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Review

Chalcones As Modulators Of Neurodegenerative Processes: Exploring Their Role In Alzheimer's And Parkinson's Diseases

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Abstract

Neurodegenerative diseases such as Alzheimer's and Parkinson's present a significant global health challenge due to their increasing prevalence and the lack of effective treatments. Chalcones, a class of natural flavonoids, have emerged as promising therapeutic agents due to their diverse biological activities, including antioxidant, anti-inflammatory, and enzyme inhibitory properties. This review comprehensively examines the role of chalcones as modulators of neurodegenerative processes, focusing on their potential therapeutic applications in Alzheimer's and Parkinson's diseases. We explore the molecular mechanisms underlying chalcone activity, including the inhibition of key enzymes like monoamine oxidases (MAOs) and acetylcholinesterase (AChE), as well as their impact on amyloid-beta aggregation, tau phosphorylation, and neuroinflammation. Additionally, we highlight recent advances in structure–activity relationship (SAR) studies that have led to the development of potent chalcone derivatives with enhanced neuroprotective properties. We also discusses the therapeutic potential and limitations of chalcones, providing insights into future research directions for the development of chalcone-based treatments for neurodegenerative diseases.

Keywords: Chalcones, Neurodegenerative disease, monoamine oxidases, acetyl cholinesterase, Structural activity relationship.

INTRODUCTION

Alzheimer's disease and Parkinsons disease are the two most prevalent neurodegenerative diseases that affect millions worldwide. Alzheimer's is especially prevalent among those over 65, with the risk increasing significantly with age. It is the 4th leading cause of mortality in US alone[1].It occurs as a result of proliferative degeneration of neuronal cells in the brain. Alzheimer's disease (AD) is not caused by a single factor (Fig.1). Instead, they are complex conditions with many contributing factors affecting our genes such as how those genes are expressed, our environment, and even how our bodies process nutrients. These factors combine in different ways for each person, making these diseases multifaceted and unpredictable[2].where as in case of parkinsons, it is a movement disorder, which is also a leading cause of motor problems and mental disabilities[3,4]. Parkinson's

disease is a complex illness caused by a combination of genes and environmental factors [1]. This disease can vary greatly between people, with symptoms differing from one individual to the next [5] (Fig.2). Several influences may play a role, including age, genetics, environment, and exposure to certain toxins that damage specific brain cells [5, 6, 7, 8]. Examples of these risk factors include pesticides, cleaning chemicals, heavy metals, and old age.

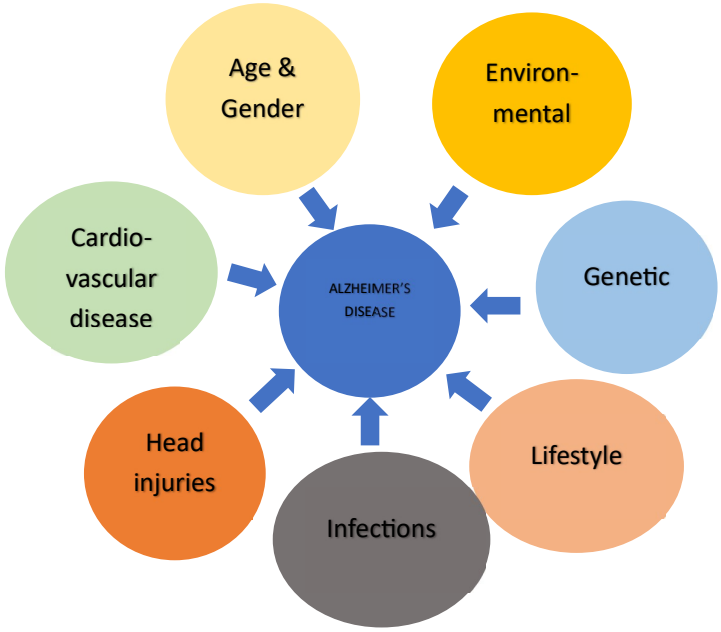


Fig 1: Factors affecting Alzheimer's disease[9]

The underlying pathology of AD includes accumulation of neurofibrillary tangles (NFT), amyloid beta (Ab) plaques, decline of acetylcholine concentration in the central nervous system along with oxidative stress and mitochondrial dysfunction [10]. However, neurofibrillary tangles (NFT) and amyloid beta (Ab) plaques are two main types of abnormal proteins found in AD brains[13,14]. Even though research suggests that amyloid beta (Aβ) and plaque buildup are important factors in Alzheimer's disease (AD), the etiopathology of AD remains unclear[15]. AD likely has multiple causes, not just one (multifactorial). Genes seem to play a role, but it's probably a combination of several genes, not just a single one (polygenic)[16]. Many things might influence how Aβ is processed in the body, and some of these influences could push things in a direction that leads to AD. There's a rare form of AD that starts young (early-onset familial AD), which suggests genetics can play a strong role in some cases[17]. Protecting against oxidative stress is also a crucial approach for treating AD as it impact all types of biological macromolecules, including nucleic acids, proteins, carbohydrates, and lipid [18].which in turn leads to the formation of amyloid plaques and neurofibrillary tangles. Additionally, transition metals such as Cu^{2+}, Zn^{2+}, Al^{3+}, and Fe^{2+} can facilitate amyloid-beta (Aβ) aggregation and contribute to the generation of reactive oxygen species (ROS) and oxidative stress, indicating that these biometals are closely linked to several key aspects of AD [19,20]. Consequently, regulating these biometals in the brain could be a potential therapeutic strategy for combating AD. Another mechanism involve selective MAO-B inhibition as an effective treatment of AD. Recent studies have demonstrated that selective MAO-B inhibitors, such as selegiline, can significantly enhance learning and memory in animal models of Alzheimer's disease (AD). Moreover, these inhibitors have shown promise in slowing disease progression in AD patients.[21].

Parkinsons disease are of two types: Primary parkinsonism caused by Parkinson's disease and Secondary parkinsonism caused by other neurodegenerative diseases[22,23]. The hallmark of Parkinson's Disease (PD) is the degeneration of dopaminergic neurons in the substantia nigra, leading to a decrease in dopamine levels, an inhibitory neurotransmitter, in the brain [24-26]. This dopamine deficiency results in reduced inhibition of striatal neurons, which regulate body movement balance, causing the movement control difficulties observed in PD patients[27]. The key mechanisms contributing to the development of Parkinson's disease encompass the formation of misfolded protein aggregates, oxidative stress, mitochondrial damage, impairment of the protein clearance pathway, neuroinflammation, and genetic mutations[28,29].

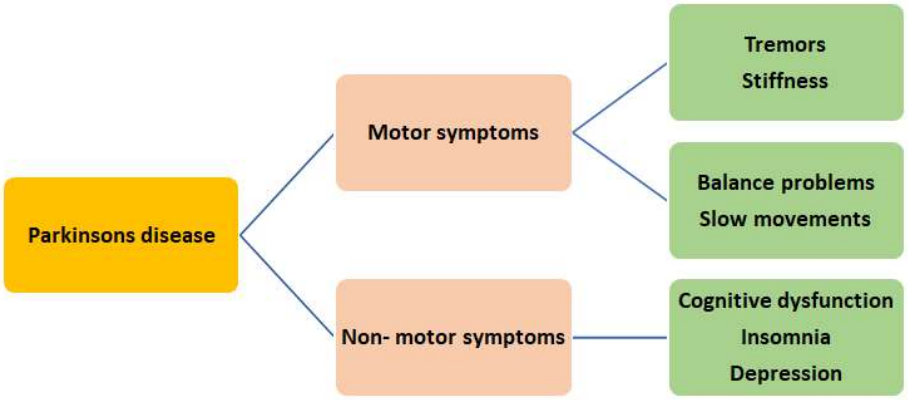


Fig 2: Symptoms of Parkinsons disease. [11,12]

Alzheimer's disease (AD) is the primary cause of dementia globally. With an aging population and no effective treatment available, the need for developing multi-target therapies has become a central focus of recent AD research. Alzheimer's disease (AD) medications focus on managing symptoms, not curing the disease. There are two main types of drugs used;

Acetylcholinesterase inhibitors (AChEIs)

These drugs (donepezil, galantamine, rivastigmine, and tacrine) increase acetylcholine levels in the brain, a neurotransmitter important for memory. While they can modestly slow mental decline in AD, their effects are temporary and come with side effects like nausea and diarrhoea.

Memantine

This medication works differently by regulating glutamate, another brain chemical[30].Because current medications have limitations, researchers are looking for new and more effective treatments for AD. As in case of Parkinson's disease (PD) the treatment focusses on increasing dopamine levels or stimulating dopamine receptors in the brain to improve movement problems.

Current medications include

Levodopa (a dopamine precursor) and Carbidopa/ Benserazide (inhibitors that enhance levodopa effects), Pramipexole and Apomorphine (drugs that mimic dopamine's actions), Selegiline, Rasagiline (irreversible), and Safinamide (reversible) - drugs that prevent dopamine breakdown, Tolcapone, Opicapone, and Entacapone (inhibitors that extend the effect of levodopa).There are limitations to these drugs, such as Safnamide's side effects. So, there's a need for new, reversible MAO-B inhibitors to improve treatment options. So far, there are no single drug which is capable of curing these diseases completely. Also several scientific studies shows that the recovery of brain functional steadiness after a neurological impairment cannot be simply accomplished by focusing on a single molecular target[38]. That is the reason why most of the research is now focusing on synthesizing drugs that can target multiple molecules at once, called multi-target directed ligands (MTDLs)[39].Among the many synthesised compounds ,chalcones are one of the most promising compounds for the treatment of neurodegenerative disease.

Chalcones: A Chemical and Biological Overview

Chalcones are Michael acceptors and could form covalent bonds with nucleophiles, e.g., the sulfhydryl group of cysteine residues in cellular peptides and proteins [40]. Moreover, chalcones can exist as two isomers cis(Z) and trans(E), but E isomers are more thermodynamically stable. Apart from central nervous system activities ,it also shows anti-bacterial, anti-cancer, anti-diabetic, anti-viral, anti-oxidant, as well as anti-inflammatory activities [41–43].The biological activity of these compounds can be rendered to the α, β-unsaturated bond adjacent to carbonyl group (Fig.3) [44]. Chalcones are promising for delivering drugs to the brain because they can easily pass through the blood-brain barrier (BBB). This is due to their chemical structure, which has two water-repelling (hydrophobic) aromatic rings and a small overall surface area[45]. A common synthetic approach for chalcones is Claisen-Schmidt condensation, which is relatively straightforward but can be slow and produce some unwanted materials. Interestingly, chalcones can also be used as building blocks to create other valuable molecules with five or six-membered rings, including pyrazole, pyrrole, furan, and pyridine derivatives[46].In recent years, chalcones have garnered significant interest from researchers as promising drug candidates for treating Parkinson's disease (PD) due to their impact on various biochemical pathways, though the

mechanisms of these interactions are often not fully understood. Numerous chalcone-based compounds have been designed, synthesized, and subjected to pharmacological evaluation. Their unique chemical structure allows for significant functional diversity, making them promising candidates for therapeutic development. In this review we focus on papers in which chalcones have been used in both alzheimer's and parkinson's disease.

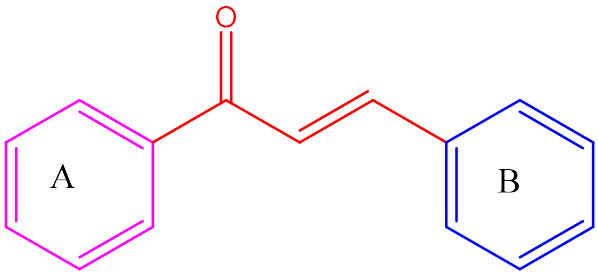


Fig 3: General structure of chalcones

Chalcones as anti-alzheimers agents: Recent advancements

Yamali et al. synthesized phenothiazine-based chalcones as ChEs and MAOs inhibitors via base-catalyzed Claisen-Schmidt condensation (Fig.4).3 out of 16 compounds synthesized, were reported for the first time. Biological evaluation of all the compounds as potential AChE and BuChE inhibitors was performed using in vitro modified-Ellman"s assay. Compounds 3 [(E) 3-(4-methoxyphenyl)-1-(10H-phenothiazin-2-yl)prop-2-en-1-one] and 9 [(E)-3-(4-nitrophenyl)-1-(10H-phenothiazin-2-yl)prop-2-en 1-one showed promising inhibition potency against AChE enzyme with IC50 values of 0.221 µM and 0.053 µM while compound 9 displayed remarkable inhibition potency towards MAO-B enzyme with IC50 value of 0.048 µM. Compound 9, as a dual-target inhibitor, selectively inhibited AChE and MAO-B enzymes. The SAR of phenothiazine based chalcones is as shown in (fig 5)[47]

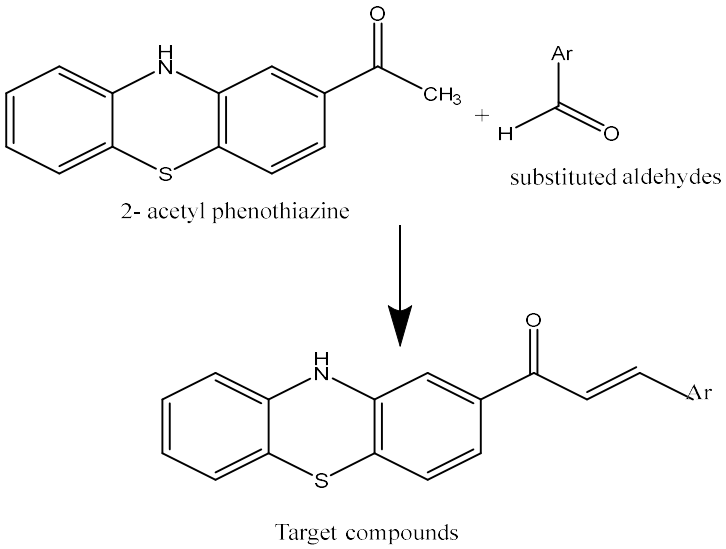


Fig 4: Synthetic scheme

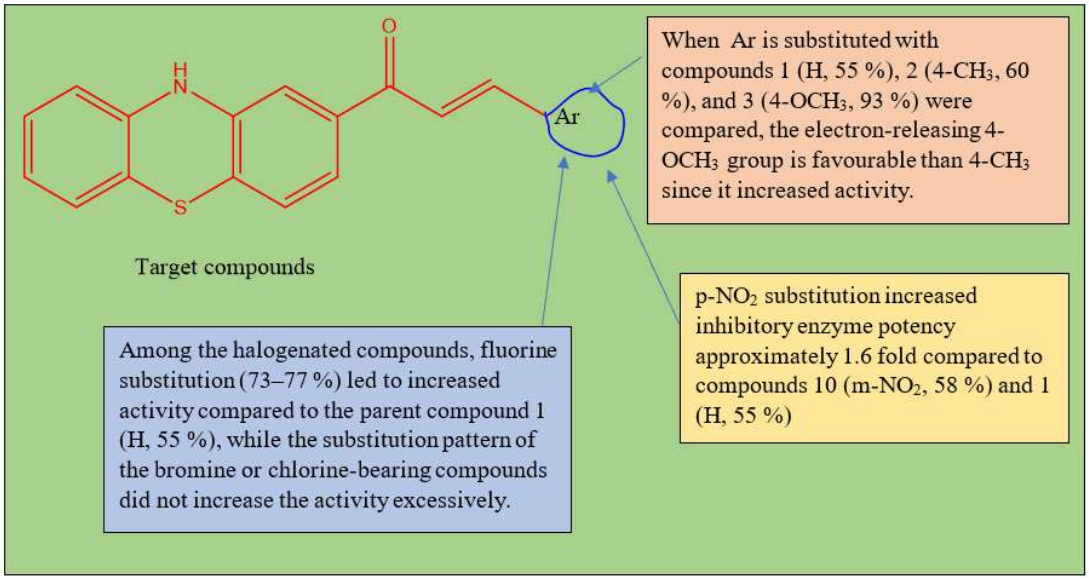


Fig 5: SAR of Phenothiazine based chalcones

Qin Wang et al. synthesized 15 chalcone derivatives as multifunctional agents for alzheimer's disease. The synthetic scheme is as shown in (Fig.6) Majority of the compounds demonstrated biological activity. In vitro studies revealed that these compounds inhibited self-induced Aβ1-42 aggregation effectively ranged from 45.9%-94.5% at 20 μM , and acted as potential antioxidants. In particular, 3-(4-dimethylamino-phenyl)-1-pyridin-2-yl-propenone (3g) exhibited an excellent inhibitory activity of 94.5% at 20 μM, and it could disassemble the self-induced Aβ1-42 aggregation fibrils with ratio of 57.1% at 20 μM concentration. In addition, it also displayed good chelating ability for Cu2+, and could effectively inhibit and disaggregate Cu2+-induced Aβ aggregation. Moreover, compound 3g exerted low cytotoxicity, significantly reversed Aβ1-42-induced SH-SY5Y cell damage. Among the electron-donating groups, compounds having amino substituent (especially dimethyl amino or diethylamino) showed the better activity (Fig.7). Due to larger steric hindrance at ortho position ,para substitution is more favourable for increasing activity [48]

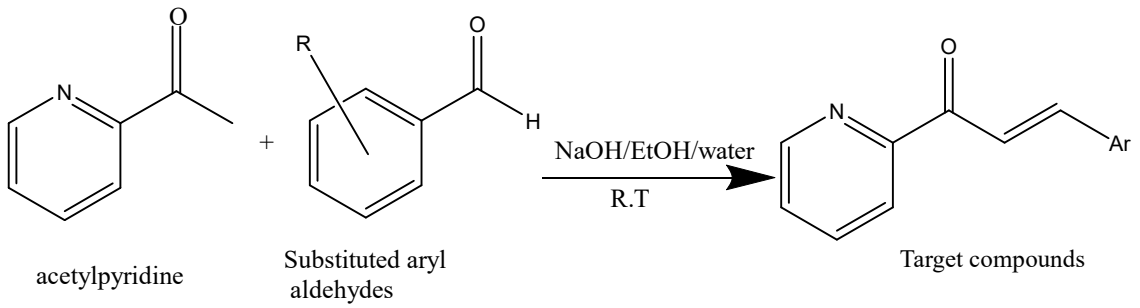


Fig 6: Synthetic scheme

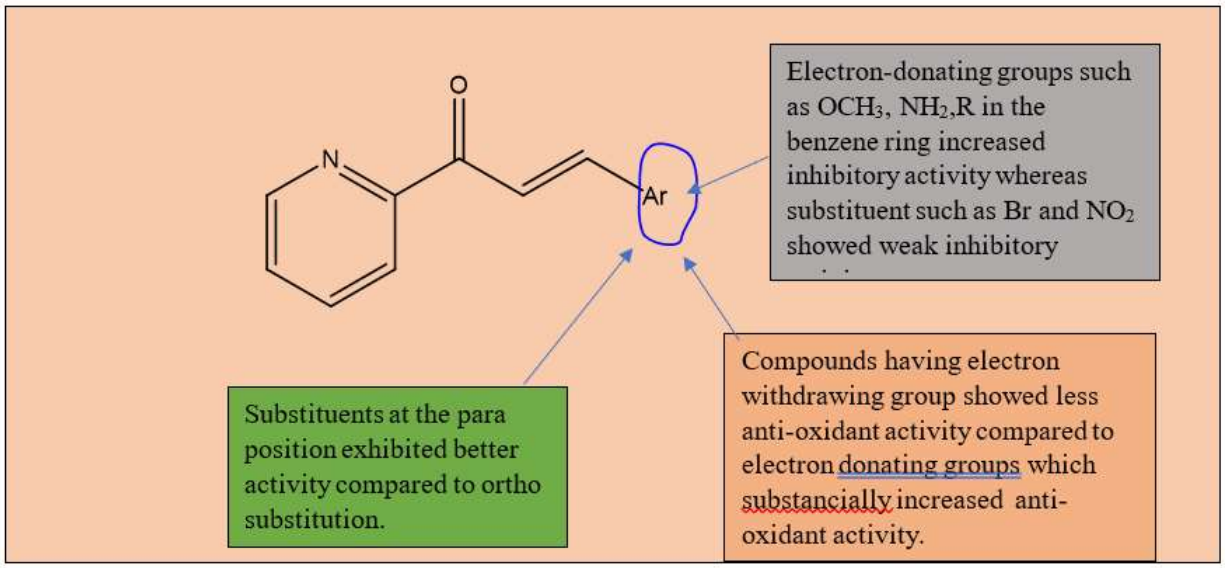


Fig 7: SAR of synthesized chalcones

Sang et al. synthesized a novel series of chalcone-Vitamin E-donepezil hybrids, developed based on multitarget-directed ligands (MTDLs) strategy. The biological results revealed that compound 17f (E)-1-(3,6-dihydroxy-2,4-dimethoxyphenyl)-3-(6(ethyl(2methoxybenzyl)amino)hexyl)oxy)phenyl)prop-2-en-1-one and 9d (E)-3-(4-(4-(ethyl(2-methoxybenzyl)amino)butoxy)phenyl)-1(6-hydroxy-2,3,4-trimethoxyphenyl)prop-2-en-1-one (Fig.8) showed good AChE inhibitory potency with IC50 values of 0.41 and 0.32mM respectively. The docking study was also performed with human MAO-B (PDB code: 2V60), which revealed its interaction with some amino acid residues which renders it with high MAO-B inhibitory potency. The kinetic analysis revealed it to be a mixed type AChE inhibitor. In addition to this it is also a good antioxidant (ORAC ¼ 3.3 eq), selective metal chelator and hu MAO-B inhibitor (IC50 ¼ 8.8mM). Moreover, it demonstrated significant inhibition of both self- and Cu2+-induced Ab1–42 aggregation, achieving rates of 78.0% and 93.5% at a concentration of 25mM, respectively. Notably, 17f exhibited a strong neuroprotective effect against H2O2-induced injury in PC12 cells and showed good permeability across the blood-brain barrier in vitro. The SAR of the synthesized compound is as shown in (Fig 9) [49]

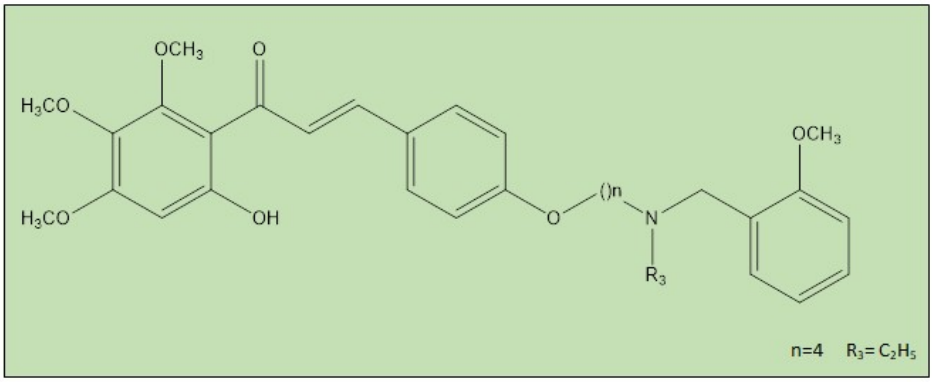


Fig 8: Compound 9d

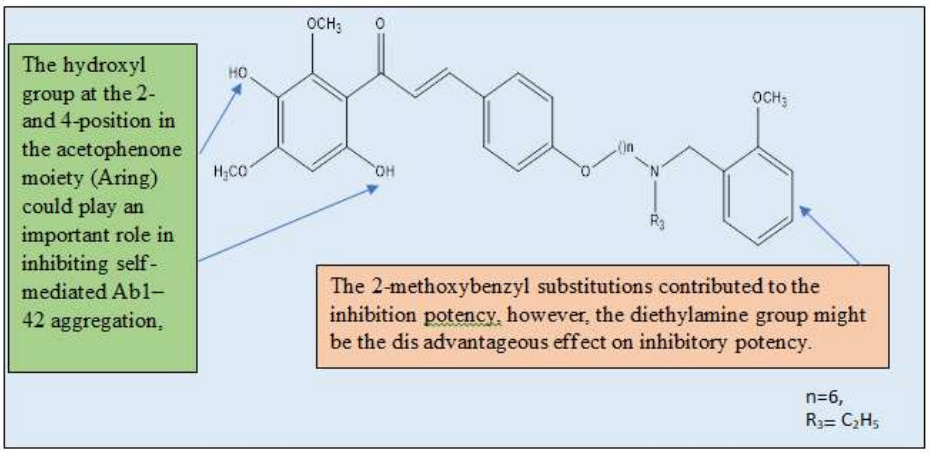


Fig 9: SAR of vitamin E- donepezil hybrid chalcones

Tian et al. synthesized a series of 7 novel flurbiprofen-chalcone hybrid Mannich base derivatives. The biological screening results indicated that most of the derivatives exhibited potent multi-target effects involved in AD. In particular, compound 6c Methyl (E)-2-(2-fluoro-4′-(3-(3-hydroxy-4-(pyrrolidin-1-ylmethyl) phenyl)acryloyl)-[1,1′-bi phenyl]-4-yl) propanoate bearing a pyrrolidine group showed the highest activities against self and Cu2+-induced Aβ1–42 aggregation (70.65% and 54.89% at 25.0 μM, respectively), highly selective inhibition towards AChE and MAO-B (IC50 = 7.15 μM and 0.43 μM respectively), good antioxidant ability and metal chelating property. Moreover, 6c displayed excellent anti-neuroinflammatory activity and appropriate BBB permeability in vitro. These outstanding results qualified compound 6c as a promising multifunctional agent for further development of disease-modifying treatment of AD. The synthesis was carried out by first reacting flurbiprofen with acetyl chloride by Friedel-Crafts acylation to obtain 4′-acetyl flurbiprofen .Then it was reacted with m-hydroxybenzaldehyde in the presence of potassium hydroxide resulted in flurbiprofen-chalcone hybrid (3), which is then followed by esterification to get the corresponding methyl product 4. Finally, the target products 6a-g were obtained by the reaction of intermediate 4 with paraformaldehyde and secondary amines under Mannich reaction condition (Fig 10). In SAR, the cyclization from diethylamine group to pyrrolidine group was profitable to inhibit Aβ1-42 aggregation, but further expansion of pyrrolidine ring to piperidine ring was adverse(Fig 11). Meanwhile, 6c was also the most active inhibitor for MAO-A (58.20% at 10 μM), which revealed that the pyrrolidine group at 4′-position of chalcone nucleus was favorable for both MAO-A and-B inhibitory efficiency.[50]

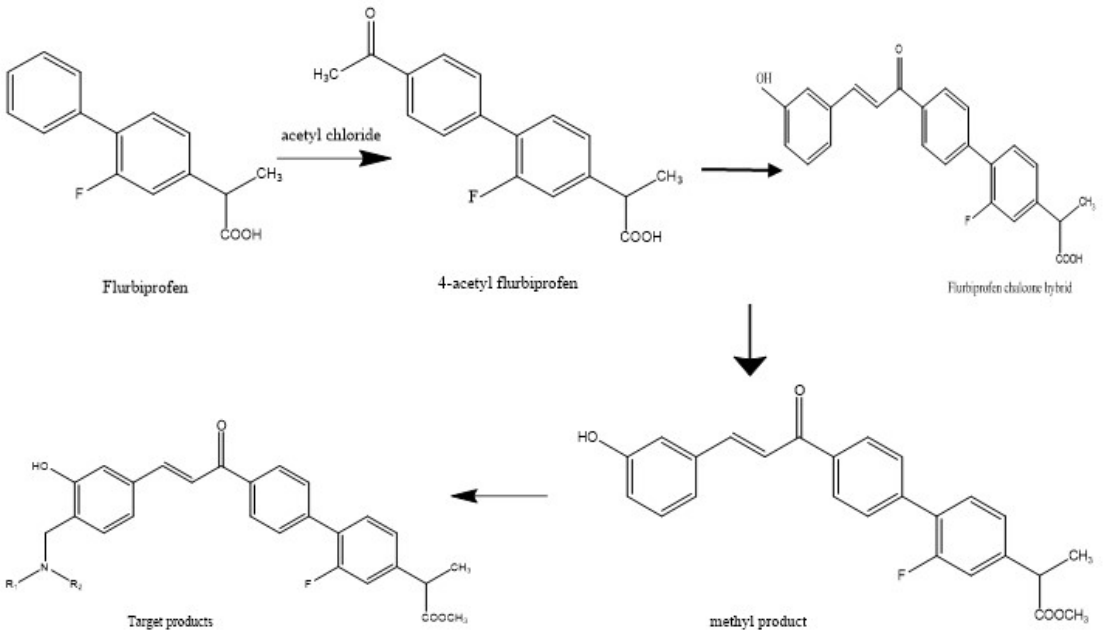


Fig 10: Synthesis of flurbiprofen-chalcone hybrid

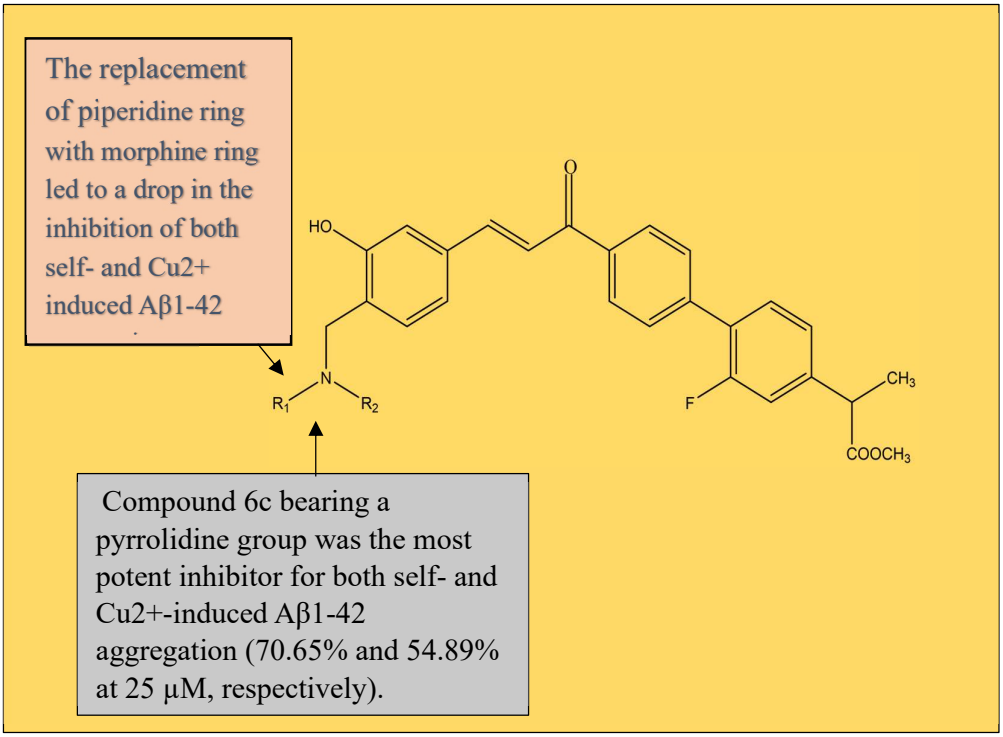


Fig 11: SAR of flurbiprofen – chalcone hybrid

Chalcones as anti-parkinsonian agents

Kumar et al. synthesized thirteen isopropyl chalcones (CA1−CA13) and evaluated for their inhibitory activity against monoamine oxidase (MAO). All compounds inhibited MAO-B more effectively than MAO-A. Compound CA4 most potently inhibited MAO-B with an IC50 value of 0.032μM, similar to that of CA3 (IC50=0.035μM) and with high selectivity index (SI) values for MAO-B over MAO-A (SI=49.75 and 353.23, respectively).The synthesis involves reacting ketones with 4 isopropyl benzaldehyde in the presence of 40% NaOH or KOH in methanol, derivatives of isopropyl tailed chalcones were created (Fig.12).The inhibition studies show that most of the compounds showed extremely low residual activity against MAO-B at a concentration of

10μM.Therefore,MAO B inhibition of the compounds was analyzed precisely at a concentration of 1 μM. The SAR studies show that MAO-B inhibition was changed when heterocyclic rings were added in place of the A ring (phenyl ring). The thiophene and benzofuran rings were more prominent for MAO-B inhibition as indole and benzimidazole ring substitution were less efficient in inhibiting MAO-B than thiophene and benzofuran substitution.(Fig 13). [51]

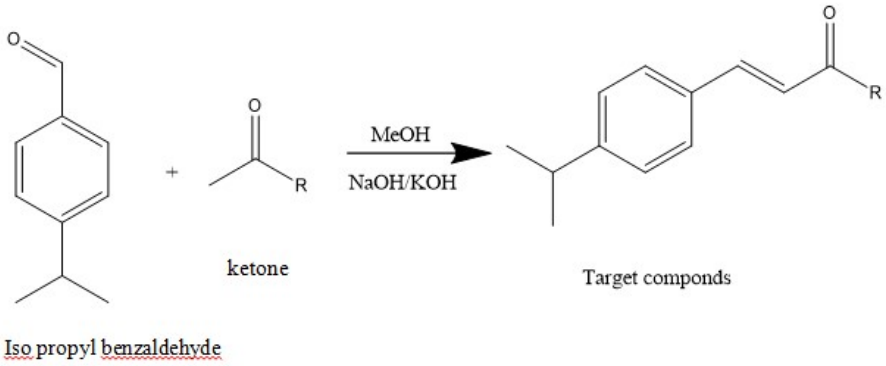


Fig 12: Synthesis of isopropyl chalcones

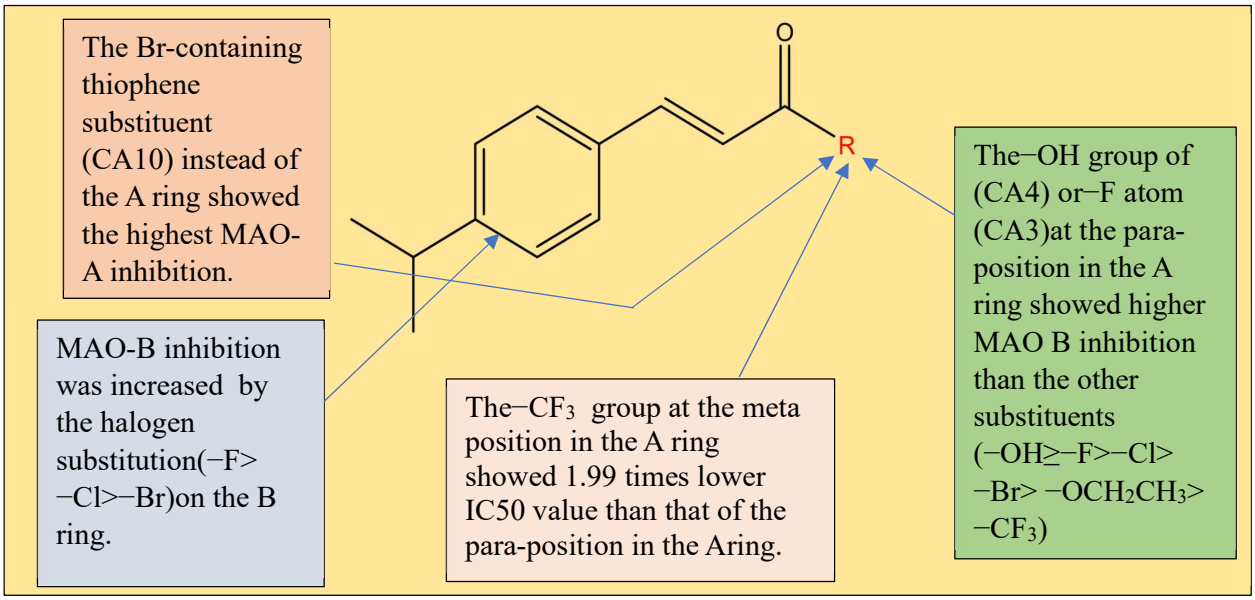
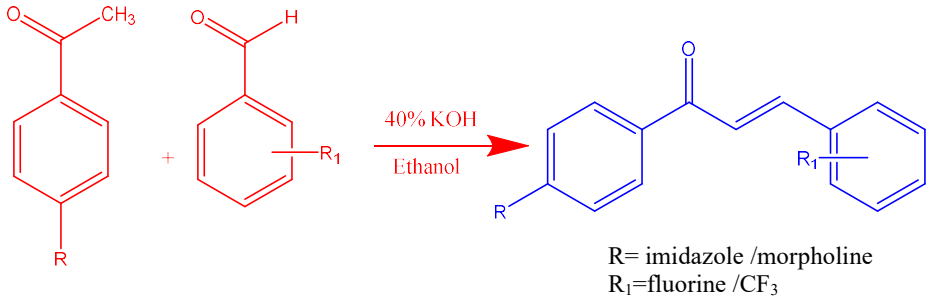


Fig 13: SAR of iso propyl based chalcones

Mathew et al. synthesized two series of fluorinated chalcones containing morpholine and imidazole-based compounds(Fig.14) (f1–f8) and evaluated for recombinant human monoamine oxidase (MAO)-A and-B as well as acetylcholinesterase inhibitory activities. While all the imidazole-based fluorinated chalcones showed weak MAO inhibitions in both isoforms, the morpholine-based compounds (f1–f4) showed moderate inhibition toward acetylcholinesterase with IC50 values ranging between 24 and 54Mm. The ortho- and para-substituted analogues f1 and f3 show slightly higher AChE inhibition compared to the meta-substituted analogue f3, unlike observed for MAO-B inhibition(Fig 14). Among the tested compounds, (2E)-3 (3-fluorophenyl)-1-[4-(morpholin-4-yl)phenyl]prop-2-en-1-one (f2) showed potent inhibitory activity for recombinant human MAO-B (IC50=0.087μM) with a high selectivity index (SI) of 517.2.the synthetic scheme is as shown in (Fig.15).[52]



R= imidazole /morpholine
R_1=fluorine /CF_3

Fig 14: Synthesis of fluorinated chalcones

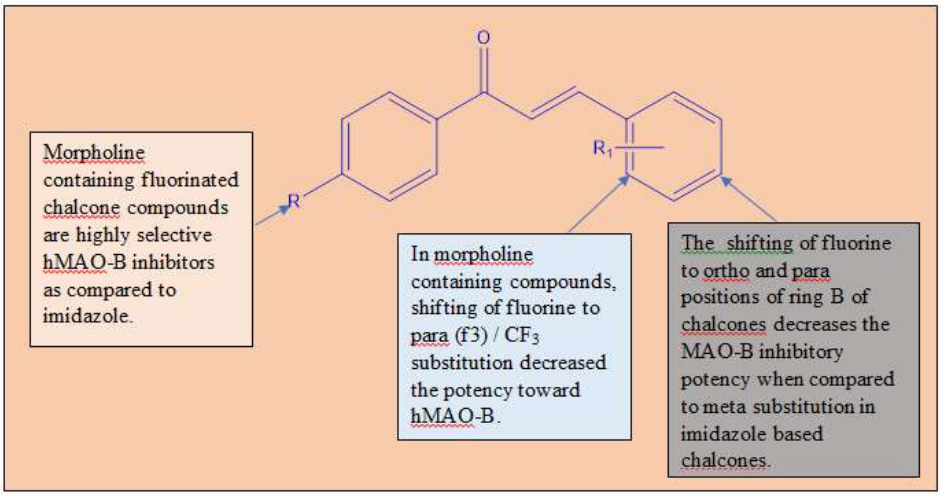


Fig 15: SAR of fluorinated chalcones

Mellado et al. presented a new series of seven prenylated chalcone derivatives (Fig.16) aimed at inhibiting MAOs. Among these, compound 3, identified as (E)-3-(4-(Dimethylamino)phenyl)-1-(4-hydroxy-3-(3-methylbut-2-en-1-yl)phenyl)prop-2-en-1-one, exhibited the highest MAO-B inhibitory activity with an IC50 value of 8.19 µM. Structure–activity relationship (SAR) studies highlighted that substitutions with phenyl and methoxy groups rendered the compound inactive due to steric hindrance at the enzyme's active site. Additionally, ortho substitutions were found to be less effective than para substitutions, and the introduction of a dimethylamino group enhanced the inhibitory potency against MAOs (Fig.17). Kinetic studies revealed that compound 3 competitively inhibited MAO-B. Both compounds 2, (E)-1(4-Hydroxy-3-(3-methylbut-2-en-1-yl)phenyl)-3-(4-methoxyphenyl)prop-2-en-1-one, and 3 demonstrated significant MAO inhibitory activity along with superior antioxidant properties compared to the standard compound BHT (Butylated hydroxytoluene). Therefore, these compounds show promise as potential leads for Parkinson's disease (PD) drug discovery.[53]

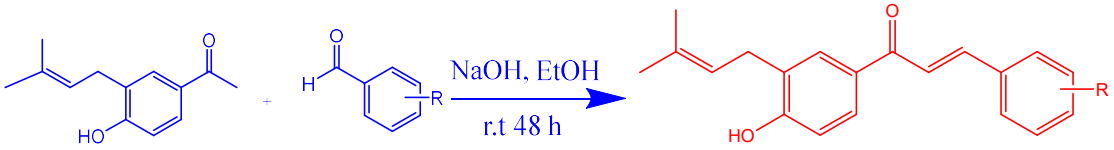


Fig 16: Synthetic scheme

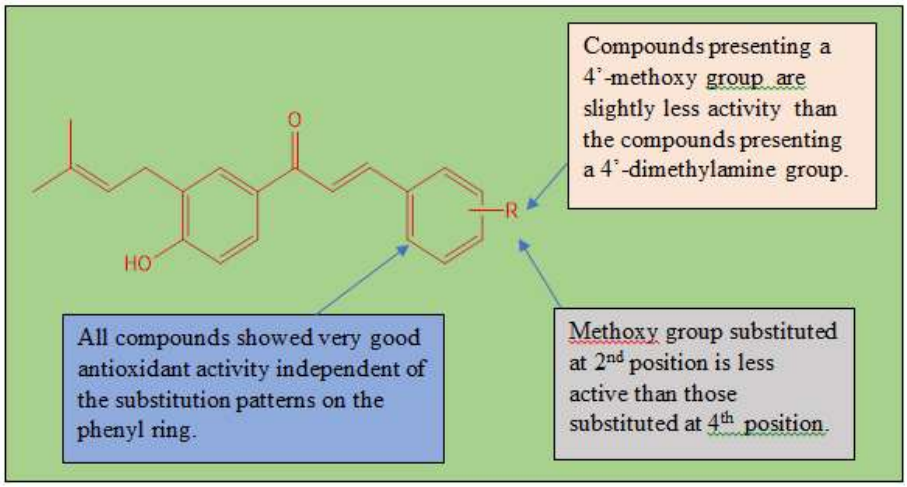


Fig 17: SAR of synthesized compounds

Parambi et al. synthesized oxygenated chalcone (O1-O26) derivatives (Fig 18) and their abilities to inhibit monoamine oxidases were determined. All 26 derivatives examined showed potent inhibitory activity against MAO-B. Compound O23 (2E)-1-(2,3-dihydro-1,4-benzodioxin-6-yl)-3-(4-fluorophenyl)prop-2-en-1-one showed the greatest inhibitory activity against MAO-B with an IC50 value of 0.0021 µM, followed by compounds O10 (2E)-1-(2H-1,3-benzodioxol-5-yl)-3-(4-fluorophenyl)prop-2-en-1-one and O17 (2E)-1-(2,3-dihydro-1,4-benzodioxin-6-yl)-3-(4-methylphenyl)prop-2-en-1-one (IC50 = 0.0030 and 0.0034 µM, respectively). The synthesis is as shown in figure. Additionally, dialysis experiments demonstrated that compounds 6 and 7 were reversible inhibitors of the MAOs enzyme. SAR studies revealed that substituting halogen atoms like fluorine from the para position to any other position led to a reduction in MAO-B inhibition. Moreover, the presence of an ethyl group at the para position caused non-selective inhibition of MAO-A. It was also found that increasing the number of alkyl groups between two oxygen atoms ('n') enhanced the inhibition potency (Fig.19). Kinetic and cytotoxicity studies was performed and the result demonstrated that compound 6 and 7 competetively inhibited both Mao isoforms and are non toxic.[54]

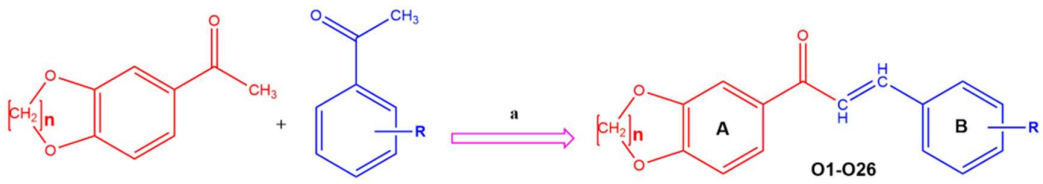


Fig 18: Synthetic scheme

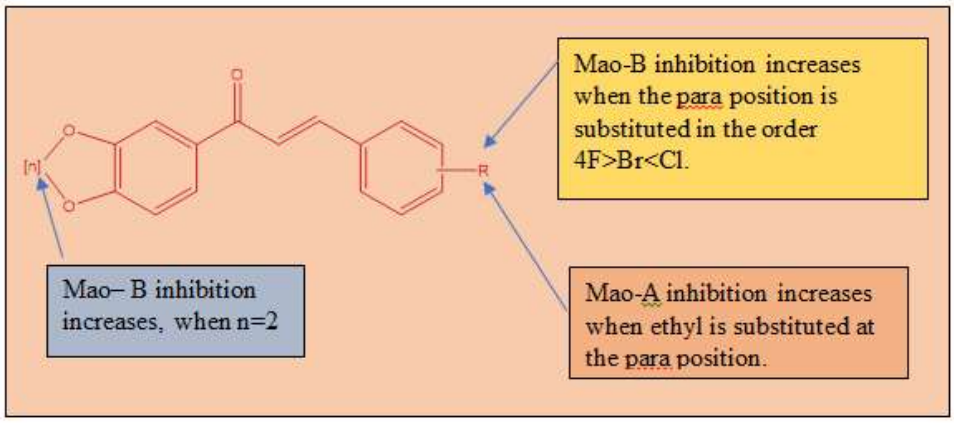


Fig 19: SAR of synthesized compounds

Future perspectives

The potential of chalcones as modulators of neurodegenerative processes opens several promising avenues for future research and therapeutic development. To fully harness their capabilities in treating Alzheimer's and Parkinson's diseases, the following future perspectives should be considered. Optimization of Structural Derivatives involving continued structure–activity relationship (SAR) studies are essential to refine chalcone derivatives with enhanced potency, selectivity, and minimal side effects. Emphasis should be placed on identifying structural modifications that improve bioavailability and stability. Developing innovative delivery systems, such as nanoparticles, liposomes, and prodrugs, can enhance the bioavailability and targeted delivery of chalcones to the brain. These technologies could overcome current limitations related to solubility and rapid metabolism. Comprehensive *In Vivo* Studies which focusses on more extensive *in vivo* studies are needed to assess the long-term efficacy and safety of chalcone derivatives in animal models of Alzheimer's and Parkinson's diseases. These studies should focus on pharmacokinetics, pharmacodynamics, and potential toxicity. Rigorous clinical trials are crucial to translate preclinical findings into clinical applications. These trials should evaluate the therapeutic effects of chalcone derivatives in human populations, assessing their efficacy, safety, and optimal dosing regimens. Considering the multifactorial nature of neurodegenerative diseases, exploring the potential of chalcones in multi-target therapeutic strategies could be beneficial. Combining chalcones with other neuroprotective agents or treatments may enhance their overall efficacy. Further investigation into the molecular mechanisms and pathways affected by chalcones will provide deeper insights into their neuroprotective actions. Understanding these mechanisms can guide the design of more effective chalcone-based therapies. Investigating the synergistic effects of chalcones with existing drugs used in the treatment of Alzheimer's and Parkinson's diseases could uncover new combination therapies that enhance treatment outcomes. Given the significant role of neuroinflammation in neurodegenerative diseases, further research into the immunomodulatory effects of chalcones could provide additional therapeutic benefits and insights. By addressing these future perspectives, researchers can advance the development of chalcone-based therapies, ultimately contributing to more effective treatments for Alzheimer's and Parkinson's diseases. The continued exploration of chalcones as modulators of neurodegenerative processes holds the potential to significantly impact the management and outcomes of these debilitating conditions.

CONCLUSION

Chalcones have emerged as promising modulators of neurodegenerative processes, offering potential therapeutic benefits for conditions such as Alzheimer's and Parkinson's diseases. The multifaceted biological activities of chalcones, including their antioxidant, anti-inflammatory, and enzyme inhibitory properties, make them valuable candidates for targeting the complex pathophysiology of these disorders. By inhibiting key enzymes like monoamine oxidases (MAOs) and acetylcholinesterase (AChE), and by impacting amyloid-beta aggregation, tau phosphorylation, and neuroinflammation, chalcones address several critical aspects of neurodegenerative diseases.Structure–activity relationship (SAR) studies have significantly advanced the development of chalcone derivatives with enhanced neuroprotective properties. These studies have identified specific structural modifications that enhance the potency and selectivity of chalcones, further validating their potential as therapeutic agents. In vitro and in vivo research has demonstrated that chalcones can cross the blood-brain barrier and interact with key molecular targets, supporting their efficacy in neurodegenerative models.

However, challenges remain, particularly regarding the bioavailability and pharmacokinetics of chalcones. Addressing these challenges through innovative delivery methods and further clinical research is essential for translating the promising preclinical findings into viable therapeutic options for patients. Overall, chalcones represent a versatile and potent class of compounds with significant potential to modulate neurodegenerative processes. Continued research and development of chalcone-based therapies could lead to new and effective treatments for Alzheimer's and Parkinson's diseases, offering hope for improved outcomes in these debilitating conditions.

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