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# Recent advancements in chromone as a privileged scaffold towards the development of small molecules for neurodegenerative therapeutics

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Neurodegenerative disorders, *i.e.*, Alzheimer's or Parkinson's disease, involve progressive degeneration of the central nervous system, resulting in memory loss and cognitive impairment. The intensification of neurodegenerative research in recent years put some molecules into clinical trials, but still there is an urgent need to develop effective therapeutic molecules to combat these diseases. Chromone is a well-identified privileged structure for the design of well-diversified therapeutic molecules of potential pharmacological interest, particularly in the field of neurodegeneration. In this short review, we focused on the recent advancements and developments of chromones for neurodegenerative therapeutics. Different small molecules were reviewed as multi-target-directed ligands (MTDLs) with potential inhibition of AChE, BuChE, MAO-A, MAO-B, Aβ plaque formation and aggregation. Recently developed MTDLs emphasized that the chromone scaffold has the potential to develop new molecules for the treatment of neurodegenerative diseases.

## 1. Introduction

Neurodegenerative disease is a broad term that can be defined as a group of disorders principally related to the neurons in the human brain.[1] In general, these disorders could be understood as the progressive degeneration of the structure and function of the central nervous system or peripheral nervous system, also denoted as age-dependent disorders.[2–4] Neurons are the building blocks of the nervous system which normally do not replicate or replace themselves;[5] therefore, damage or death of neurons results in some memory and cognitive impairments in humans, while in some cases it affects a person's ability to move, speak and breathe.[6] The most common neurodegenerative diseases are Alzheimer's disease (AD),[7] Parkinson's disease (PD),[8] and Huntington's disease along with other disorders such as prion disease, amyotrophic lateral sclerosis (ALS),[9] motor neuron diseases (MNDs),[10] frontotemporal dementia,[11] spinal muscular atrophy (SMA), and spinocerebellar ataxia (SCA).[12] In 2020, the World Health Organization (WHO)[13] estimated that around 50 million people have dementia worldwide with an increase of nearly 10 million new cases every year. The WHO reported that AD may contribute to nearly 60–70% of cases of dementia.

Presently, the available treatments may help relieve some of the physical or mental symptoms associated but no effective treatment is available to cure neurodegenerative diseases or to slow the progression of these diseases,[6,14,15] although several studies of new treatments are being investigated in various stages of clinical trials. However, effective treatments are desperately needed to support and improve the lives of people with dementia and their carers and families. As related to medicinal chemistry, several studies were reported on the development of new inhibitors of known biological targets related to neurodegenerative diseases, such as acetylcholinesterase (AChE),[16,17] butyrylcholinesterase (BuChE),[18] glycogen synthase kinase 3 beta (GSK3β),[19] monoamine oxidase A and B (MAO-A and MAO-B),[20] plasma membrane redox enzymes,[21] *etc.*, and disaggregation of misfolded proteins,[22,23] *i.e.*, τ-protein,[24,25] amyloid-β (Aβ),[26,27] TAR DNA binding protein 43 (TDP-43),[28] α-synuclein,[29,30] *etc.*, using small therapeutic molecules. Most of the small molecules were synthesized using privileged scaffolds of medicinal importance such as pyrimidine,[31] pyrazine,[32] acridine,[33] triazolopyrimidine,[34,35] triazene,[36] coumarin,[37] chromones, *etc.*

Chromones (4*H*-chromen-4-one, 4*H*-1-benzopyran-4-one, or benzo-γ-pyrone) are a large class of heterocyclic

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compounds that are ubiquitous in nature, especially in plants.[38] The term chromone indicates its characteristic and is derived from the Greek word chroma, meaning "color", because several chromones exhibit a variety of colors.[39] The chromone moiety is the main scaffold of numerous flavonoids, such as flavones and isoflavones.[40,41] From a chemistry perspective, the chromone scaffold represents itself as a privileged core domain that permits unlimited structural diversifications to develop chromone-based drug candidates. Due to their synthetic accessibility and structural diversity, these compounds particularly attracted the interest of medicinal chemists to develop new molecules of medicinal interest. Chromones exhibit a wide range of biological activities such as anti-allergic,[42] anti-inflammatory,[43,44] anti-diabetic,[45] antitumor, antimicrobial, *etc.*[46] Chromone-based FDA-approved cromoglicic acid is widely used for long-term management of bronchial asthma by acting as a mast cell stabilizer,[47] while other chromone-based drugs such as disodium cromoglycate (DSGC) and pranlukast (Fig. 1) are used for the treatment of mild to moderate asthma and allergic rhinitis, respectively.[41]

Among these biological activities, chromones are also important for neurodegenerative diseases (Fig. 2), *i.e.*, inhibitory activities related to MOA, AChE, Aβ fibril formation, neuroprotection,[48–50] neurogenesis properties,[51,52] *etc.*

In fact, an old dogma that neurons cannot generate or be replaced after birth has now been questioned during the past decades. Neurogenesis is the progression of the neurons and nervous system cells by neural stem cells (NSCs) which are found in all species of animals excluding placozoans and *Porifera* (sponges).[53] Immunohistochemistry enables researchers to validate the generation of neurons by using bromodeoxyuridine (BrdU), an analog of thymidine that binds DNA in the S-phase in the brain of all adult mammals including humans.[54] Neurogenesis continues in specific brain regions of adult mammals, known as neurogenic niches, which are extremely dynamic and are controlled by several physiological stimuli and pathological states.[55] These two neurogenic niches are defined as the subventricular zone (SVZ) of the lateral ventricle and the subgranular zone (SGZ) of the dentate gyrus (DG) where NSCs proliferate, divide and differentiate into mature neurons. Recent studies indicated that adult neurogenesis could also occur in other areas of the brain along with the ventricular system, mostly in pathological conditions.[56] A natural chromone baicalin **3**, isolated from the root of *Scutellaria baicalensis*, found the ability to promote neuron differentiation of neural stem/progenitor cells (NSPCs) and stimulate neurogenesis, which also makes chromone a privileged scaffold for developing clinically relevant small molecules to manipulate NSPCs for brain repair.[57–60]

So far, the chromone scaffold has been reviewed by Gaspar *et al.*[40] in detail for a medicinal chemistry perspective in 2014 and updated by Reis *et al.*[41] in 2017; still, a focused literature review related to the recent exploration of chromones in the area of neurodegenerative disease is missing. Hence, the purpose of this short review is to analyze and summarize the recent work in the last five years related to chromones to look at their potential therapeutic application in medicinal chemistry to develop new anti-neurodegenerative agents. In addition, we have also summarized the synthetic strategies of the reported chromone derivatives.

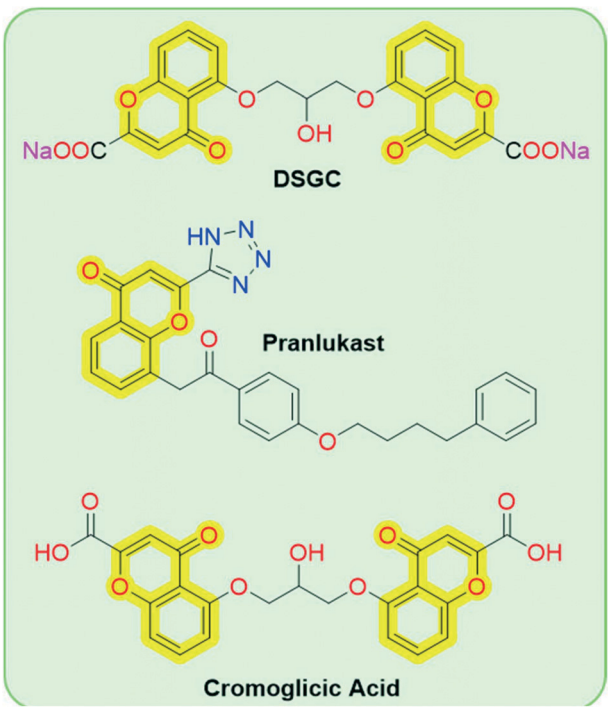



**Fig. 1** Chemical structures of chromone-based drugs.

## 2. Chromones with anti-neurodegenerative properties

Chromones with remarkable anti-neurodegenerative properties and that act in numerous ways such as having inhibitory activity against AChE, BuChE, MOA, Aβ aggregation, and having neuroprotection activities have recently been explored. By moving through different pieces of literature, several studies were found related to the development and isolation of natural and synthetic chromones for the treatment of neurodegenerative diseases. In this section, we have tried to put all studies of natural and synthetic chromones related to the neurodegenerative therapeutics reported in the last five years under the umbrella.

### 2.1. Natural chromones

As we discussed, chromones originated from nature; therefore researchers working on natural products continuously try to identify and isolate new chromones from natural sources. For this, recently Kittisrisopit *et al.*[48]

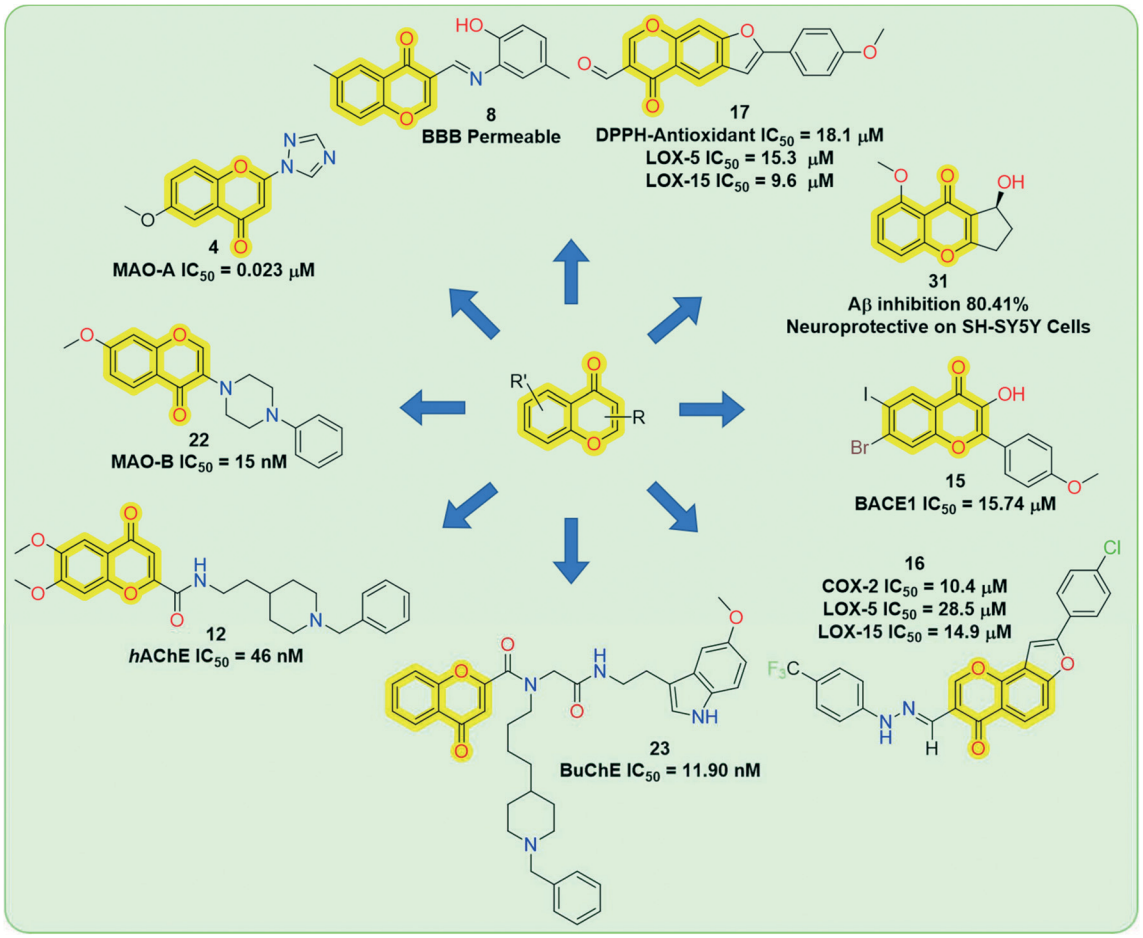



Fig. 2 General structure of the chromone scaffold and its activities for different biological targets for neurodegenerative therapeutics.

identified and isolated nine new chromone analogs **1**(**a**–**i**) from the soil actinomycete *Microbispora* sp. TBRC6027 as shown in Fig. 3.

The authors established the chemical structures of the isolated chromones through NMR spectroscopy methods and examined their neuroprotective activity *in vitro* using P19-derived neurons. The reported results indicated that most of the compounds showed neuron viability against oxidative stress at the concentration of 1 ng $mL^{-1}$ with a %viability of 44–53% without any significant neurotoxicity. The study suggested that the reported chromone analogs may be used as a model in designing potential neuroprotective agents. Another study of do Nascimento *et al.*[61] also contributed towards the identification and isolation of a new unusual *C*-glycoside chromone from the crude methanolic extract of *Macrolobium latifolium*, named macrolobin **2**, shown in Fig. 3. The authors used $^{1}H$, $^{13}C$, heteronuclear single quantum coherence (HSQC), and heteronuclear multiple-bond coherence (HMBC) NMR spectroscopy along with IR and mass spectrometry to establish the chemical structure of the isolated phytochemicals. The study indicated that macrolobin displayed significant inhibitory activity against AChE with an $IC_{50}$ value of 0.8 μM along with some antimicrobial activity. The results suggested that further structural modification in **2** may turn it into a good inhibitor of AChE for the treatment of Alzheimer's disease. Recently, He *et al.*[62] isolated two chromones, **3** and **4**, from the resinous heartwood of *Aquilaria sinensis* (Thymelaeaceae) (Fig. 3) and evaluated them for their neuroprotective activities using models of BACE1 inhibition and PC12 cells with corticosterone- and 1-methyl-4-phenylpyridine ion ($MPP^{+}$)-induced damage. Kim *et al.*[63] analyzed the anti-oxidative and anti-inflammatory response of natural chromone capillarisin **5** (Fig. 3) by activating Nrf2/HO-1 signaling in neuroblastoma SHSY5Y cells and microglial BV2 cells. The authors reported that **5** leads to Nrf2 phosphorylation, upregulation of downstream molecules such as heme oxygenase-1 (HO-1) and NAD(P)H: quinone oxidoreductase 1, and subsequent activation of antioxidant response element (ARE)-mediated transcription. The study indicated that **5** possessed inflammatory responses in lipopolysaccharide-treated BV2 cells and protects SH-SY5Y cells from induced oxidative stress. The authors discussed that chromone **5** induces the activation of c-Jun N-terminal kinase in SH-SY5Y and BV2 cells which lead to the phosphorylation of Nrf2 and HO-1 upregulation.

Hiep *et al.*[64] isolated ten new isoflavones along with some known isoflavones from the extract of fruits of *Cudrania tricuspidata* and analyzed their neuroprotective effect against

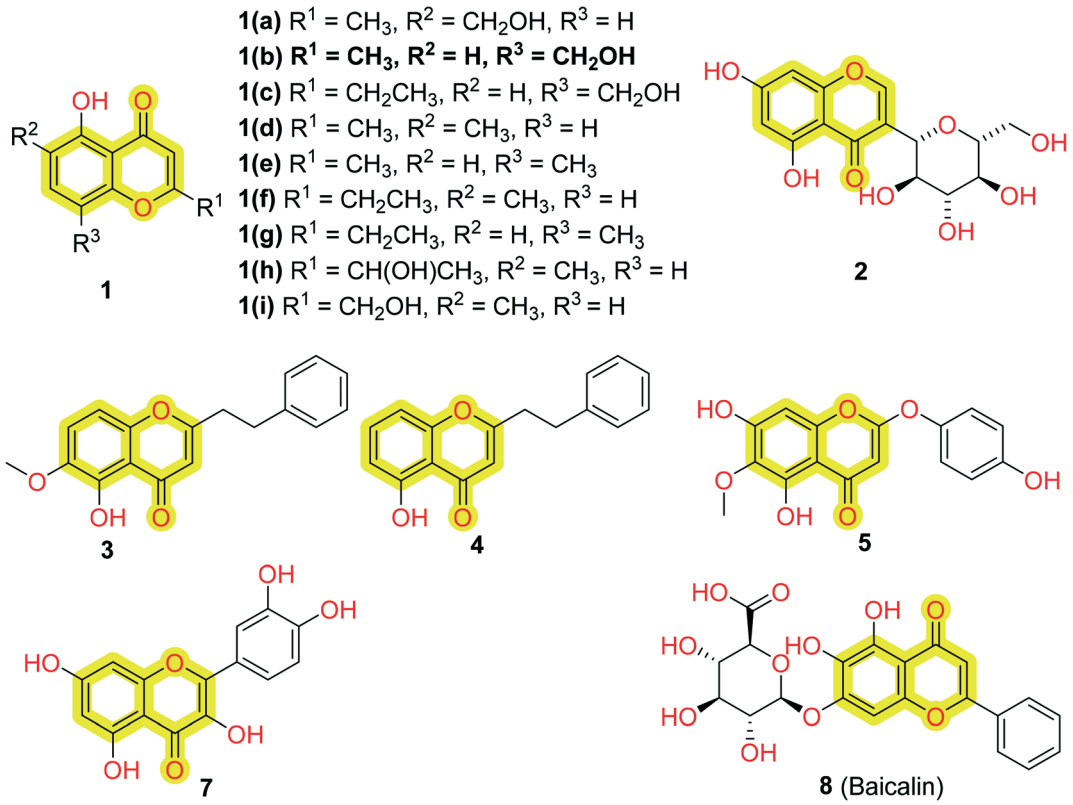
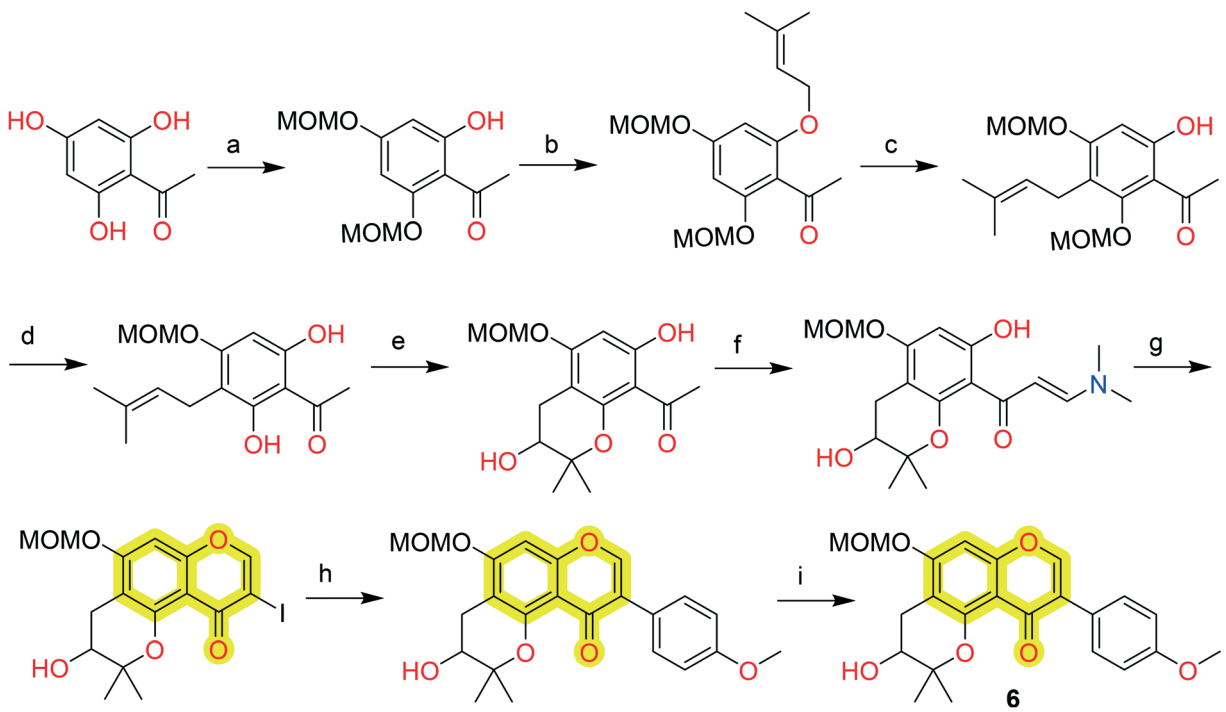



**Fig. 3** Chemical structure of natural chromone analogs **1** isolated from the soil actinomycete *Microbispora* sp. TBRC6027, macrolobin **2** from *Macrolobium latifolium*, **3**, **4**, **5**, **7**, and baicalin **8**.




**Scheme 1** Total synthesis of the natural chromone **6**. Reagents and conditions: (a) MOMCl, DIPEA, DCM, 0 °C to room temperature (rt); (b) prenyl bromide, $K_2CO_3$, acetone, reflux; (c) *N*,*N*-diethylaniline, microwave; (d) 2N HCl, DCM, MeOH; (e) *m*-CPBA, M-K10, DCM; (f) DMF-DMA, reflux; (g) $I_2$, MeOH, rt; (h) 4-methoxyphenylboronic acid, $Pd(OAc)_2$, $K_2CO_3$, PEG-400; and (i) 3N HCl, DCM, MeOH, reflux.

6-hydroxydopamine-induced cell death in human neuroblastoma SH-SY5Y cells. The study came out with the most potent compound **6** with an $EC_{50}$ value of 0.5 μM for human neuroblastoma SH-SY5Y cells. Later, Lu *et al.*[65] reported the total synthesis of compound **6** using Claisen rearrangement and Suzuki coupling reaction as the key steps that are discussed in Scheme 1. They utilized a modified Mosher's method to elucidate the absolute configuration of naturally occurring chromone **6**. A natural chromone, quercetin **7** (Fig. 3), also has been reviewed for its neuroprotective, MAO, and AChE inhibition properties.[66,67]

Interesting studies were found in the literature discussing the critical role of a natural chromone baicalin **8** (Fig. 3) to promote NSPCs toward neuronal differentiation[68] and prevent depressive-like behaviors in a chronic mild stress (CMS) animal model.[69] A study by Zhang *et al.*[70] highlighted that **8** promotes hippocampal neurogenesis *via* SGK1- and FKBP5-mediated glucocorticoid receptor phosphorylation in a neuroendocrine mouse model of anxiety/depression. Gao *et al.*[71] highlighted that **8** promotes neurogenesis through modulating APPL2/glucocorticoid receptor signaling cascade and reduced emotional and olfactory dysfunctions in chronic corticosterone-induced depression. Another study highlighted that **8** inhibits activation of the GSK3β/NF-κB/NLRP3 signal pathway and shows remarkable neuroprotective effects in a rat model of depression.[72] Zhang *et al.*[73] explored that **8** was able to promote neuronal differentiation and survival through the Akt/FOXG1 pathway and could reverse the reduction of *p*-Akt, FOXG1, and FGF2 caused by chronic unpredictable mild stress (CUMS)-induced depression; it was also supported by the study of Fang *et al.*[74] Recent studies highlighted that **8** acts through several pathways such as the BDNF/ERK/CREB signaling pathway,[75] Wnt/β-catenin pathway,[76] and activation of TLR4/MYD88/caspase-3 pathway[77] to improve cognitive dysfunctions induced by CUMS and promotes neurogenesis in an animal model of depression. Recently, Li *et al.*[78] explored **8** to analyze its antiepileptic effects and found that it exhibited a significant antiepileptic effect by regulating astrocyte phenotype to maintain systemic homeostasis. The authors reported that **8** suppresses neuron autophagy and apoptosis in pentylenetetrazol-induced epileptic rats and PC12 cells. These results highlighted the importance of chromones in neurogenesis and it could be a prominent template to develop new molecules for neurogenesis by targeting different pathways.

### 2.2. Synthetic chromones

Synthetic chromones attracted medicinal chemists due to the widespread possibilities for the design and development of new therapeutic small molecules of structural versatility with suitable different biological properties. As evidenced from the literature, structurally versatile chromone derivatives were explored for their biological activities such as anti-neurodegenerative, anti-allergic, anti-inflammatory, anti-diabetic, antitumor, antimicrobial, *etc.* in the past decade. Accordingly, this review will report only chromones including the data related to anti-neurodegenerative activity and described for the first time in the last 5 years along with their synthetic route.

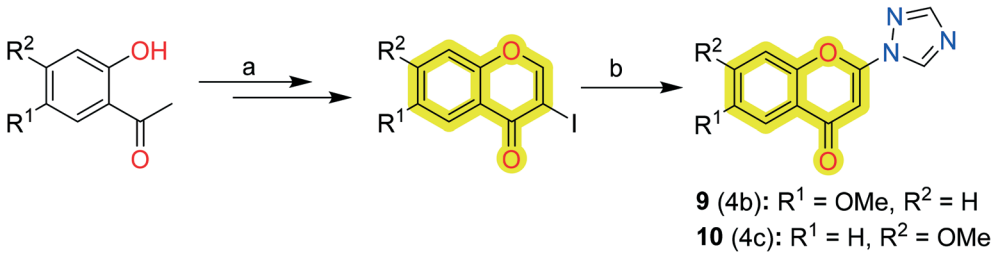
Towards the development of new potent chromone-based inhibitors of MAO-A and MAO-B for the treatment of neurodegenerative diseases, Takao *et al.*[79] reported a series of 2-azolylchromone derivatives with their respective inhibitory activities, shown in Scheme 2. The study indicated that the derivatives showed potent inhibitory activities against MAO-A with an $IC_{50}$ value of 0.023–0.32 μM with the most potent compound **9**, while against MAO-B, the $IC_{50}$ value was reported to be 0.019–0.73 μM with the most potent compound **10**. The authors suggested that 6-methoxy substitution was good for MAO-A inhibition, and 7-methoxy substitution was feasible for inhibition of MAO-B. The study highlights the importance of 2-triazolylchromone in designing new MAO inhibitors.

Wang *et al.*[80] reported a series of structurally diverse benzyloxy substituted small molecules towards monoamine oxidase inhibition as anti-neurodegenerative agents. The study included the MAO-A and MAO-B inhibition data and neuroprotective effects investigated in 6-OHDA- and rotenone neurotoxin-treated PC12 cells. The results indicated that most of the compounds of the study exhibited potent inhibition activity against the MAO enzyme and an increase in the survival of PC12 cells treated with neurotoxins. The chromone-based compound **11** (Scheme 3) was reported with an $IC_{50}$ value of 15.62 nM and 13.61 μM for MAO-B and MAO-A, respectively. Compound **11** shows 115% and 106% survival of 6-OHDA- and rotenone neurotoxin-treated PC12 cells. The results highlighted the importance of the chromone scaffold for the development of therapeutic molecules for Parkinson's disease.

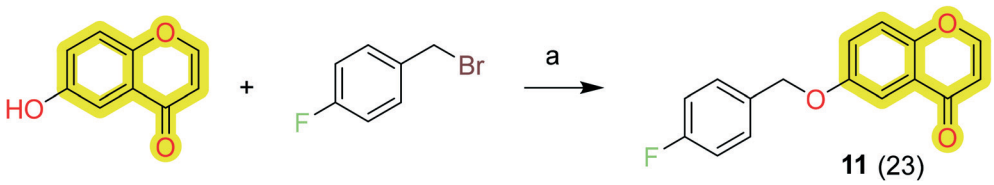
Further, Reis *et al.*[81] synthesized and biologically evaluated chromone-based MAO-B inhibitors by following the lead optimization approach. The results highlighted that the compound *N*-(3′,4′-dimethylphenyl)-4-oxo-4*H*-chromene-3-carboxamide **12** (Scheme 4) was the most potent against MAO-B with an $IC_{50}$ value of 0.67 nM that was acting as a non-competitive reversible inhibitor. The authors discussed that the amide spacer and the direct linkage of the carbonyl group to the γ-pyrone ring along with the presence of *meta* and *para* substituents in the exocyclic ring were highly important for its improved biological activities. Compound **12** also possessed a favorable toxicological profile and physicochemical properties that pointed toward BBB permeability; thus the authors suggested it as a valid candidate for subsequent animal studies.

Jia *et al.*[82] explored flavone-based MAO inhibitors with structural versatility by retaining the core chromone scaffold using click chemistry (CuAAC reaction) between 6-$N_3$-2-phenyl chromones and alkynes, shown in Scheme 5. The study indicated that compound **13** was the best compound with inhibitory activity $IC_{50}$ = 1.6 μm for MAO-A and 2.1 μm

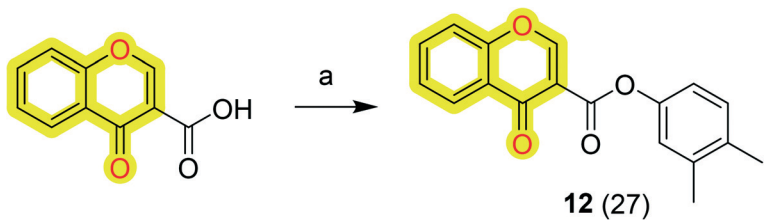
 



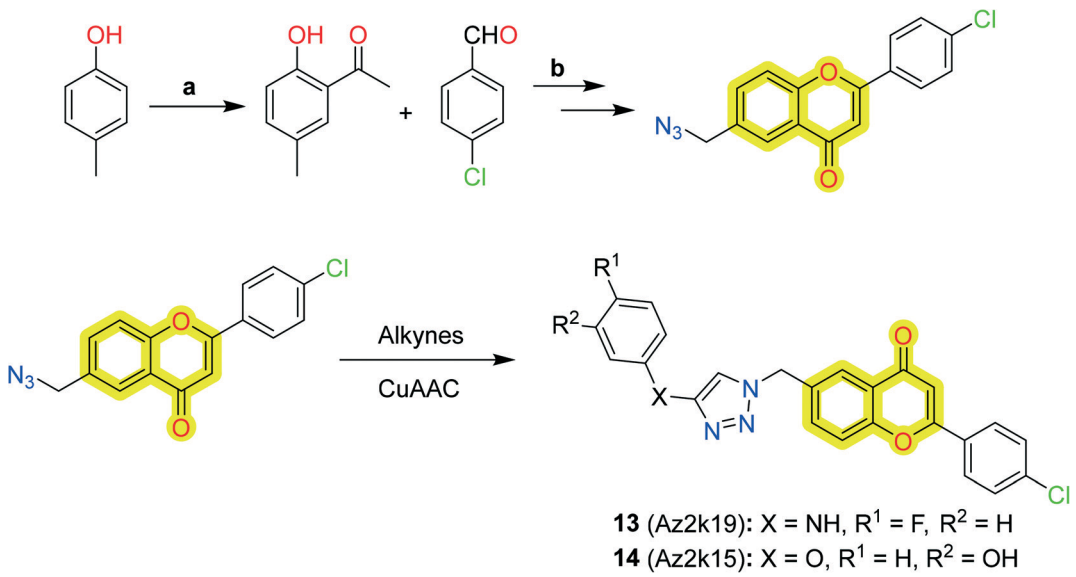

**Scheme 2** Synthetic protocol for the 2-azolylchromone derivatives. Reagents and conditions: (a) (i) DMF-DMA, 95 °C, (ii) pyridine, $I_2$, $CHCl_3$; (b) azole, $K_2CO_3$, DMF, 80 °C.




**Scheme 3** Synthesis of compound **11**. Reagents and conditions: (a) $K_2CO_3$, acetonitrile, reflux, 8 h.



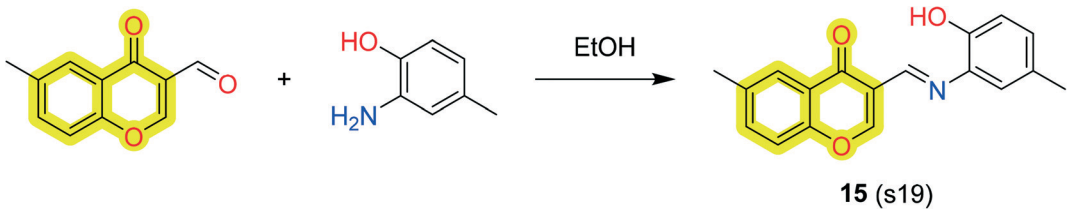

**Scheme 4** Synthetic route for compound **12**. Reagents and conditions: (a) $POCl_3$, DMF, *N*-methylaniline, rt, 1–5 h.




**Scheme 5** Synthesis of flavone-based MAO inhibitors using click chemistry (CuAAC reaction). Reagents and conditions: (a) 1. $CH_3COCl$, pyridine; 2. $AlCl_3$, 130 °C; (b) 1. $Ba(OH)_2$, EtOH; 2. $I_2$, DMSO, 130 °C; 3. NBS, BPO, $CCl_4$, reflux; 4. $NaN_3$, DMF.

for MAO-B, while the compound with better selectivity (SI >14.0) towards MAO-B was **14.** The study will be helpful in designing new MAO inhibitors from C6 substitution of flavone derivatives for the treatment of neurodegenerative diseases.

Li *et al.*[83] reported the synthesis and pharmacological evaluation of novel chromone derivatives with multi-target activity as an anti-Alzheimer's agent, shown in Scheme 6. The authors reported that the best compound **15** exhibits good inhibitory potency for *h*MAO-A with $IC_{50}$ values of 5.12 μM




**15** (s19)

**Scheme 6** Synthesis of the designed compound **15**.

and 0.816 μM for *h*MAO-B. Moreover, the compound also inhibited 75% aggregation of amyloid-β at 20 μM with metal chelation, control of ROS generation, and antioxidant activity (ORAC = 3.62). The authors also reported molecular docking results using MOE 2008.10 and found that compound **15** established a π–π stacking interaction with Phe208, while a carbonyl group was involved with Gln215. The docking image shown in Fig. 4 indicated that the chromone moiety was sited within the substrate cavity of the enzyme, in close proximity to the flavin adenine dinucleotide (FAD) cofactor, while the phenyl group was involved in making a π–π stacking interaction with Tyr435. The other interactions were also discussed in the parent study which indicated that the compound has well interacted with the protein. The results indicated that the compound was able to reduce PC12 cell death induced by oxidative stress and penetrate the blood–brain barrier (BBB).

Chromone-based hybrid analogs were also reported as an effective molecule against neurodegenerative disorders. Nesi *et al.*[84] presented a series of chromone–rivastigmine-based new anti-Alzheimer's agents (Scheme 7) with both AChE and BuChE inhibitory activity and % inhibition of the self-mediated amyloid-$\beta_{1-42}$ aggregation. The study indicated that 2-chromonecarboxylic acid hybrid **16** exhibited inhibitory activity with an $IC_{50}$ for BuChE of 511 nM and able to inhibit 22% AChE at 500 nM concentration. Compound **16** was also

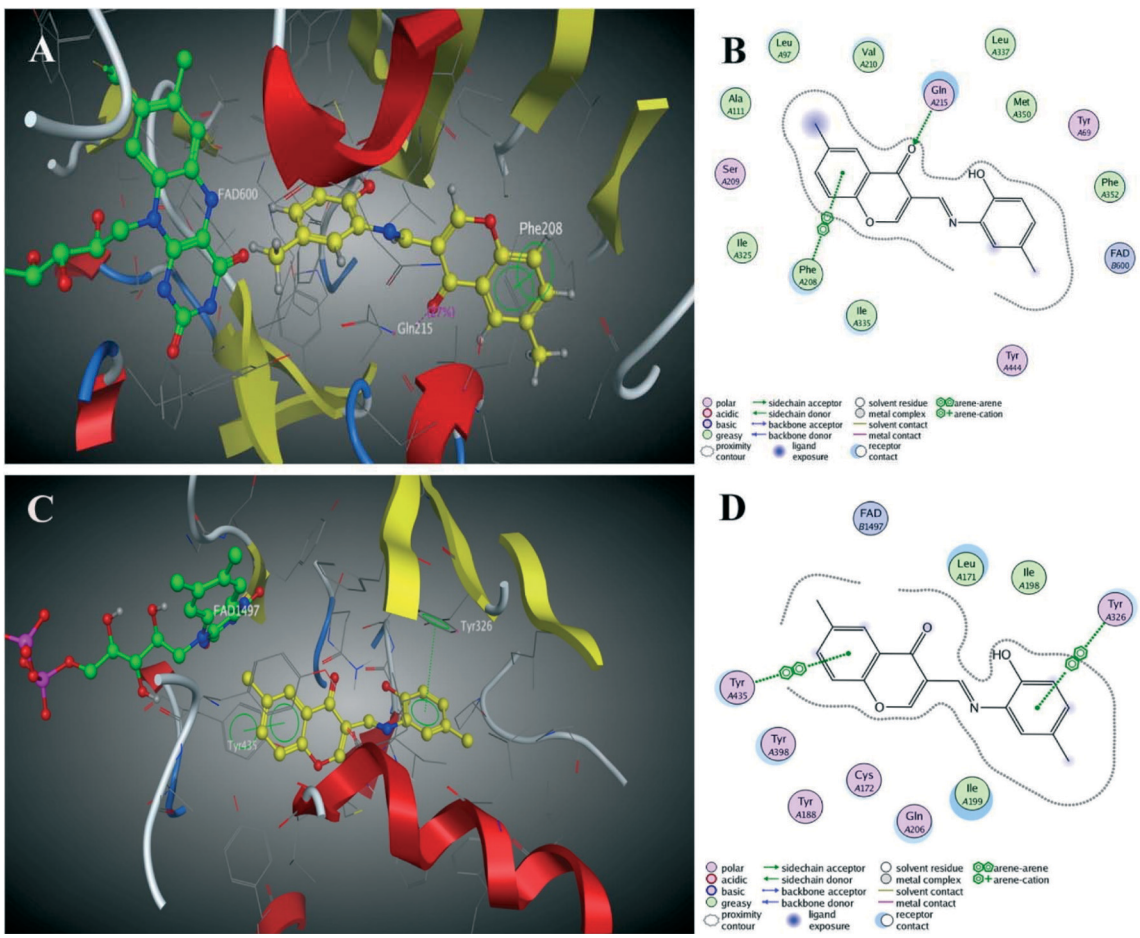
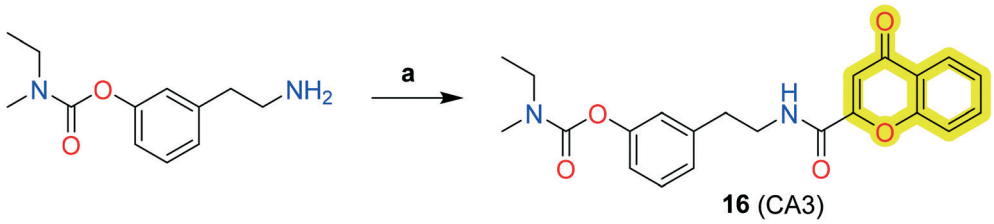



**Fig. 4** (A) 3D docking model of **15** with MAO-A. (B) 2D schematic diagram of docking model of **15** with MAO-A. (C) 3D docking model of **15** with MAO-B. (D) 2D schematic diagram of docking model of **15** with MAO-B (adapted with permission from ref. 83. Copyright 2017 Elsevier).




**Scheme 7** Synthesis of chromone–rivastigmine hybrid compounds (a) 4-oxo-4*H*-1-benzopyran-2-carboxylic acid, BOP, TEA, rt, 12 h.

able to inhibit self-mediated amyloid-β aggregation with 67% inhibition. The results indicated that further investigation and structural improvements may be helpful in elucidating the importance of their anti-neurodegenerative profile.

Reis *et al.*[85] reported chromone derivatives as novel potent and reversible *h*MAO-B inhibitors and discussed their inhibition mechanism through crystallographic and biochemical analysis. The authors disclosed that the chromone moiety of the inhibitors is located in front of the FAD cofactor and all bind in the active site cavity of *h*MAO-B, as shown in Fig. 5.

The results evidenced that the compounds are well fit with the hydrophobic site of the protein and formed two hydrogen bonds with Tyr435 and Cys172. The efficient inhibition of the compounds was also evidenced with a $K_i$ value of 17 nM for the compound *N*-(3′-chlorophenyl)-4-oxo-4*H*-chromene-3-carboxamide **17**. The authors stated that the reported compounds were 1000-fold more effective than L-deprenyl in reducing the cellular levels of reactive oxygen species (ROS). Later, the authors[86] again reported a new study on chromone-based new derivatives with *h*AChE and MAO activities. The best compound **18** was reported with $IC_{50}$ and $K_i$ values of 0.21 μM and 0.19 μM for *h*AChE and dual inhibitory activity for *h*MAO-A and *h*MAO-B with $IC_{50}$ and $K_i$ values of 0.94, 0.057 μM and 3.81, 0.48 μM, respectively. The authors recorded the cytotoxicity profile of compound **18** in differentiated human neuroblastoma (SH-SY5Y) and human hepatocarcinoma (HepG2) cells after a 48 h incubation period as shown in Fig. 6 and found that compound **11** exhibited significant cytotoxic effects towards SH-SY5Y cells at 25 and

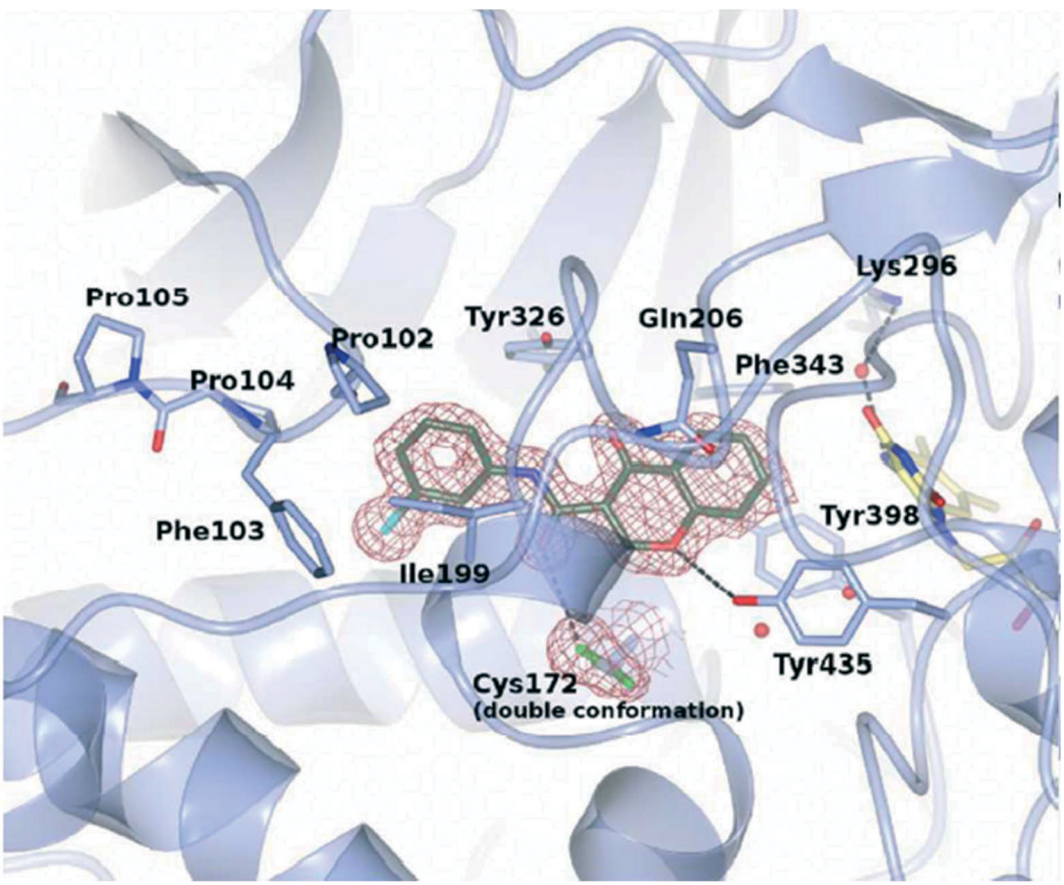



**Fig. 5** Crystal structure zoomed view of *h*MAO-B active site in complex with chromone inhibitor **17** (PDB code 6FW0) (adapted with permission from ref. 85. Copyright 2018 American Chemical Society).

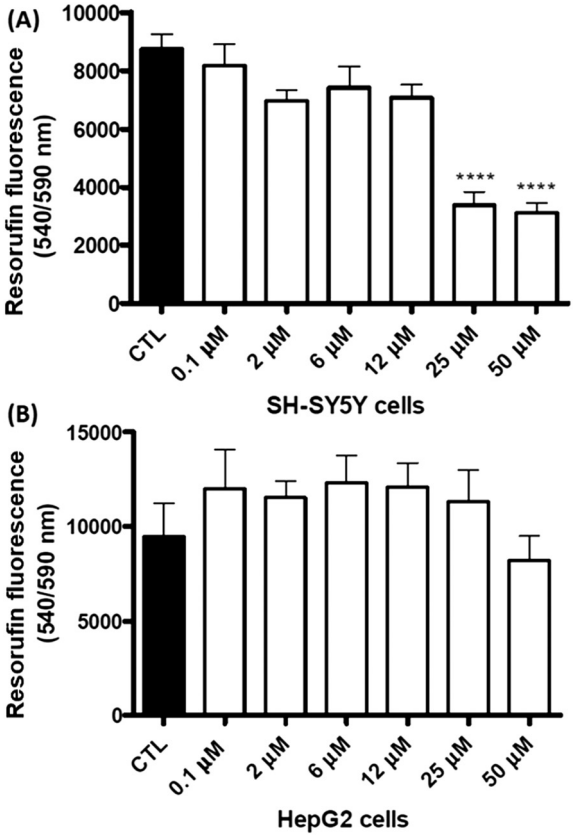


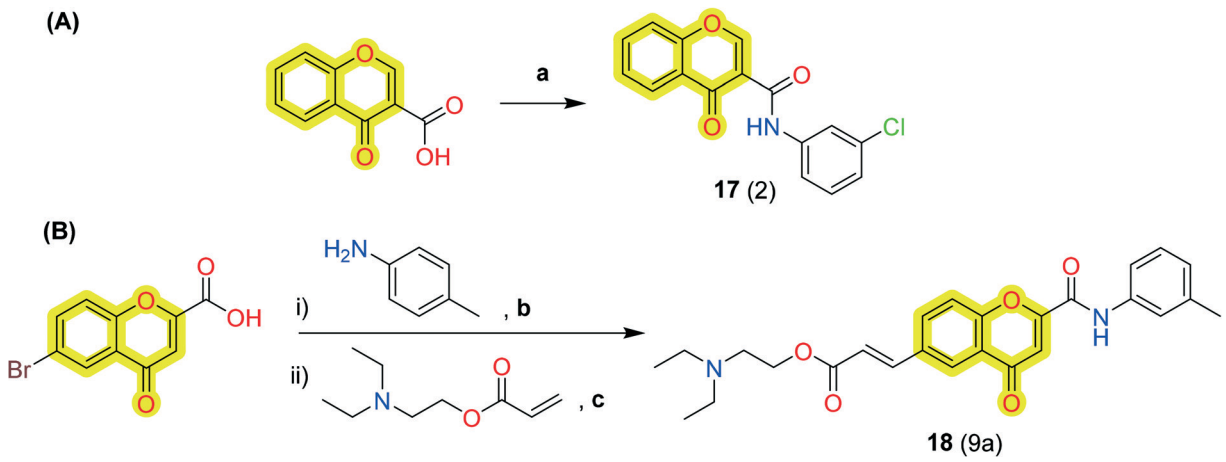

Fig. 6 Cytotoxicity profile of compound **18** measured by changes in cellular metabolic activity on (A) human neuroblastoma SH-SY5Y and (B) human hepatocarcinoma HepG2 cells (adapted with permission from ref. 86. Copyright 2018 Elsevier).

50 μM concentration, while it was safe on HepG2 cells, demonstrating low-risk drug-induced hepatotoxicity. The synthetic protocol of the reported inhibitors **17** and **18** is shown in Scheme 8.

In another study, Valencia *et al.*[87] synthesized a series of donepezil–chromone-based hybrid molecules for the treatment of Alzheimer's disease which exhibited nanomolar affinities for the sigma-1 receptor (s1R) and inhibition of key enzymes such as AChE, lipoxygenase-5 (LOX-5), and MAOs. The authors described compound **19** (Scheme 9) as the best compound of the study with $IC_{50}$ values of 46 ± 4 nM, 74 ± 3 μM, 15 ± 1 μM, and 5 ± 0.3 μM for *h*AChE, LOX-5, *h*MAO-A, and *h*MAO-B, respectively. The affinity constant $K_i$ towards *h*AChE, $\sigma_1$, and $\sigma_2$ receptors was reported as 39, 37 and 239 nM, respectively. The compound also reported neuroprotection activity against mitochondrial oxidative stress. Further, to evaluate compound **19** as a neurogenic agent, the authors isolated adult mice neural stem cells (NSCs) from the subgranular zone of the hippocampal dentate gyrus and cultured them as neurospheres (NSs) for 7 days in the presence and absence of the compound. As shown in Fig. 7, compound **19** promoted the differentiation of NSCs and their further maturation to a neuronal phenotype. To visualize early proliferation and neuronal maturation, β-III-tubulin (clone TuJ1; green) and microtubule-associated protein 2 (MAP-2: red) antibodies were used, respectively, inside the neurosphere (inner part) and in the distal area (outer part). The exploration of these hybrid compounds may turn them into a new clinical candidate for the treatment of Alzheimer's disease.

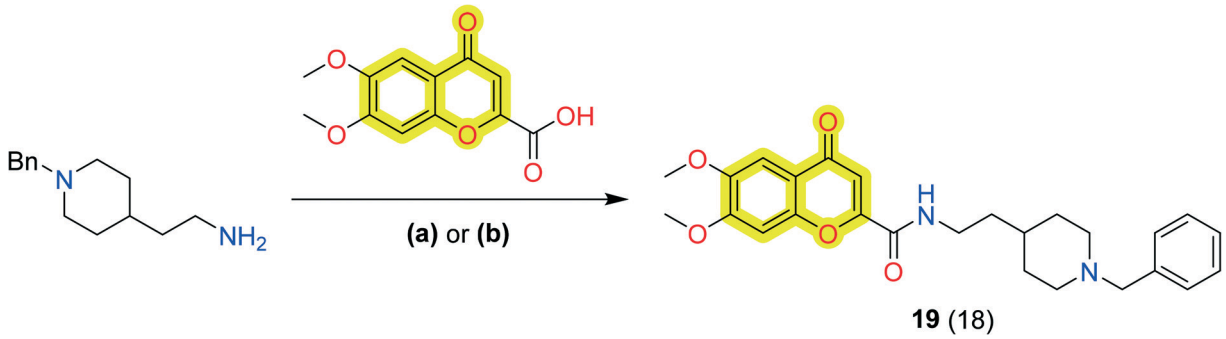
Makhaeva *et al.*[88] reported a series of substituted chromeno[3,2-*c*]pyridines as selective BuChE inhibitors for potential Alzheimer's disease therapeutics. The enzyme inhibitory activity indicated that compound **20** was the most potent compound of the study with $IC_{50}$ and $K_i$ values of 2 and 2 μM for *h*BuChE, respectively. The synthetic protocol for compound **20** is shown in Scheme 10.

Makhaeva *et al.*[89] synthesized and reported a series of substituted chromeno[3,2-*c*]pyridines for the inhibition of BuChE as anti-Alzheimer's agents. The study also contained the inhibitory assay of the synthesized compounds against AChE, BuChE, and carboxylesterase (CaE) by following the methods of enzyme kinetics and molecular docking. The results have shown that compound **21** (Scheme 11) was the




Scheme 8 Synthesis of the chromone-based *h*MAO-B inhibitors (A) **17** and (B) **18**. Reagents and conditions: (a) aniline derivatives, $POCl_3$, DMF, rt, 1–5 h; (b) $POCl_3$, DCM, DMF; (c) $NaHCO_3$, TBAB, $Pd(OAc)_2$.




**Scheme 9** Synthetic protocol for the preparation of donepezil–chromone-based hybrid molecule **19**. Reagents and conditions: (a) (i) acid, CDI, DMF, mw, 120 °C, 10 min, (ii) amine, mw, 150 °C, 10 min; (b) BOP, $Et_3N$, DMF, overnight, rt.

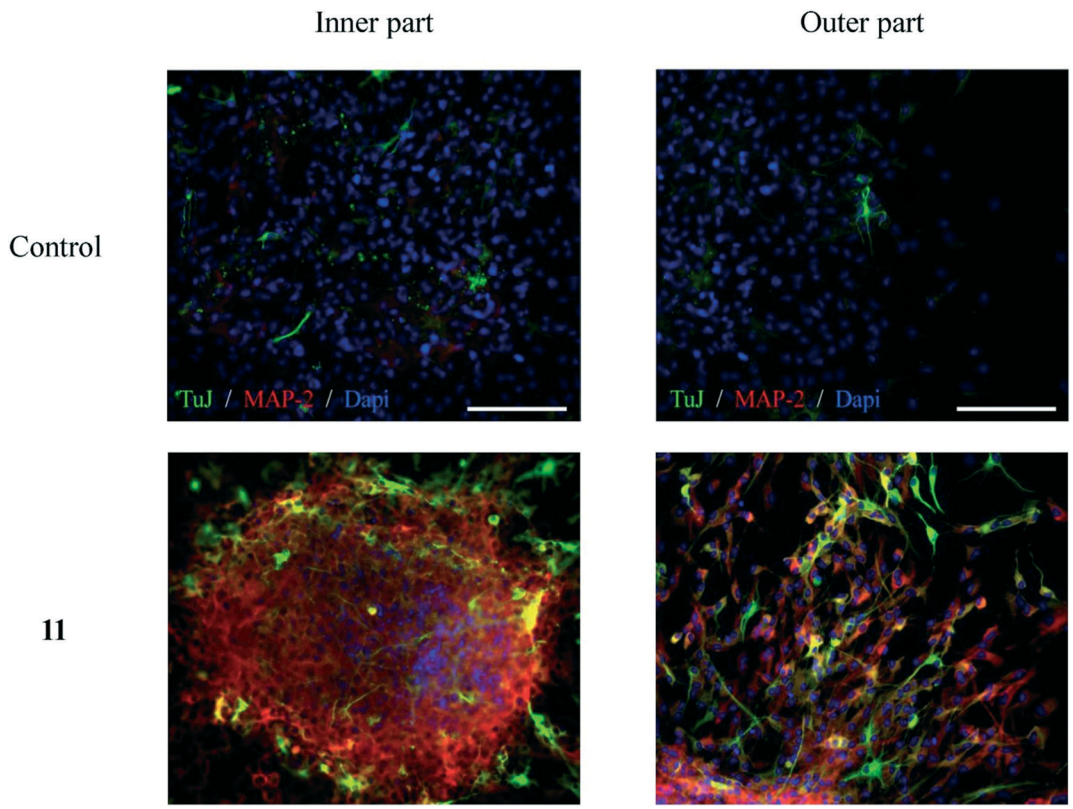
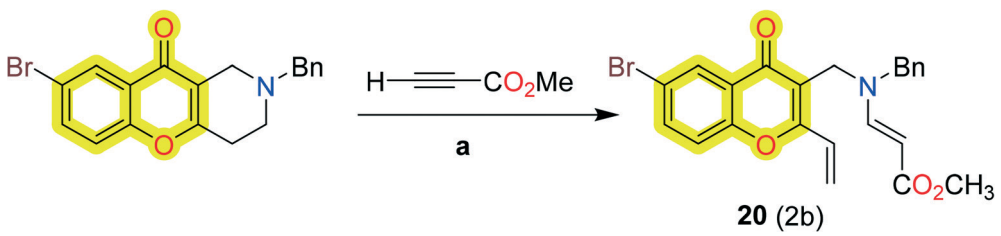


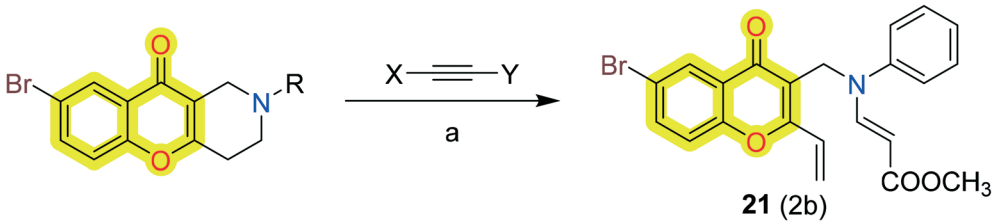

**Fig. 7** *In vitro* neurogenic effect of hybrid **19** (10 μM) on mice hippocampal SGZ derived spheres (adapted with permission from ref. 87. Copyright 2018 Elsevier).




**Scheme 10** Reactions of chromeno[3,2-c]pyridine with activated alkynes. Reagents and conditions: (a) (i) MeOH, rt.

most potent against BuChE with an $IC_{50}$ value of 2.27 μM and $K_i$ of 1.55 μM.

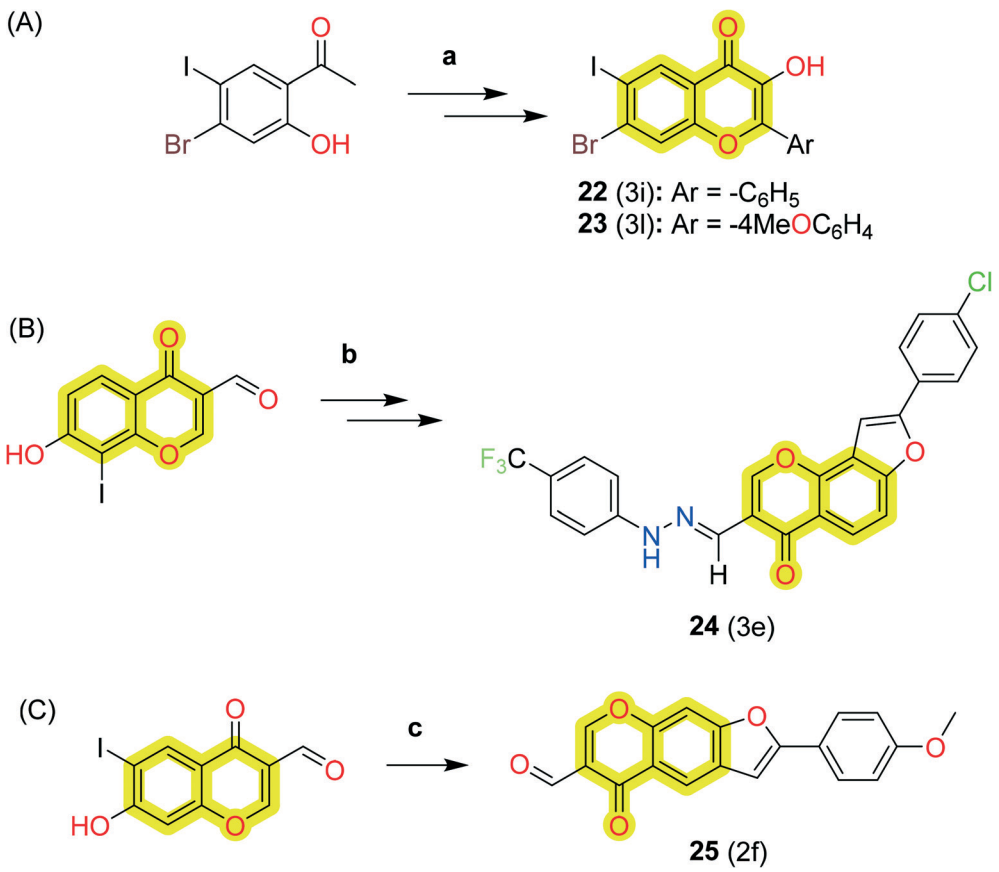
Mphahlele *et al.*[90] synthesized a series of substituted 2-aryl-3-hydroxy-6-iodo-4*H*-chromen-4-ones and evaluated the




**Scheme 11** Synthetic route for the compound **21**. Reagents and conditions: (a) X = H, Y = $CO_2Me$, MeOH, rt.

inhibitory activities against AChE, BuChE, and β-secretase (BACE1) *in vitro* and reported that chromone-based chalcone derivative **22** exhibited a significant inhibitory effect against AChE and BuChE with an $IC_{50}$ value of 10 and 6 μM, respectively, and compound **23** exhibited $IC_{50}$ = 16 μM for BACE-1. The modes of binding of the reported inhibitors with the protein were evaluated using molecular docking studies and could be accessed from the original research article. Later, the authors also explored 4-oxo-4*H*-furo[2,3-*h*] chromene derivatives[91] as potential multi-target inhibitors for cholinesterases, BACE1, and cyclooxygenase-2 and LOX-5 and LOX-15. The authors reported compound **24** as the most potent compound of the study with $IC_{50}$ values of 5 μM, 10 μM, 14 μM, 10 μM, 15 μM, and 29 μM for AChE, BuChE, BACE1, COX-2, LOX-15, and LOX-5, respectively. Further, they reported 5-oxo-5*H*-furo[3,2-*g*]chromene-6-carbaldehyde derivatives[92] as potential anti-Alzheimer's agents. The study suggested that the compound 2-(4-methoxyphenyl)-5-oxo-5*H*-furo[3,2-*g*]chromene-6-carbaldehyde **25** was the most potent against *h*AChE, *h*BuChE, LOX-15, and LOX-5 with *in vitro* $IC_{50}$ values of 10 μM, 5 μM, 10 μM, and 15 μM, respectively. DPPH antioxidant activity was reported at 18 μM for compound **25**. The results indicated that compound **25** was found to be cytotoxic against the breast cancer MCF-7 cell line. The synthetic protocol to obtain compounds **22**, **23**, **24**, and **25** is shown in Scheme 12.

Further, Lemke *et al.*[93] synthesized a library of substituted chromen-4-ones as multi-target-directed ligands for



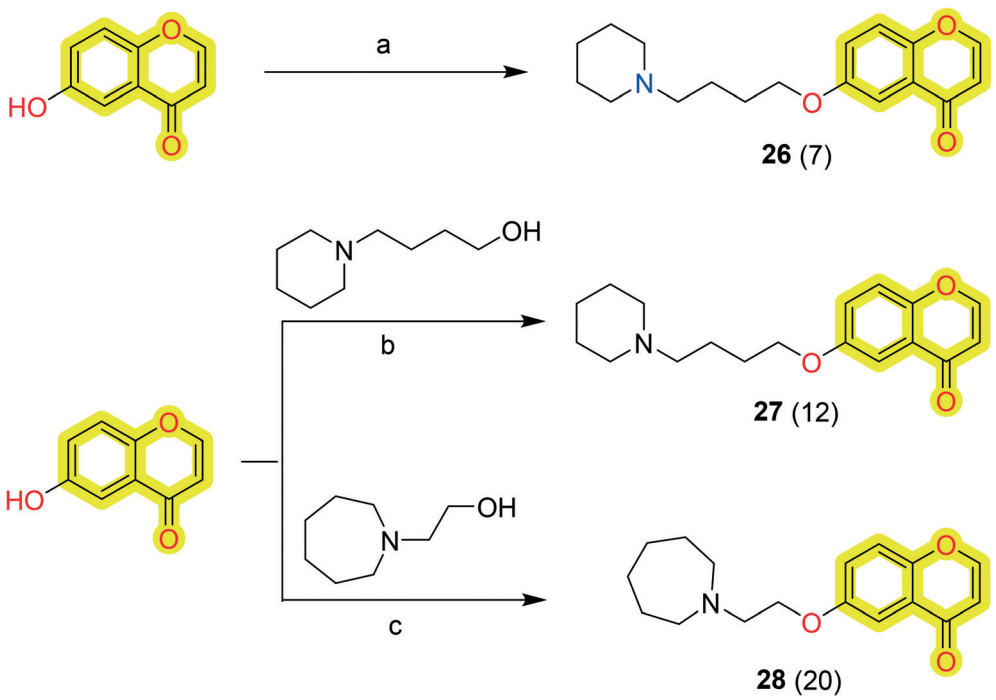

**Scheme 12** The synthetic protocol to obtain compounds (A) **22** and **23**, (B) **24**, and (C) **25**. Reagents and conditions: (a) (i) $RC_6H_4CHO$, 5% KOH (aq), EtOH, rt, 78 h, (ii) 3 M KOH (aq), $H_2O_2$, MeOH, 0 °C-rt, 3 h; (b) (i) alkyne, $PdCl_2(PPh_3)_2$, CuI, $PPh_3$, $K_2CO_3$, DMF (aq), 0 °C, 3 h, (ii) 4-$CF_3C_6H_4$-$NHNH_2$, EtOH, pyridine, reflux, 6 h; (c) alkyne, $PdCl_2(PPh_3)_2$, CuI, $K_2CO_3$, DMF (aq), 70 °C, 3 h.

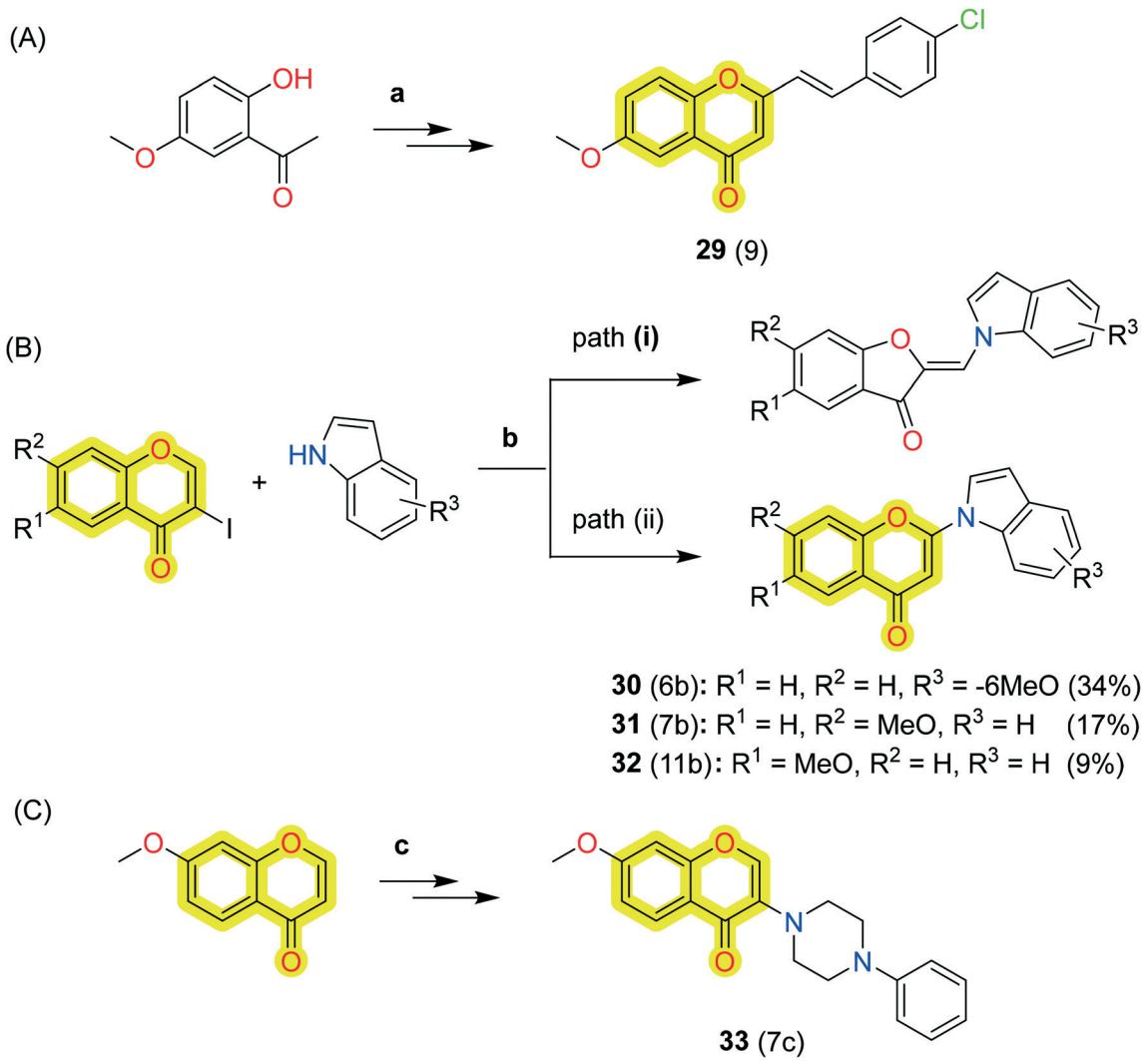
neurodegenerative therapy. The results highlighted the compound 6-(4-(piperidin-1-yl)butoxy)-4*H*-chromen-4-one **26** as the dual-target most potent inhibitor against AChE and MAO-B with $IC_{50}$ values of 5.58 and 7.20 μM, respectively. The authors also developed the molecules **27** and **28** in the study that were later reported by Deuther-Conrad *et al.*[94] as an extension of the study to analyze the affinity towards sigma (σ) receptors, potential agents for the treatment of several disorders, including Alzheimer's disease and neuropathic pain. The authors highlighted compound 6-((5-morpholinopentyl)oxy)-4*H*-chromen-4-one **27** as the most potent compound of the study with a $K_i$ value of 19.6 nM to $h\sigma_1$ receptor and selectivity index of 130 towards rat $\sigma_2$ receptor. Another molecule of the study, 6-(3-(azepan-1-yl) propoxy)-4*H*-chromen-4-one **28**, was reported with a $K_i$ value of 27.2 nM for $\sigma_1$ and selectivity ($\sigma_1/\sigma_2$) = 28, that combined the desired $\sigma_1$ receptor affinity with a dual inhibitory capacity against both AChE and BuChE with an $IC_{50}$ value of 10.6 and 25.0 μM, respectively. The study supported the future development of chromone-based molecules for neurodegenerative therapy. The synthetic procedure to achieve compounds **26**, **27**, and **28** is shown in Scheme 13.

Takao *et al.*[95] synthesized a series of 2-styrylchromone derivatives and reported their MAO-A and MAO-B inhibitory activities. The study highlighted compound **29** as the most potent against MAO-B with a minimal half-inhibitory activity of 17 nM and best selectivity over MAO-A of 1500. The mode of inhibition of compound **29** was reported as reversible, and quantitative structure–activity relationship (QSAR) analyses were also included with the study. These data suggested that the 2-styrylchromone structure might be a useful scaffold for the design and development of novel MAO-B inhibitors. The authors also explored 2-(indolyl)-4*H*-chromen-4-one derivatives[96] as novel monoamine oxidase inhibitors for neurodegenerative therapeutics. The study indicated that compound **32** was active against both MAO-A and MAO-B with $IC_{50}$ values of 0.32 μM and 0.63 μM, respectively, while compounds **30** and **31** were highly selective towards MAO-B with $IC_{50}$ = 0.15 μM and selectivity index of >670. The authors reported molecular docking studies to explain the types of interaction of the reported inhibitors with the protein. Further, the authors explored 2- and 3-(*N*-cyclicamino)chromone derivatives[97] as monoamine oxidase inhibitors and showed that the 3-(*N*-cyclicamino)chromone derivatives (with a few exceptions) significantly and selectively inhibit MAO-B. The authors marked compound **33**, 7-methoxy-3-(4-phenyl-1-piperazinyl)-4*H*-1-benzopyran-4-one, as the most potent and selective inhibitor of MAO-B with an $IC_{50}$ of 15 nM and an MAO-B selectivity index of more than 6700. To elucidate the mechanism of the inhibitory activity of compound **33**, the authors used a molecular docking study which revealed that the mode of inhibition was competitive and reversible. The study revealed that the 3-(*N*-cyclicamino)-chromones are useful to lead compounds for the development of selective inhibitors of MAO-B. The synthetic protocol for the development of compounds **29**, **30**, **31**, **32**, and **33** is shown in Scheme 14.

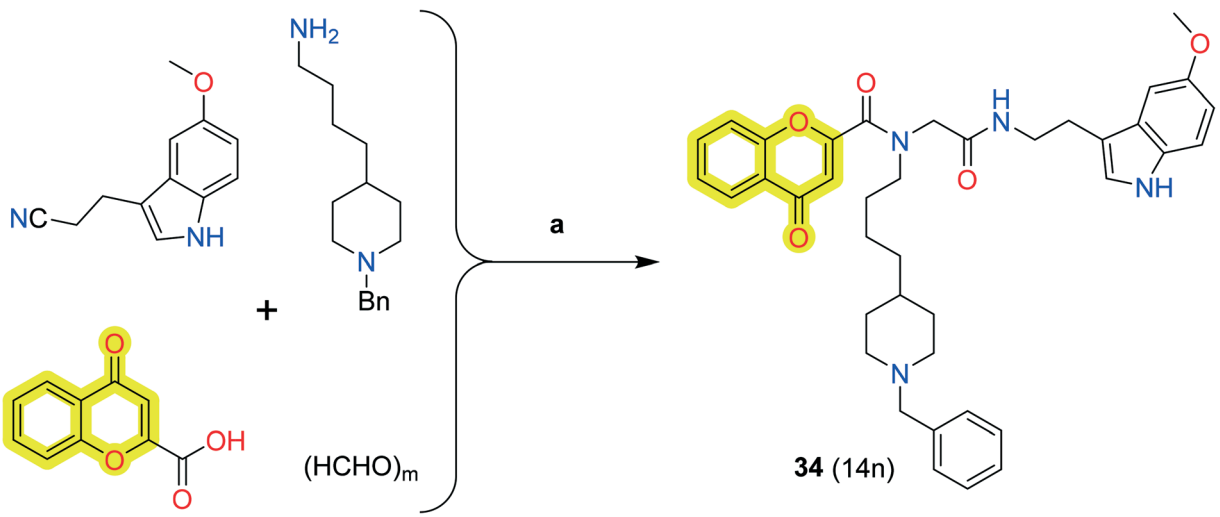
Pachón-Angona *et al.*[98] synthesized new hybrid molecules from chromone–melatonin–donepezil for Alzheimer's disease therapeutics. The authors reported that their compounds




**Scheme 13** Synthesis of the compounds **26**, **27**, and **28**. Reagents and conditions: (a) (i) $(CH_2)_4Br_2$, $CH_3CN$, $K_2CO_3$, 50 °C; (ii) piperidine, $Et_3N$, 50 °C; (b) cyanomethylenetributylphosphorane (CMBP), toluene, 100 °C; (c) $Ph_3P$, DCM, di-*tert*butyl azodicarboxylate (DBAD), rt.




**Scheme 14** Synthetic protocol for the development of compounds (A) **29**; (B) **30**, **31**, and **32**; (C) **33**. Reagents and conditions: (a) (i) Na, AcOEt, rt, (ii) conc. HCl, MeOH, rt, (iii) 4-chlorobenzaldehyde, NaOMe, MeOH, reflux; (b) $K_2CO_3$, DMF, 80 °C; (c) (i) $H_2O_2$, $PhCH_2N^+(CH_3)_3$ $OH^-$, $Et_2O$, 0 °C, (ii) cyclic amine, $CH_3CN$, and rt.




**Scheme 15** Synthesis of the donepezil–chromone–melatonin hybrid **34**. Conditions: (a) $MeOH/CH_2Cl_2$ (3 : 1), rt, 24 h.

exhibited multi-target activity. The study described that compound **34** (Scheme 15) was the most potent inhibitor for BuChE with an $IC_{50}$ value of 12 nM along with moderate inhibition activity for *h*AChE, *h*MAO-A, and *h*MAO-B with $IC_{50}$ values of 2 μM, 3 μM, and 21 μM, respectively, and strong antioxidant power (3.04 TE, ORAC test). The study is useful for the design and development of hybrid molecules for the treatment of neurodegenerative disorders.

Mpitimpiti *et al.*[99] reported the synthesis and MAO inhibition of chromone 3-carboxylic acid derivatives for neurodegenerative disease therapeutics. The authors reacted aromatic and aliphatic amines and alcohols with chromone 3-carboxylic acid in the presence of carbonyldiimidazole (CDI), which yielded chromane-2,4-dione and ester chromone derivatives as shown in Scheme 16. The study indicated that compound **35**, 4-chlorobenzyl 4-oxo-4*H*-chromene-3-carboxylate, was a dual-acting inhibitor for both MAO-A and MAO-B with $IC_{50}$ values of 19 μM and 10 μM, respectively. The study provides an insight to design MAO inhibitors for the treatment of neurodegenerative disease.

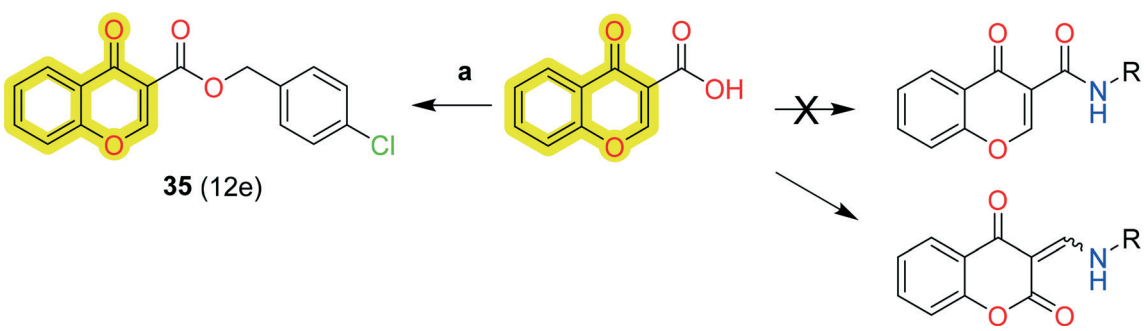
Wang *et al.*[100] worked on a molecular hybridization approach to develop a new multi-target-directed ligand for the inhibition of cholinesterase and monoamine oxidase as anti-Alzheimer's agents. The study revealed compound **36** as the most potent inhibitor of BuChE, AChE, and MAO-B with $IC_{50}$ values of 5.24, 0.37, and 0.272 μM, respectively. The authors discussed that compound **36** was a mixed-type inhibitor that binds concurrently to peripheral and active sites of AChE. It also acts as a competitive inhibitor of MAO-B which occupied the substrate and entrance cavities of the enzyme. The toxicity profile to rat pheochromocytoma (PC12) cells was reported within the limits that marked compound **36** as a multitarget drug lead molecule for the development of new potent anti-neurodegenerative agents. The synthetic route to achieve compound **36** is shown in Scheme 17.

Suwanhom *et al.*[101] synthesized chromone-2-carboxamido-alkylamines and reported them as potent acetylcholinesterase inhibitors for the treatment of neurodegenerative diseases. The authors marked compound **37** (Scheme 18) as the most potent compound with an $IC_{50}$ value of 0.09 μM for AChE, which was higher than that of the clinical drug, tacrine. The results indicated that compound **37** was not cytotoxic against SH-SY5Y cells and was found to be neuroprotective. The authors concluded that compound **37** may be a promising lead candidate for the development of anti-Alzheimer's agents.

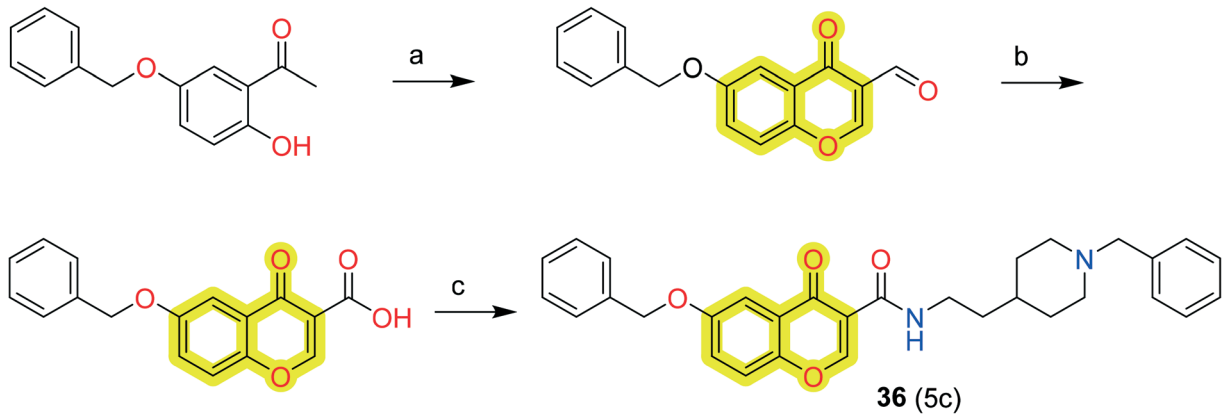
Further, a study by Shaikh *et al.*[102] was related to the development of new chromone-derived aminophosphonates as a cholinesterase inhibitor using porcine pancreatic lipase (PPL) as a catalyst for the treatment of neurodegenerative diseases, as shown in Scheme 19. The authors found compound **38** as the most potent compound of the study with an $IC_{50}$ value of 0.1 μM for AChE. The authors revealed that the aliphatic analogs of the study were efficiently inhibited AChE, while aromatic analogs were more potent for BuChE inhibition. The results defined that compound **38** was twofold more potent than tacrine, 35-fold more potent than galantamine, and 50-fold more potent than rivastigmine. The mode of binding with protein was explained using molecular docking studies which revealed that compound **38** binds to both the peripheral anionic site and the catalytic anionic site of AChE and BuChE. The antioxidant activities and DNA nicking activity were also performed which could be accessed from the original research.

Rao *et al.*[103] synthesized a series of bifunctional 7-benzyloxy-2,3-dimethyl-4-oxo-4*H*-chromene-8-carboxamide derivatives (Scheme 20) as potent and selective *h*MAO-B inhibitors using Jones oxidation and HBTU/HOBt as selective amide coupling agents. The authors marked compound **39** as the most potent against *h*MAO-B with an $IC_{50}$ value of 0.1 μM (while 4 μM for *h*MAO-A) and compound **40** as the most selective towards *h*MAO-B with an $IC_{50}$ value of 0.1 μM and selectivity index of 323.97. The study indicated that compound **39** showed reversibility of MAO-B inhibition in a dialysis method with a relative recovery percentage of up to 70%.

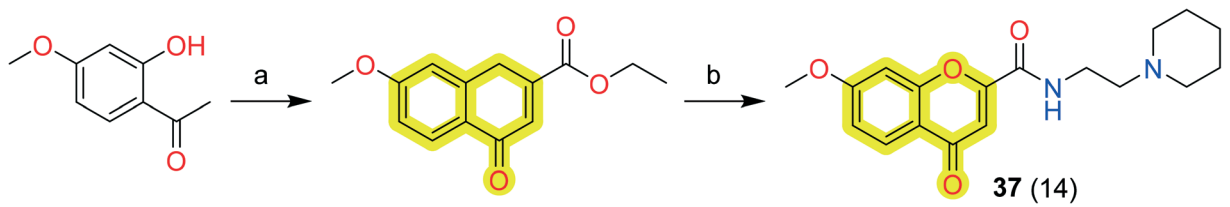
Malafaia *et al.*[104] reported the design, synthesis, and biological evaluation of a family of 2-styrylchromones as AChE and amyloid-β aggregation dual inhibitors. The authors reported that compound **41** (Scheme 21) was observed to be a well-balanced dual-target inhibitor with an $IC_{50}$ value of 3 μM for eeAChE and inhibitory percentage of 66% for amyloid-β aggregation. The molecular docking results of the study indicated that most of the compounds were bound to the AChE *via* H-bonds with the residues of the catalytic triad and π-stacking interactions. The promising activities of the



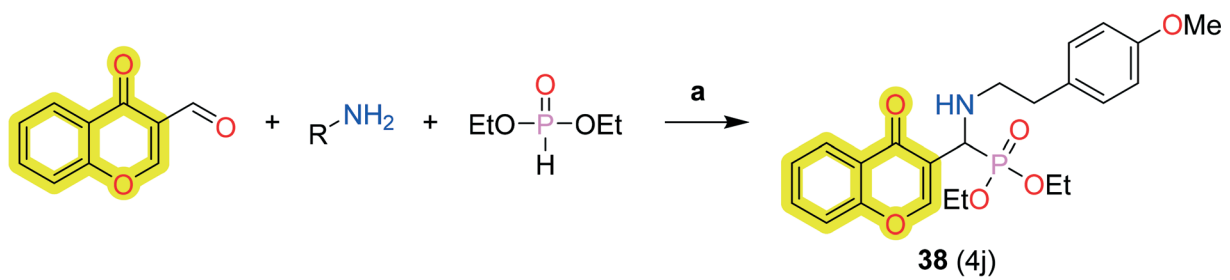

**Scheme 16** Synthesis of chromone 3-carboxylic acid derivative **35**. Reagents and conditions: (a) CDI, DMF, 60 °C, 2 h.



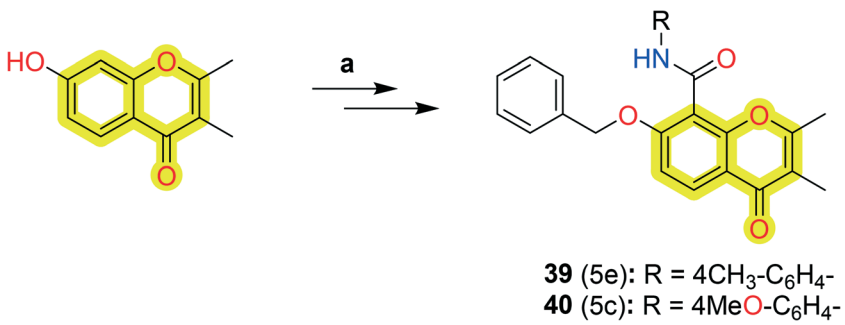

**Scheme 17** Synthesis of compound **36**. Reagents and conditions: (a) $POCl_3$, DMF, 0 °C, 2 h; (b) $NaClO_2$, $NH_2HSO_3$, $CH_2Cl_2$, 0 °C, 3 h; (c) thionyl chloride, reflux; 2-(1-benzylpiperidin-4-yl)ethanamine.




**Scheme 18** Synthesis of compound **37**. Reagents and conditions: (a) diethyl oxalate, NaH/THF, rt; (b) amine/$CH_2Cl_2$/reflux, then $CH_3COOH$, 70 °C.




**Scheme 19** Synthesis of chromone-based α-aminophosphonate **38**. Reagents and conditions: (a) PPL, solvent-free, 50 °C.

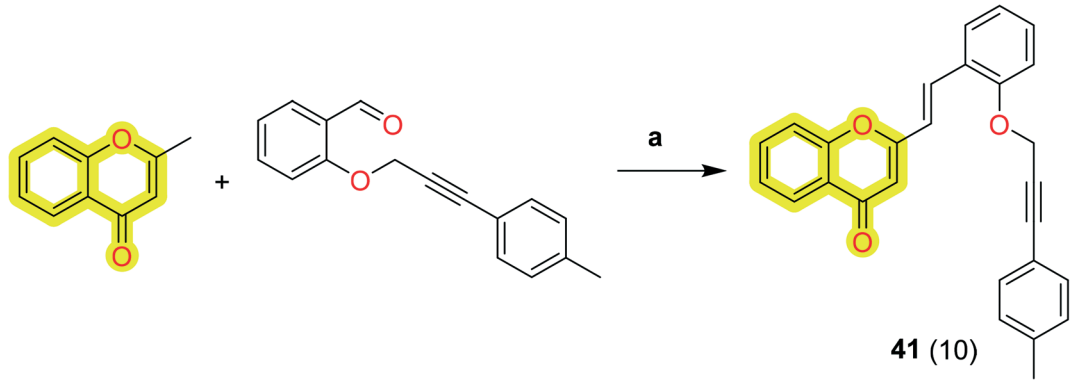



**Scheme 20** Synthetic route of 7-benzyloxy-2,3-dimethyl-4-oxo-4*H*-chromene-8-carboxamides (**39** and **40**). Reagents and conditions: (a) (i) AcOH, HMTA, 90 °C, 10 h; (ii) $PhCH_2Br$, $K_2CO_3$, 0–80 °C, 5 h; (iii) Jones reagent, 0 °C, 4 h; (iv) R-$NH_2$, HBTU–HOBT, rt, 20 h.

developed compounds will be useful in designing new multi-target molecules for Alzheimer's disease therapeutics. The SAR profile of the compound towards eeAChE is shown in Fig. 8.

Abdpour *et al.*[105] explored a family of 7-hydroxy-chromone derivatives bearing a pyridine moiety as multi-target-directed ligands against Alzheimer's disease. The authors reported that most of the compounds were found to be competitive




**Scheme 21** Synthesis of (*E*)-2-styrylchromone **41**. Reagents and conditions: (a) Na, EtOH, rt, 5 h.

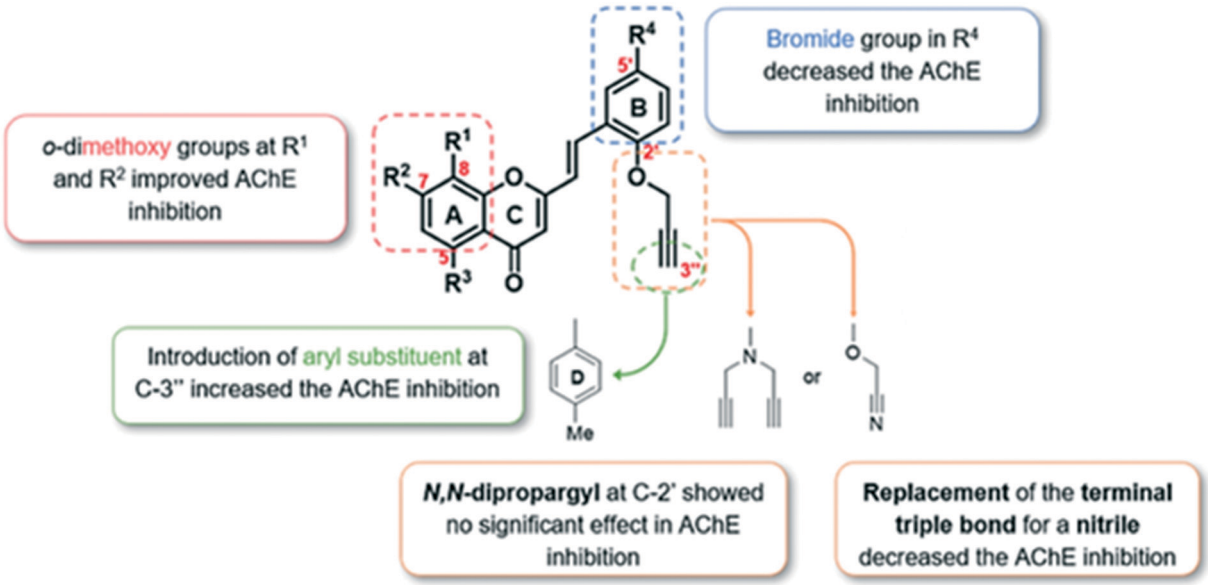
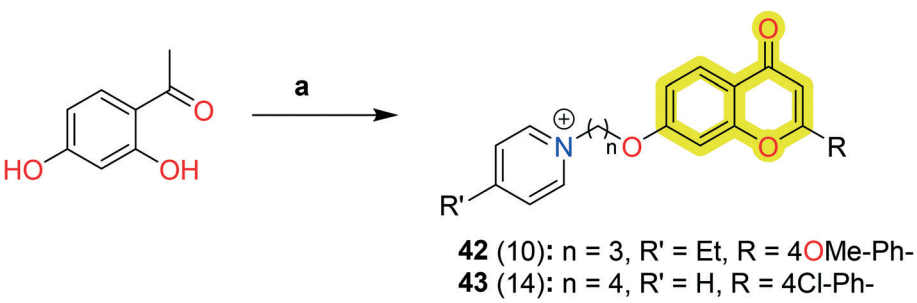



**Fig. 8** SAR profile towards eeAChE of (*E*)-2-styrylchromones (adapted with permission from ref. 104. Copyright 2021, licensed under CC BY 4.0).

AChE inhibitors with an $IC_{50}$ value of 10–0.7 μM and potent inhibitors of BuChE with an $IC_{50}$ value of 2–0.006 μM. The results indicated that compounds **42** and **43** showed the best multi-target efficacy with $IC_{50}$ values of 3 μM and 0.7 μM for eeAChE, respectively, and 0.006 μM and 2 μM for equine serum BuChE, respectively. Both compounds **42** and **43** also showed remarkable amyloid-β inhibition against both self-induced amyloid-β aggregation and AChE-induced amyloid-β inhibition with a percent inhibition of 32% and 37% and 28% and 22%, respectively. The study indicated that both




**Scheme 22** Synthetic routes to compounds **42** and **43**. Reagents and conditions: (a) (i) KOH (30%), MeOH, appropriate benzaldehyde, stir, 72 h, then DMSO, $I_2$, reflux, 45 min; (ii) $Br(CH)_nBr$ (*n* = 3, 4), anhydrous $K_2CO_3$, acetone, reflux, 4 h; (iii) pyridine, 110 °C, 24 h.

compounds showed acceptable neuroprotective activity on $H_2O_2$- and amyloid-β-induced neurotoxicity in PC12 cells, more than that of standard drugs, which suggested that the compounds may be a pioneer in designing chromone-based multi-target ligands for the treatment of Alzheimer's disease. The synthetic protocol to obtain compounds **42** and **43** is shown in Scheme 22.

To identify chromones as neuroprotective and amyloid-β disaggregating agents, Tan *et al.*[106] investigated the efficacy of synthetic chromones, diaportheones **44** and **45**, shown in Fig. 8. The authors used thioflavin T (ThT) assay to evaluate the impact of both chromones on amyloid-β and the cell viability, ROS, and mitochondrial membrane potential were evaluated with human neuroblastoma SH-SY5Y cells. The study indicated that the diaportheones **44** and **45** were able to inhibit the aggregation of amyloid-β by 80% and 74%, respectively, and both compounds showed neuroprotection on SH-SY5Y cells induced by amyloid-β and $H_2O_2$. Moreover, Jalili-Baleh *et al.*[107] synthesized multi-functional chromone–lipoic acid conjugates through click reaction and evaluated their neuroprotective, anticholinesterase, anti-amyloid aggregation, antioxidant, and metal-chelation activities. The authors reported that compound **46** (Fig. 9) was the most potent against BuChE with an $IC_{50}$ value of 8 μM and discussed that it has shown non-competitive mixed-type inhibition of BuChE analyzed through docking and kinetic studies. The study indicated that the compound was also moderately able to inhibit self-mediated amyloid-β aggregation (13%) and selectively chelate with copper ions in a 2 : 1 M ratio. The results highlight the significance of the chromone scaffold in designing multi-target ligands for the treatment of neurodegenerative diseases.

As a molecular hybrid molecule development, the development of a series of isoflavone/benzo-δ-sultam hybrids

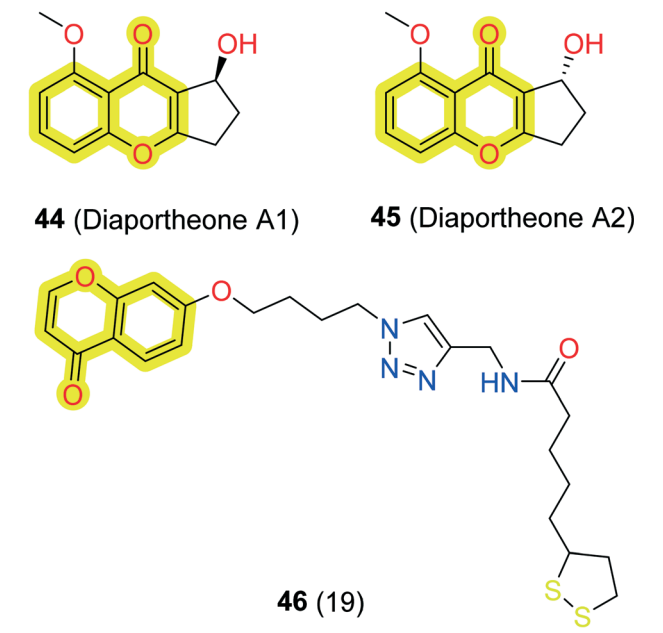



Fig. 9 Chemical structures of compounds **44**, **45**, and **46**.

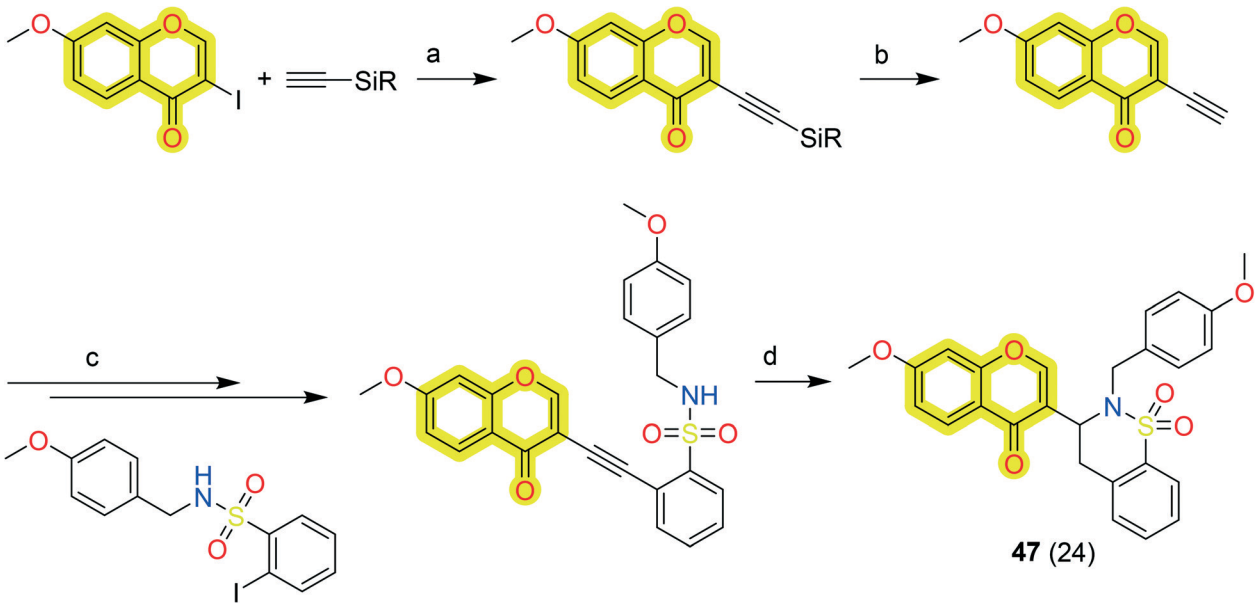
was reported by Mengheres *et al.*,[108] who analyzed them as potential anti-inflammatory and neuroprotective agents in LPS-activated BV2 microglia. The authors synthesized these hybrid molecules using a two-step reaction by coupling 2-halobenzenesulfonamide derivatives with terminal alkynes, followed by a 6-*endo*-dig cyclization. The authors performed a biological assay for the inhibition of TNF-α production and nitric oxide (NO) in LPS-stimulated BV2 microglial cells. The results indicated that the most potent hybrid compound, **47**, of the study reduced NO production to 41% and TNF-α to 34% at 20 μM, which could be taken for further development. The synthetic route to achieve chromone **47** is shown in Scheme 23.

## 3. Concluding remark and future perspective

The evidence presented in this mini-review defines that the treatment of neurodegenerative diseases may be done through actions in several molecular mechanisms, which include inhibition of enzymes such as cholinesterases, BACE1, MAOs, *etc.*, inhibition of amyloid-β formation or disaggregation, and controlling other mechanisms such as oxidative stress, τ-hyperphosphorylation, inflammation, and metal regulation, among others. Currently, due to limitations of available drugs which provide only short-term improvements from a symptomatic perspective, medicinal chemists are continuously working to find new molecules which could be able to seize or cure neurodegenerative diseases completely. Over the past years, the advancement of pharmacologically active molecules highlighted the fruitfulness of the privileged structure concept. These privileged scaffolds exhibit good drug-like properties, possibilities to develop structurally diverse small molecules, and versatile binding properties such as chromone.

The use of the chromone scaffold in medicinal chemistry to develop new anti-neurodegenerative molecules is due to its excellent biological properties and absence of toxic effects. Nevertheless, the structural differences between derivatives tend to direct these compounds toward the desired activities, without taking the risk of off-target effects, in a semi-selective action. Moreover, the potential of chromones for neurodegenerative therapeutics, widely preferred in the last five years, glorified this scaffold for further structural optimizations. The research included in the review indicates that chromones are one of the preferred scaffolds to develop new multi-target molecules for the treatment of neurodegenerative diseases. The chromone derivatives were found potent not only against MAOs, but they were also remarkably potent against AChE, BuChE, BACE1, amyloid-β aggregation, oxidative stress, *etc.* The optimal length of the linker in designing AChE inhibitors might allow the inhibition of both active sites of the enzyme (CAS and PAS) and a terminal amine group may facilitate the compound–active site interaction. Furthermore, studies indicated that chromones also have the properties of neurogenesis, *i.e.*, the




**Scheme 23** Synthetic route for the synthesis of compound **47**. Reagents and conditions: (a) (i) $[Pd(PPh_3)_2Cl_2]$ (3 mol%), CuI (20 mol%), THF, TEA, $N_2$, 0 °C; (ii) 3 h, rt, $N_2$; (b) (i) TBAF, CSA, THF, 0 °C; (ii) rt, 3 h; (c) (i) 10% Pd/C (3 mol%), $PPh_3$ (12 mol%), CuI (5 mol%), vacuum/$N_2$; (ii) MeCN, 10 min, $N_2$, 0 °C; (iii) $Et_3N$, $N_2$, 0 °C, 5 min; (iv) 80 °C, overnight; (d) $AgNO_3$ (20 mol%), $Et_3N$, EtOH, N2, 80 °C, 10 min.

natural chromone was successfully demonstrated by several authors to promote neuron differentiation of neural stem/progenitor cells (NSPCs) and stimulate neurogenesis.

Therefore, in our opinion, it is expected that the optimization of chromone-type compounds to act as multi-target ligands will have positive outcomes for the treatment of neurodegenerative diseases. Furthermore, computational techniques might be beneficial to synthetic chemists to design and produce new compounds by studying *in silico* inhibition of each enzyme with promising compounds. The lack of *in vivo* studies as well as cytotoxicity studies creates limitations in optimization of the most promising compounds; thus these evaluations must be started as the next step for the development of new anti-neurodegenerative agents. In the upcoming years, it is expected that the development of new therapeutic small molecules with the chromone scaffold will disclose further exciting features in the field of neurodegenerative drug discovery.

## Conflicts of 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.

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