticancer drug that is both reliable and efficient. Following this, a number of structural alterations in pyran-based heterocycles are assessed, and their potential application in the treatment of neuroprotective disorders is presented. In this review, we have attempted to provide an overview of the various pyran-based drugs that are used in the treatment of AD. Pyran-based congeners

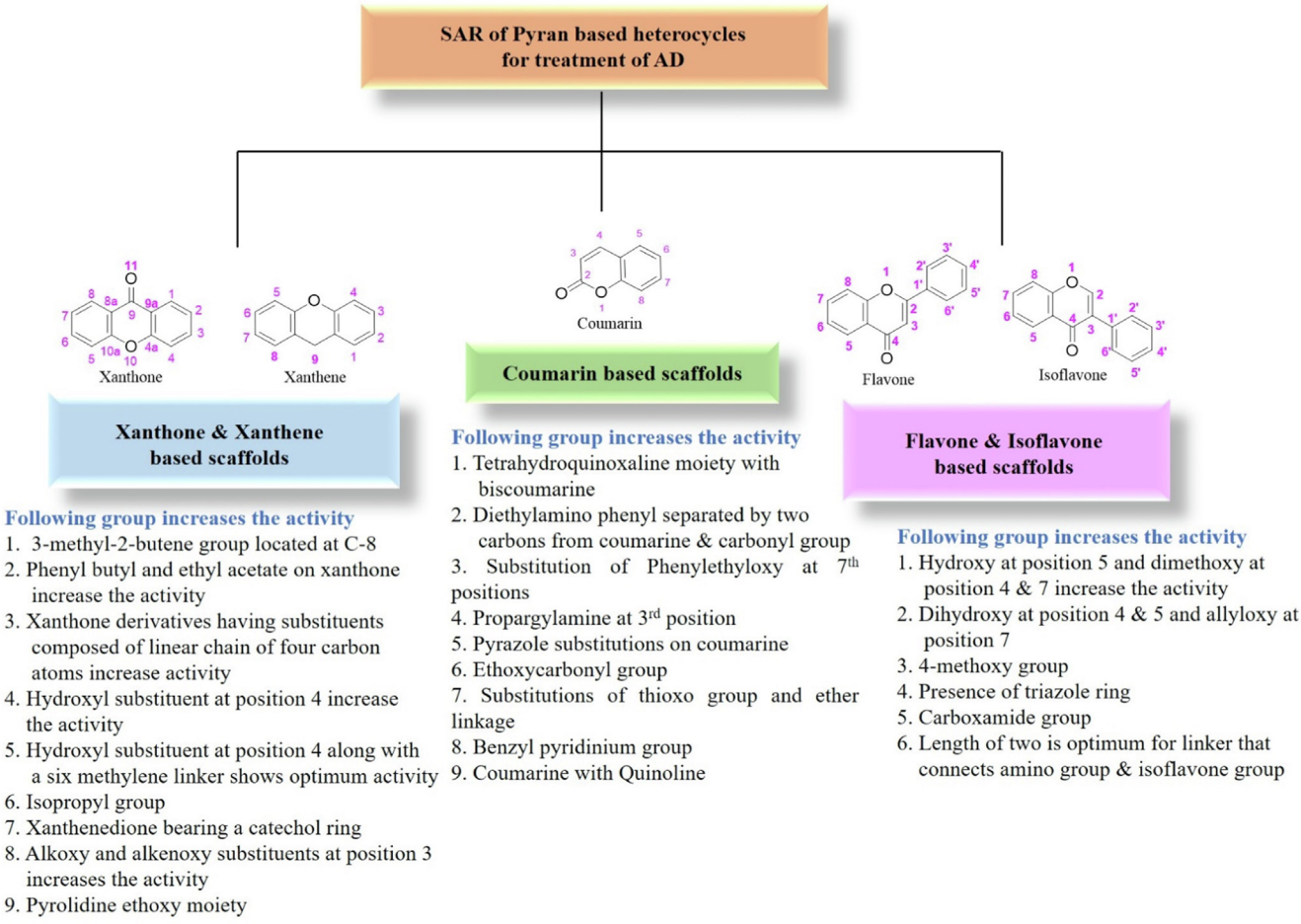


Fig. 9. SAR of Pyran based heterocycles for the treatment of AD.

were found to be active against both AChE and BuChE, and they were also discovered to have potential in AD. The docking and *in-vivo* outcomes of many investigations provided support for these studies. SAR investigations of pyran derivatives have aided in identifying essential structural properties crucial for anti-Alzheimer's action as well as providing insights into the design of more potent and effective molecules for the treatment of this disease.

5. Future perspectives

This review will give researchers with a comprehensive grasp of the pyran moiety, which will aid in the construction of a large number of prospective pyran compounds having a significant effect on treating AD. The SAR discussed in the paper will certainly help the researchers to develop more possible drugs for the treatment of AD. As in recent years, a large number of new and repurposed pyran-based molecules have been in clinical trials, so the researchers should critically analyse this moiety as a lead for developing future therapies for AD. Because Alzheimer's disease is multifactorial, researchers must consider pyran-based molecules that may have pleiotropic effects and target more than one factor.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgment

The author is immensely grateful to Umm Al-Qura University in Saudi Arabia for their unwavering support and providing the necessary resources that helped me successfully complete this work.

References

Abu-Aisheh, M.N., Al-Aboudi, A., Mustafa, M.S., El-Abadelah, M.M., Ali, S.Y., Ul-Haq, Z., Mubarak, M.S., 2019. Coumarin derivatives as acetyl- and butyrylcholinestrase inhibitors: An in vitro, molecular docking, and molecular dynamics simulations study. Heliyon 5, e01552.

Ahmad, N., Feyes, D.K., Nieminen, A.L., Agarwal, R., Mukhtar, H., 1997. Green Tea Constituent Epigallocatechin-3-Gallate and Induction of Apoptosis and Cell Cycle Arrest in Human Carcinoma Cells. JNCI J. Natl. Cancer Inst. 89, 1881–1886. https://doi.org/10.1093/JNCI/89.24.1881.

Ali, S.I., Venugopalan, V., 2021. Mosquito larvicidal potential of hydroxy-2-methyl-4H-pyran-4-one (MALTOL) isolated from the methanol root extract of Senecio laetus Edgew. and its in-silico study. Nat. Prod. Res. 35, 1741–1745. https://doi.org/10.1080/14786419.2019.1634712.

Alipour, M., Khoobi, M., Moradi, A., Nadri, H., Homayouni Moghadam, F., Emami, S., Hasanpour, Z., Foroumadi, A., Shafiee, A., 2014. Synthesis and anti-cholinesterase activity of new 7-hydroxycoumarin derivatives. Eur. J. Med. Chem. 82, 536–544. https://doi.org/10.1016/J.EJMECH.2014.05.056.

Andrade, S., Ramalho, M.J., Loureiro, J.A., Do Carmo Pereira, M., 2019. Natural Compounds for Alzheimer's Disease Therapy: A Systematic Review of Preclinical and Clinical Studies. Int. J. Mol. Sci. 20, 2313. https://doi.org/10.3390/IJMS20092313.

Ansari, M.A., Abdul, H.M., Joshi, G., Opii, W.O., Butterfield, D.A., 2009. Protective effect of quercetin in primary neurons against Aβ(1–42): relevance to Alzheimer's disease. J. Nutr. Biochem. 20, 269–275. https://doi.org/10.1016/J.JNUTBIO.2008.03.002.

Ary Ano, M.S., Hristopher Rnesto, C.E., Onald T Homas, R.G., Elville K Lauber, M.R., Imberly Chafer, K.S., Ichael Rundman, M.G., Eter Oodbury, P.W., Ohn Rowdon, J.

G., Arl C Otman, C.W., Ric Feiffer, E.P., S S Chneider, L.O., Eon T Hal, L.J., 1997. A Controlled Trial of Selegiline, Alpha-Tocopherol, or Both as Treatment for Alzheimer's Disease. N. Engl. J. Med. 336, 1216–1222. 10.1056/NEJM199704243361704.

Basha, S.J., Mohan, P., Yeggoni, D.P., Babu, Z.R., Kumar, P.B., Rao, A.D., Subramanyam, R., Damu, A.G., 2018. New Flavone-Cyanoacetamide Hybrids with a Combination of Cholinergic, Antioxidant, Modulation of β-Amyloid Aggregation, and Neuroprotection Properties as Innovative Multifunctional Therapeutic Candidates for Alzheimer's Disease and Unraveling Their Mechan. Mol. Pharm. 15, 2206–2223. https://doi.org/10.1021/ACS.MOLPHARMACEUT.8B00041/SUPPL_FILE/MP8B00041_SI_001.PDF.

Biasibetti, R., Tramontina, A.C., Costa, A.P., Dutra, M.F., Quincozes-Santos, A., Nardin, P., Bernardi, C.L., Wartchow, K.M., Lunardi, P.S., Gonçalves, C.A., 2013. Green tea (−)epigallocatechin-3-gallate reverses oxidative stress and reduces acetylcholinesterase activity in a streptozotocin-induced model of dementia. Behav. Brain Res. 236, 186–193. https://doi.org/10.1016/J.BBR.2012.08.039.

Bischoff, S.C., 2008. Quercetin: Potentials in the prevention and therapy of disease. Curr. Opin. Clin. Nutr. Metab. Care 11, 733–740. https://doi.org/10.1097/MCO.0B013E32831394B8.

Bui, T.T., Nguyen, T.H., 2017. Natural product for the treatment of Alzheimer's disease. J. Basic Clin. Physiol. Pharmacol. 28, 413–423. https://doi.org/10.1515/JBCPP-2016-0147.

Chang, X., Rong, C., Chen, Y., Yang, C., Hu, Q., Mo, Y., Zhang, C., Gu, X., Zhang, L., He, W., Cheng, S., Hou, X., Su, R., Liu, S., Dun, W., Wang, Q., Fang, S., 2015. (−)-Epigallocatechin-3-gallate attenuates cognitive deterioration in Alzheimer's disease model mice by upregulating neprilysin expression. Exp. Cell Res. 334, 136–145. https://doi.org/10.1016/J.YEXCR.2015.04.004.

Chen, J.J., Liao, H.R., Chen, K.S., Cheng, M.J., Shu, C.W., Sung, P.J., Lim, Y.P., Wang, T.C., Kuo, W.L., 2017. A New 2 H-Pyran-2-One Derivative and Anti-inflammatory Constituents of Alpinia zerumbet. Chem. Nat. Compd. 53, 40–43. https://doi.org/10.1007/s10600-017-1906-6.

Chiu, Y.J., Lin, T.H., Chen, C.M., Lin, C.H., Teng, Y.S., Lin, C.Y., Sun, Y.C., Hsieh-Li, H.M., Su, M.T., Lee-Chen, G.J., Lin, W., Chang, K.H., 2021. Novel Synthetic Coumarin-Chalcone Derivative (E)-3-(3-(4-(Dimethylamino)Phenyl)Acryloyl)-4-Hydroxy-2 H -Chromen-2-One Activates CREB-Mediated Neuroprotection in A β and Tau Cell Models of Alzheimer's Disease. Oxid. Med. Cell. Longev. 2021, Article ID 3058861 (Pages-19). 10.1155/2021/3058861.

Cruz, M.I., Cidade, H., Pinto, M., 2017. Dual/multitargeted xanthone derivatives for Alzheimer's disease: where do we stand? Future Med. Chem. 9, 1611–1630. https://doi.org/10.4155/FMC-2017-0086.

Defant, A., Mancini, I., Tomazzolli, R., Balzarini, J., 2015. Design, synthesis, and biological evaluation of novel 2H-pyran-2-one derivatives as potential HIV-1 reverse transcriptase inhibitors. Arch. Pharm. 348, 23–33. https://doi.org/10.1002/ardp.201400235.

Dysken, M.W., Sano, M., Asthana, S., Vertrees, J.E., Pallaki, M., Llorente, M., Love, S., Schellenberg, G.D., McCarten, J.R., Malphurs, J., Prieto, S., Chen, P., Loreck, D.J., Trapp, G., Bakshi, R.S., Mintzer, J.E., Heidebrink, J.L., Vidal-Cardona, A., Arroyo, L. M., Cruz, A.R., Zachariah, S., Kowall, N.W., Chopra, M.P., Craft, S., Thielke, S., Turvey, C.L., Woodman, C., Monnell, K.A., Gordon, K., Tomaska, J., Segal, Y., Peduzzi, P.N., Guarino, P.D., 2014. Effect of Vitamin E and Memantine on Functional Decline in Alzheimer Disease: The TEAM-AD VA Cooperative Randomized Trial. JAMA 311, 33–44. https://doi.org/10.1001/JAMA.2013.282834.

Feng, B., Li, X., Xia, J., Wu, S., 2017. Discovery of novel isoflavone derivatives as AChE/BuChE dual-targeted inhibitors: synthesis, biological evaluation and molecular modelling. J. Enzyme Inhib. Med. Chem. 32, 968–977. https://doi.org/10.1080/14756366.2017.1347163/SUPPL_FILE/IENZ_A_1347163_SM5073.PDF.

Fu, X., Zhang, J., Guo, L., Xu, Y., Sun, L., Wang, S., Feng, Y., Gou, L., Zhang, L., Liu, Y., 2014. Protective role of luteolin against cognitive dysfunction induced by chronic cerebral hypoperfusion in rats. Pharmacol. Biochem. Behav. 126, 122–130. https://doi.org/10.1016/J.PBB.2014.09.005.

Garkavtsev, I., Chauhan, V.P., Wong, H.K., Mukhopadhyay, A., Glicksman, M.A., Peterson, R.T., Jain, R.K., 2011. Dehydro-α-lapachone, a plant product with antivascular activity. Proc. Natl. Acad. Sci. 108, 11596–11601. https://doi.org/10.1073/PNAS.1104225108.

Ghai, R., Nagarajan, K., Arora, M., Grover, P., Ali, N., Kapoor, G., 2020. Current Strategies and Novel Drug Approaches for Alzheimer Disease. CNS Neurol. Disord. - Drug Targets 19, 676–690. https://doi.org/10.2174/1871527319666200717091513.

Grover, P., Bhardwaj, M., Mehta, L., Kapoor, G., Chawla, P.A., 2021. Current Developments in the Pyran-Based Analogues as Anticancer Agents. Anticancer. Agents Med. Chem. 22, 3239–3268. https://doi.org/10.2174/1871520621666211119090302.

Hamulakova, S., Kozurkova, M., Kuca, K., 2017. Coumarin Derivatives in Pharmacotherapy of Alzheimer's Disease. Curr. Org. Chem. 21, 602–612. https://doi.org/10.2174/1385272820666160601155411.

Hassan, N.A., Alshamari, A.K., Hassan, A.A., Elharrif, M.G., Alhajri, A.M., Sattam, M., Khattab, R.R., 2022. Advances on Therapeutic Strategies for Alzheimer's Disease: From Medicinal Plant to Nanotechnology. Molecules 27, 4839. https://doi.org/10.3390/MOLECULES27154839.

Hassan, M.Z., Osman, H., Ali, M.A., Ahsan, M.J., 2016. Therapeutic potential of coumarins as antiviral agents. Eur. J. Med. Chem. 123, 236–255. https://doi.org/10.1016/J.EJMECH.2016.07.056.

Hirbod, K., Jalili-Baleh, L., Nadri, H., Ebrahimi, S.E.S., Moradi, A., Pakseresht, B., Foroumadi, A., Shafiee, A., Khoobi, M., 2017. Coumarin derivatives bearing benzoheterocycle moiety: synthesis, cholinesterase inhibitory, and docking simulation study. Iran. J. Basic Med. Sci. 20, 631. https://doi.org/10.22038/IJBMS.2017.8830.

Hiremathad, A., Chand, K., Keri, R.S., 2018. Development of coumarin–benzofuran hybrids as versatile multitargeted compounds for the treatment of Alzheimer's Disease. Chem. Biol. Drug Des. 92, 1497–1503. https://doi.org/10.1111/CBDD.13316.

Hu, X., Liu, C., Wang, K., Zhao, L., Qiu, Y., Chen, H., Hu, J., Xu, J., 2022. Multifunctional Anti-Alzheimer's Disease Effects of Natural Xanthone Derivatives: A Primary Structure-Activity Evaluation. Front. Chem. 10,. https://doi.org/10.3389/FCHEM.2022.842208/FULL 842208.

Hu, Y.H., Yang, J., Zhang, Y., Liu, K.C., Liu, T., Sun, J., Wang, X.J., 2019. Synthesis and biological evaluation of 3-(4-aminophenyl)-coumarin derivatives as potential anti-Alzheimer's disease agents. J. Enzyme Inhib. Med. Chem. 34, 1083–1092. https://doi.org/10.1080/14756366.2019.1615484/SUPPL_FILE/IENZ_A_1615484_SM0118.PDF.

Huang, C.C., Chang, K.H., Chiu, Y.J., Chen, Y.R., Lung, T.H., Hsieh-Li, H.M., Su, M.T., Sun, Y.C., Chen, C.M., Lin, W., Lee-Chen, G.J., 2021. Multi-Target Effects of Novel Synthetic Coumarin Derivatives Protecting Aβ-GFP SH-SY5Y Cells against Aβ Toxicity. Cells 10, 3095. https://doi.org/10.3390/CELLS10113095.

Hwang, Y.J., Lee, E.J., Kim, H.R., Hwang, K.A., 2013. Molecular mechanisms of luteolin-7-O-glucoside-induced growth inhibition on human liver cancer cells: G2/M cell cycle arrest and caspase-independent apoptotic signaling pathways. BMB Rep. 46, 611. https://doi.org/10.5483/BMBREP.2013.46.12.133.

Jiménez-Aliaga, K., Bermejo-Bescós, P., Benedí, J., Martín-Aragón, S., 2011. Quercetin and rutin exhibit antiamyloidogenic and fibril-disaggregating effects in vitro and potent antioxidant activity in APPswe cells. Life Sci. 89, 939–945. https://doi.org/10.1016/J.LFS.2011.09.023.

Johnson, L.E., Dietz, A., 1968. Kalafungin, a New Antibiotic Produced by Streptomyces tanashiensis Strain Kala. Appl. Microbiol. 16, 1815–1821. https://doi.org/10.1128/AM.16.12.1815-1821.1968.

Karampuri, S., Ojha, D., Bag, P., Chakravarty, H., Bal, C., Chattopadhyay, D., Sharon, A., 2014. Anti-HSV activity and mode of action study of α-pyrone carboxamides. RSC Adv. 4, 17354–17363. https://doi.org/10.1039/C4RA01303D.

Karimi Askarani, H., Iraji, A., Rastegari, A., Abbas Bukhari, S.N., Firuzi, O., Akbarzadeh, T., Saeedi, M., 2020. Design and synthesis of multi-target directed 1,2,3-triazole-dimethylaminoacryloyl-chromenone derivatives with potential use in Alzheimer's disease. BMC Chem. 14, 1–13. https://doi.org/10.1186/S13065-020-00715-0/TABLES/3.

Konreddy, A.K., Toyama, M., Ito, W., Bal, C., Baba, M., Sharon, A., 2014. Synthesis and anti-HCV activity of 4-hydroxyamino α-pyranone carboxamide analogues. ACS Med. Chem. Lett. 5, 259–263. https://doi.org/10.1021/ml400432f.

Kou, X., Song, L., Wang, Y., Yu, Q., Ju, H., Yang, A., Shen, R., 2020. Design, synthesis and anti-Alzheimer's disease activity study of xanthone derivatives based on multi-target strategy. Bioorg. Med. Chem. Lett. 30,. https://doi.org/10.1016/J.BMCL.2019.126927 126927.

Kryscio, R.J., Abner, E.L., Caban-Holt, A., Lovell, M., Goodman, P., Darke, A.K., Yee, M., Crowley, J., Schmitt, F.A., 2017. Association of Antioxidant Supplement Use and Dementia in the Prevention of Alzheimer's Disease by Vitamin E and Selenium Trial (PREADViSE). JAMA Neurol. 74, 567–573. https://doi.org/10.1001/JAMANEUROL.2016.5778.

Kumar, D., Sharma, P., Singh, H., Nepali, K., Gupta, G.K., Jain, S.K., Ntie-Kang, F., 2017. The value of pyrans as anticancer scaffolds in medicinal chemistry. RSC Adv. 7, 36977–36999. https://doi.org/10.1039/C7RA05441F.

Kumar, S., Tyagi, Y.K., Kumar, M., Kumar, S., 2020. Synthesis of novel 4-methylthiocoumarin and comparison with conventional coumarin derivative as a multi-target-directed ligand in Alzheimer's disease. 3. Biotech 10, 1–19. https://doi.org/10.1007/S13205-020-02481-1/METRICS.

Lee, Y.J., Choi, D.Y., Yun, Y.P., Han, S.B., Oh, K.W., Hong, J.T., 2013. Epigallocatechin-3-gallate prevents systemic inflammation-induced memory deficiency and amyloidogenesis via its anti-neuroinflammatory properties. J. Nutr. Biochem. 24, 298–310. https://doi.org/10.1016/J.JNUTBIO.2012.06.011.

Lee, J.W., Lee, Y.K., Ban, J.O., Ha, T.Y., Yun, Y.P., Han, S.B., Oh, K.W., Hong, J.T., 2009. Green Tea (-)-Epigallocatechin-3-Gallate Inhibits β-Amyloid-Induced Cognitive Dysfunction through Modification of Secretase Activity via Inhibition of ERK and NF-κB Pathways in Mice. J. Nutr. 139, 1987–1993. https://doi.org/10.3945/JN.109.109785.

Lei, K., Li, P., Yang, X.F., Wang, S.B., Wang, X.K., Hua, X.W., Sun, B., Ji, L.S., Xu, X.H., 2019. Design and synthesis of novel 4-hydroxyl-3-(2-phenoxyacetyl)-pyran-2-one derivatives for use as herbicides and evaluation of their mode of action. J. Agric. Food Chem. 67, 10489–10497. https://doi.org/10.1021/acs.jafc.9b03109.

Li, R., Huang, Y.G., Fang, D., Le, W.D., 2004. (−)-Epigallocatechin gallate inhibits lipopolysaccharide-induced microglial activation and protects against inflammation-mediated dopaminergic neuronal injury. J. Neurosci. Res. 78, 723–731. https://doi.org/10.1002/JNR.20315.

Li, X., Jia, Y., Li, J., Zhang, P., Li, T., Lu, L., Yao, H., Liu, J., Zhu, Z., Xu, J., 2022. Novel and Potent Acetylcholinesterase Inhibitors for the Treatment of Alzheimer's Disease from Natural (±)-7,8-Dihydroxy-3-methyl-isochroman-4-one. Molecules 27, 3090. https://doi.org/10.3390/MOLECULES27103090/S1.

Liu, R., Meng, F., Zhang, L., Liu, A., Qin, H., Lan, X., Li, L., Du, G., 2011. Luteolin Isolated from the Medicinal Plant Elsholtzia rugulosa (Labiatae) Prevents Copper-Mediated Toxicity in β-Amyloid Precursor Protein Swedish Mutation Overexpressing SH-SY5Y Cells. Molecules 16, 2084–2096. https://doi.org/10.3390/MOLECULES16032084.

Loh, Z.H., Kwong, H.C., Lam, K.W., Teh, S.S., Ee, G.C.L., Quah, C.K., Ho, A.S.H., Mah, S. H., 2021. New 3-O-substituted xanthone derivatives as promising

acetylcholinesterase inhibitors. J. Enzyme Inhib. Med. Chem. 36, 627–639. https://doi.org/10.1080/14756366.2021.1882452/SUPPL_FILE/IENZ_A_1882452_SM7065.PDF.
Lopez-Lazaro, M., 2008. Distribution and Biological Activities of the Flavonoid Luteolin. Mini-Reviews Med. Chem. 9, 31–59. https://doi.org/10.2174/138955709787001712.
Malafaia, D., Oliveira, A., Fernandes, P.A., Ramos, M.J., Albuquerque, H.M.T., Silva, A. M.S., 2021. Chromeno[3,4-b]xanthones as first-in-class ache and aβ aggregation dual-inhibitors. Int. J. Mol. Sci. 22, 4145. https://doi.org/10.3390/IJMS22084145/S1.
Martins, P., Jesus, J., Santos, S., Raposo, L.R., Roma-Rodrigues, C., Baptista, P.V., Fernandes, A.R., 2015. Heterocyclic Anticancer Compounds: Recent Advances and the Paradigm Shift towards the Use of Nanomedicine's Tool Box. Molecules 20, 16852–16891. https://doi.org/10.3390/MOLECULES200916852.
Masamune, S., Castellucci, N.T., 1962. γ-Pyran. J. Am. Chem. Soc. 84, 2452–2453. https://doi.org/10.1021/ja00871a037.
McCord, R.S., Breinig, M.K., Morahan, P.S., 1976. Antiviral effect of pyran against systemic infection of mice with herpes simplex virus type 2. Antimicrob. Agents Chemother. 10, 28–33. https://doi.org/10.1128/AAC.10.1.28.
Menéndez, C.A., Biscussi, B., Accordino, S., Paula Murray, A., Gerbino, D.C., Appignanesi, G.A., 2017. Design, synthesis and biological evaluation of 1,3-dihydroxyxanthone derivatives: Effective agents against acetylcholinesterase. Bioorg. Chem. 75, 201–209. https://doi.org/10.1016/J.BIOORG.2017.09.012.
Miean, K.H., Mohamed, S., 2001. Flavonoid (Myricetin, Quercetin, Kaempferol, Luteolin, and Apigenin) Content of Edible Tropical Plants. J. Agric. Food Chem. 49, 3106–3112. https://doi.org/10.1021/JF000892M.
Moreno, L.C.G.E.I., Puerta, E., Suárez-Santiago, J.E., Santos-Magalhães, N.S., Ramirez, M.J., Irache, J.M., 2017. Effect of the oral administration of nanoencapsulated quercetin on a mouse model of Alzheimer's disease. Int. J. Pharm. 517, 50–57. https://doi.org/10.1016/J.IJPHARM.2016.11.061.
Mzezewa, S.C., Omoruyi, S.I., Zondagh, L.S., Malan, S.F., Ekpo, O.E., Joubert, J., 2021. Design, synthesis, and evaluation of 3,7-substituted coumarin derivatives as multifunctional Alzheimer's disease agents. J. Enzyme Inhib. Med. Chem. 36, 1607–1621. https://doi.org/10.1080/14756366.2021.1913137.
Narayanan, S.E., Narayanan, H., Mukundan, M., Balan, S., Vishnupriya, C.P., Gopinathan, A., Rajamma, R.G., Marathakam, A., 2021. Design, synthesis and biological evaluation of substituted pyrazoles endowed with brominated 4-methyl 7-hydroxy coumarin as new scaffolds against Alzheimer's disease. Futur. J. Pharm. Sci. 7, 1–10. https://doi.org/10.1186/S43094-021-00278-4.
Nazari, P., Bazi, A., Ayatollahi, S.A., Dolati, H., Mahdavi, S.M., Rafighdoost, L., Amirmostofian, M., 2017. Synthesis and evaluation of the antimicrobial activity of spiro-4h-pyran derivatives on some Gram positive and Gram negative bacteria. Iran J Pharm Res. 16, 943–952.
Ossola, B., Kääriäinen, T.M., Männistö, P.T., 2009. The multiple faces of quercetin in neuroprotection. Expert Opin Drug Saf 8, 397–409. https://doi.org/10.1517/14740330903026944.
Park, J., 2015. Mortality from Alzheimer's disease in Canada: A multiple-cause-of-death analysis Mortality from Alzheimer's disease in Canada: A multiple-cause-of-death analysis, 2004 to 2011. Stat. Canada 27, 17–21.
Petersen, R.C., Thomas, R.G., Grundman, M., Bennett, D., Doody, R., Ferris, S., Galasko, D., Jin, S., Kaye, J., Levey, A., Pfeiffer, E., Sano, M., van Dyck, C.H., Thal, L.J., 2005. Study questions effectiveness of Alzheimer's drug. Nat. Rev. Drug Discov. 4, 361. https://doi.org/10.1056/NEJMOA050151/SUPPL_FILE/NEJMOA050151SA1.PDF.
Qin, J., Lan, W., Liu, Z., Huang, J., Tang, H., Wang, H., 2013. Synthesis and biological evaluation of 1, 3-dihydroxyxanthone mannich base derivatives as anticholinesterase agents. Chem. Cent. J. 7, 1–11. https://doi.org/10.1186/1752-153X-7-78/FIGURES/6.
Rastegari, A., Nadri, H., Mahdavi, M., Moradi, A., Mirfazli, S.S., Edraki, N., Moghadam, F.H., Larijani, B., Akbarzadeh, T., Saeedi, M., 2019. Design, synthesis and anti-Alzheimer's activity of novel 1,2,3-triazole-chromenone carboxamide derivatives. Bioorg. Chem. 83, 391–401. https://doi.org/10.1016/J.BIOORG.2018.10.065.
Russo, M., Spagnuolo, C., Tedesco, I., Bilotto, S., Russo, G.L., 2012. The flavonoid quercetin in disease prevention and therapy: Facts and fancies. Biochem. Pharmacol. 83, 6–15. https://doi.org/10.1016/J.BCP.2011.08.010.
Seca, A.M.L., Leal, S.B., Pinto, D.C.G.A., Barreto, M.C., Silva, A.M.S., 2014. Xanthenedione Derivatives, New Promising Antioxidant and Acetylcholinesterase Inhibitor Agents. Molecules 19, 8317–8333. https://doi.org/10.3390/MOLECULES19068317.
Seelinger, G., Merfort, I., Schempp, C.M., 2008. Anti-oxidant, anti-inflammatory and anti-allergic activities of luteolin. Planta Med. 74, 1667–1677. https://doi.org/10.1055/S-0028-1088314/ID/4.
Shi, S., Wang, H., Wang, J., Wang, Y., Xue, X., Hou, Z., Yao, G.D., Huang, X.X., Zhao, H., Liu, Q., Song, S.J., 2020. Semi-synthesis and biological evaluation of flavone hybrids as multifunctional agents for the potential treatment of Alzheimer's disease. Bioorg. Chem. 100,. https://doi.org/10.1016/J.BIOORG.2020.103917 103917.
Singh, M., Kaur, M., Vyas, B., Silakari, O., 2018. Design, synthesis and biological evaluation of 2-Phenyl-4H-chromen-4-one derivatives as polyfunctional compounds against Alzheimer's disease. Med. Chem. Res. 27, 520–530. https://doi.org/10.1007/S00044-017-2078-4/METRICS.
Sung, S., Yao, Y., Uryu, K., Yang, H., Lee, V.M.Y., Trojanowski, J.Q., Praticò, D., 2004. Early vitamin E supplementation in young but not aged mice reduces Abeta levels and amyloid deposition in a transgenic model of Alzheimer's disease. FASEB J. 18, 323–325. https://doi.org/10.1096/FJ.03-0961FJE.
Tran, T.H., Vo, T.T.H., Vo, T.Q.N., Cao, T.C.N., Tran, T.S., 2021. Synthesis and Evaluation of the Acetylcholinesterase Inhibitory Activities of Some Flavonoids Derived from Naringenin. Sci. World J. 2021, 4817900. https://doi.org/10.1155/2021/4817900.
Turhan, K., Pektaş, B., Türkan, F., Tuğcu, F.T., Turgut, Z., Taslimi, P., Karaman, H.S., Gulcin, I., 2020. Novel benzo[b]xanthene derivatives: Bismuth(III) triflate-catalyzed one-pot synthesis, characterization, and acetylcholinesterase, glutathione S-transferase, and butyrylcholinesterase inhibitory properties. Arch. Pharm. (Weinheim). 353, 2000030. https://doi.org/10.1002/ARDP.202000030.
Van Cauwenberghe, C., Van Broeckhoven, C., Sleegers, K., 2015. The genetic landscape of Alzheimer disease: clinical implications and perspectives. Genet. Med. 18, 421–430. https://doi.org/10.1038/gim.2015.117.
Vanessa, V.V., Teh, S.S., Lam, K.W., Mah, S.H., 2022. Synthesis of 1-hydroxy-3-O-substituted xanthone derivatives and their structure-activity relationship on acetylcholinesterase inhibitory effect. Nat. Prod. Res. 1–13. https://doi.org/10.1080/14786419.2022.2137800.
Varikasuvu, S.R., Prasad, V.S., Kothapalli, J., Manne, M., 2019. Brain Selenium in Alzheimer's Disease (BRAIN SEAD Study): a Systematic Review and Meta-Analysis. Biol. Trace Elem. Res. 189, 361–369. https://doi.org/10.1007/S12011-018-1492-X/METRICS.
Wang, H., Wang, H., Cheng, H., Che, Z., 2016. Ameliorating effect of luteolin on memory impairment in an Alzheimer's disease model. Mol. Med. Rep. 13, 4215–4220. https://doi.org/10.3892/MMR.2016.5052/HTML.
Yang, A., Yu, Q., Ju, H., Song, L., Kou, X., Shen, R., 2020. Design, Synthesis and Biological Evaluation of Xanthone Derivatives for Possible Treatment of Alzheimer's Disease Based on Multi-Target Strategy. Chem. Biodivers. 17, e2000442.
Youdim, M.B.H., Edmondson, D., Tipton, K.F., 2006. The therapeutic potential of monoamine oxidase inhibitors. Nat. Rev. Neurosci. 2006 74 7, 295–309. 10.1038/nrn1883.
Zare-Akbari, Z., Edjali, L., Eshaghi, M., 2022. Synthesis of Novel Bis-Coumarin Derivatives as Potential Acetylcholinesterase Inhibitors: An In Vitro, Molecular Docking, and Molecular Dynamics Simulations Study. Pharm. Biomed. Res. 8, 131–142. https://doi.org/10.18502/PBR.V8I2.11027.
Zhang, Z., Guo, J., Cheng, M., Zhou, W., Wan, Y., Wang, R., Fang, Y., Jin, Y., Liu, J., Xie, S. S., 2021. Design, synthesis, and biological evaluation of novel xanthone-alkylbenzylamine hybrids as multifunctional agents for the treatment of Alzheimer's disease. Eur. J. Med. Chem. 213,. https://doi.org/10.1016/J.EJMECH.2021.113154 113154.
Zhang, Y., Ye, Q., Ponomareva, L.V., Cao, Y., Liu, Y., Cui, Z., Van Lanen, S.G., Voss, S.R., She, Q.B., Thorson, J.S., 2019. Total synthesis of griseusins and elucidation of the griseusin mechanism of action. Chem. Sci. 10, 7641–7648. https://doi.org/10.1039/C9SC02289A.
Zhou, F., Chen, S., Xiong, J., Li, Y., Qu, L., 2012. Luteolin reduces zinc-induced tau phosphorylation at Ser262/356 in an ROS-dependent manner in SH-SY5Y cells. Biol. Trace Elem. Res. 149, 273–279. https://doi.org/10.1007/S12011-012-9411-Z/METRICS.