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Review Article

Multi-target monoamine oxidase-B (MAO-B) inhibitors in the treatment of Parkinson's disease

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Abstract

Parkinson's disease (PD) is a fast-advancing disorder of the nervous system, ranking only behind Alzheimer's disease as the most prevalent neurodegenerative condition associated with aging. Its incidence increases with age – being relatively rare in people in their fifties and sixties but much more frequent in individuals older than eighty-five. Although extensive research over the past two centuries has been carried out to uncover the causes and mechanisms behind PD, its exact origins and underlying biology remain unclear. In the management of PD, monoamine oxidase-B (MAO-B) inhibitors are among the most frequently used drugs. In recent years, the multitarget-directed ligand (MTDL) approach has gained attention in neuropharmacology. This strategy involves designing compounds capable of acting on multiple biological pathways implicated in neurodegeneration at once, rather than targeting a single mechanism. This review summarizes recent progress in the development of such multi-target drugs for Parkinson's disease. It begins with an overview of PD, then discusses the primary mechanisms involved in its pathogenesis, current treatment options, and the emergence of multi-target therapies – with a particular focus on MAO-B inhibitors. For each group of compounds discussed, the relationship between their chemical structure and biological activity is examined and analyzed.

Keywords

Parkinson's disease, multitarget-directed ligands, MAO-B inhibitors

Introduction

Neurodegenerative disorders are among the most complex and challenging conditions present in modern medicine. They represent the third leading cause of disability and premature death across the European Union (EU), and projections indicate that both their prevalence and severity will rise as the population continues to age. This demographic shift has fueled growing scientific interest in developing new treatments for these diseases (Deuschl et al. 2017). Over many years of research, it has become clear that neurodegenerative diseases are influenced by a multitude of factors, including genetic predisposition, internal physiological processes, and environmental exposures. Major risk contributors include autoimmune responses, environmental toxins, viral infections, family history, advancing age, dietary habits, and pollution. As the number of elderly individuals increases – currently about 16% of

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Europe's population is over 65, with estimates suggesting this will reach 25% by 2030 – the burden of neurodegenerative diseases is expected to escalate, leading to higher morbidity, mortality, and healthcare costs. The economic impact is substantial, with annual expenditures for treating neurodegenerative conditions exceeding 130 billion euros in Europe alone (Adejare 2017). Parkinson's disease (PD) is a progressive neurodegenerative disorder and ranks as the second most prevalent age-related neurodegenerative condition after Alzheimer's disease. The likelihood of developing PD increases with age, with an incidence of 0.3 per 1,000 individuals between ages 55 and 65, rising to 4.4 per 1,000 in those over 85 (Darweesh et al. 2016).

Despite two centuries of investigation into its origins, the precise causes and mechanisms underlying PD remain unclear. While some cases are connected to inherited genetic mutations, the majority are sporadic. The hallmark pathological change in PD is the progressive loss of dopamine-producing neurons and the accumulation of misfolded alpha-synuclein (αSyn) within cytoplasmic Lewy bodies. In addition to the substantia nigra, pathological changes can be found in other brain regions, including the locus coeruleus, pedunculopontine nucleus, raphe nuclei, olfactory bulb, autonomic nervous system, Meynert nucleus, and cerebral cortex. The degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNpc) is primarily recorded as motor symptoms – tremor, slowed movement, muscle rigidity, and postural instability. However, non-motor symptoms such as anxiety, depression, hallucinations, cognitive impairment, sleep disturbances, and autonomic dysfunction are increasingly recognized as significant contributors to diminished quality of life as the disease progresses (Balestrino and Schapira 2020).

Among the pharmacological options for PD, monoamine oxidase-B (MAO-B) inhibitors, including selegiline and rasagiline, play a central role. These agents act by selectively blocking the MAO-B enzyme, thereby reducing dopamine breakdown in the brain and increasing its availability for neurotransmission. This mechanism enhances both the effectiveness and duration of dopamine's action. MAO-B inhibitors can be used alone in early PD or in combination with levodopa in advanced stages, where they help manage motor fluctuations and extend the therapeutic window of levodopa treatment (Tan et al. 2022).

This review will examine the pathogenesis of PD, highlighting key factors that contribute to its development. Furthermore, it will also discuss current therapeutic strategies, including the latest advancements in PD treatment and novel multi-target compounds, incorporating data compiled from 2021 onwards.

Pathogenesis of PD

Several mechanisms have been associated with the development of PD, with the accumulation of α-synuclein considered a key factor in its pathogenesis. In addition to this, research indicates that disruptions in protein clearance, problems with mitochondrial function, and inflammation within the nervous system may also contribute to both the onset and advancement of the disease. Despite these findings, the exact connections and interactions among these different biological pathways are not yet fully understood. In the current article, we focused on α-synuclein misfolding and aggregation, mitochondrial dysfunction, neuroinflammation, and environmental factors (Balestrino and Schapira 2020).

α-Synuclein: misfolding and aggregation

PD is marked by the progressive loss of dopamine-producing neurons in the midbrain, the buildup of α-synuclein protein aggregates within nerve cells, and ongoing inflammation in the nervous system. The crystal structure of α-synuclein is given in Fig. 1 (Roodveldt et al. 2024).

These abnormal protein clumps are known in the literature as Lewy bodies (LBs) and are found alongside Lewy neurites, which are located in the axons (Spillantini et al. 1997).

LBs appear as dense clusters within neurons, composed of a mixed granular and fibrous center encircled by a lighter peripheral zone, as depicted in Fig. 2A. These structures vary significantly in size, typically measuring between 5 and 30 micrometers across, and multiple LBs may cluster within a single nerve cell. Two primary variants exist: the well-defined brainstem type with a halo and the smaller, fainter cortical type without this clear boundary (Fig. 2B). Additionally, similar protein accumulations form in neuronal extensions (axons), where they are termed Lewy neurites (Fig. 2C). In the substantia nigra, early-stage LB precursors called "pale bodies" occasionally develop before maturing into full LBs (Fig. 2D) (Spillantini et al. 1998).

Lewy bodies are primarily made up of filamentous α-synuclein, a protein that is widely present in the brain. In PD and other synucleinopathies, α-synuclein adopts an abnormal, amyloid-like filamentous form and becomes excessively phosphorylated and aggregated (Goedert et al. 2013). Alongside α-synuclein, Lewy bodies contain a variety of other proteins, including ubiquitin, tau, parkin, and heat shock proteins, as well as oxidized and nitrated proteins. They also include cytoskeletal components such as neurofilaments, microtubule-associated proteins (MAPs), and tubulin, in addition to elements from the proteasomal and lysosomal systems. The presence of these diverse proteins underscores the complex disturbances in protein handling and cellular stress responses that occur in affected neurons (Xia et al. 2008).

In its natural form in the brain, α-synuclein is mostly unstructured and does not possess a stable three-dimensional shape. However, in aqueous environments, it can assemble into stable tetramers that are less likely to aggregate (Burré et al. 2013). When α-synuclein comes into contact with negatively charged lipids – such as the phospholipids found in cell membranes – it undergoes a conformational change. This interaction causes the protein, particularly through its N-terminal region, to fold into α-helical structures. These structural transitions help regulate its normal function and influence its tendency to form aggregates under pathological conditions (Eliezer et al. 2001; Lashuel et al. 2023).

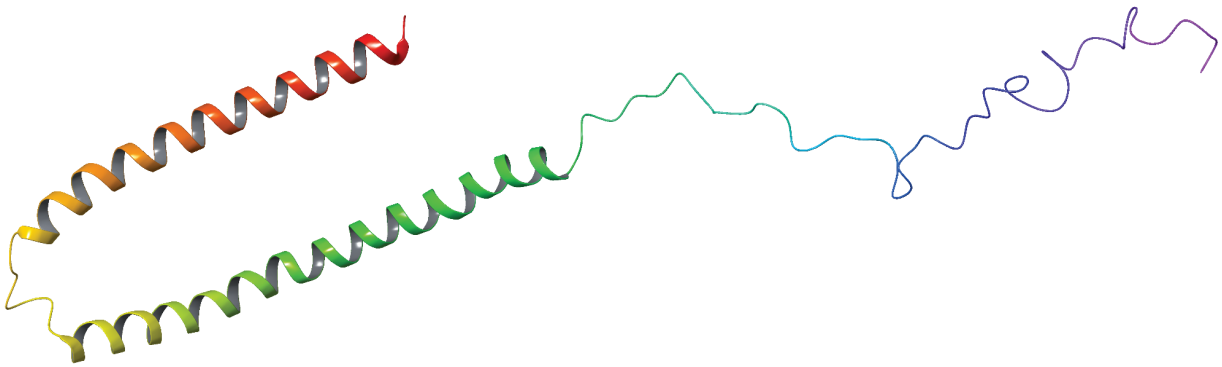

Figure 1. Crystal structure of human micelle-bound α-synuclein (PDB: 1XQ8) visualized through Maestro (Schrödinger).

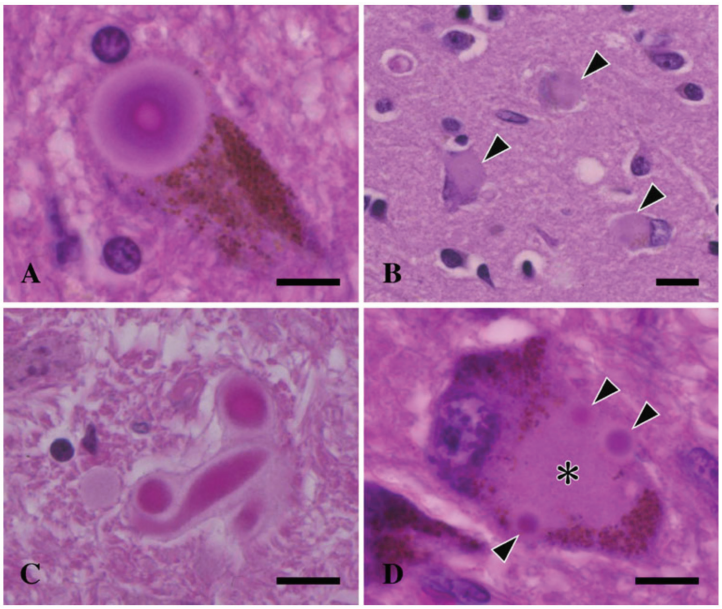

Figure 2. Hematoxylin and eosin stain of Lewy bodies and pale bodies. **A.** Concentric LB present in the substantia nigra; **B.** Cortical LB in the temporal cortex; **C.** Intraneuritic LB; **D.** Pale body (asterisk) and Lewy bodies (arrowheads) found in a pigmented neuron in the substantia nigra. Taken from Wakabayashi et al. (2013). Scale bars: 10 μm.

In PD, α-synuclein undergoes structural reorganization, transitioning into a β-sheet-dominated amyloid configuration that promotes clumping. These aberrant protein assemblies form filamentous structures measuring 5–10 nanometers in diameter, which are prominent components of Lewy bodies. Multiple pathways are implicated in driving this pathological transformation – such as phosphorylation at the serine 129 residue, attachment of ubiquitin molecules, and cleavage of the protein's C-terminal region. This results in a spectrum of α-synuclein forms within affected brain tissue, ranging from disordered single molecules and soluble intermediate clusters to elongated protofibrils and densely packed, insoluble fibrillar aggregates (Fig. 3) (Baba et al. 1998).

Emerging research using animal models highlights oligomeric forms of α-synuclein – small, soluble clusters of misfolded protein – as primary drivers of neuronal damage in PD, surpassing the toxicity of larger, insoluble fibrils. Cellular studies consistently demonstrate that these oligomers disrupt membrane integrity, trigger inflammatory responses, and induce mitochondrial dysfunction more potently than their fibrillar counterparts. A critical mechanism underlying their pathogenicity involves their role as "seeds" that template further misfolding of native α-synuclein, propagating aggregation cascades across neural networks. This seeding activity is hypothesized to facilitate the cell-to-cell transmission of pathological α-synuclein, contributing to the progressive spread of neurodegeneration observed in PD. Experimental evidence further indicates that fibrils dynamically release oligomeric species during their growth phase, with shorter fibrils generating higher oligomer concentrations due to increased surface area for secondary nucleation (Karpinar et al. 2009; Winner et al. 2011).

Over the past twenty years, laboratory, tissue-based, and animal studies have repeatedly demonstrated that microglial and astrocytic activation drives inflammatory processes in PD, which are triggered by misfolded α-synuclein aggregates or distress signals from compromised

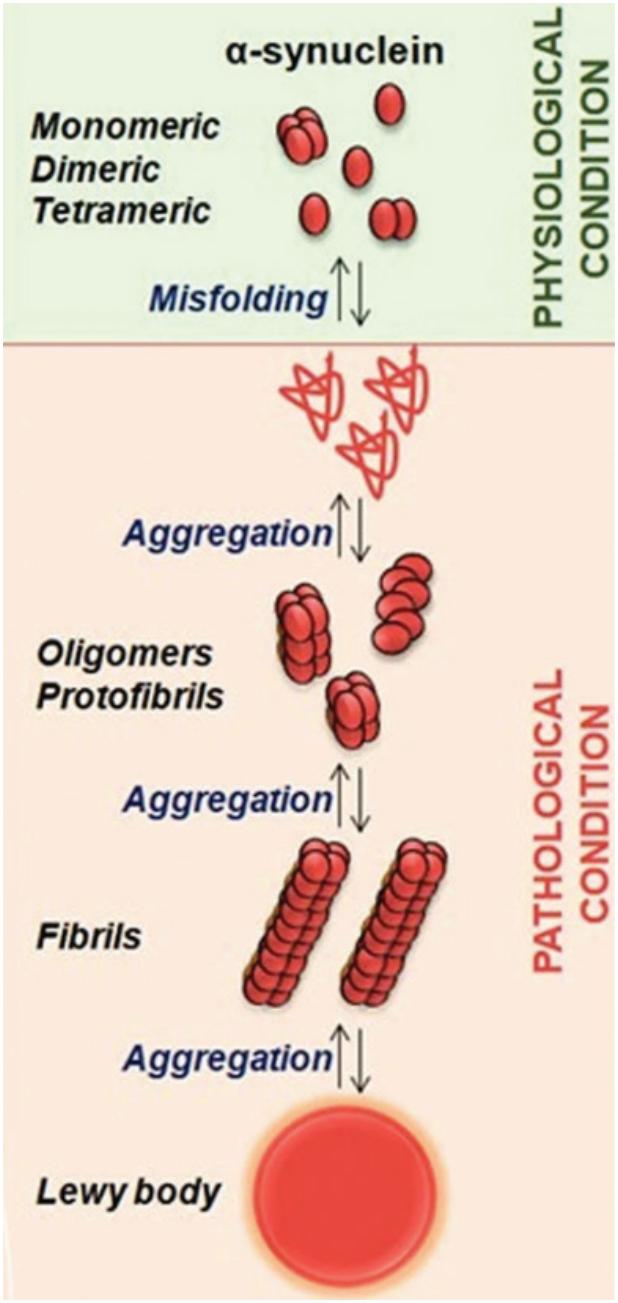

Figure 3. Physiological and pathological conditions of *α*Syn (Calabresi et al. 2023).

neurons and neighboring cells, directly contributing to neuronal loss and disease progression. Beyond central nervous system immune dysregulation – such as T cell migration into brain regions – emerging research highlights systemic immune adaptations affecting both innate and adaptive immunity. Notably, monocytes and T lymphocyte subsets (including CD4+ and CD8+ cells) exhibit altered functional profiles, reflecting broader immune system engagement in PD pathogenesis (Danzer et al. 2009).

Mitochondrial dysfunction

Mitochondrial dysfunction is recognized as a crucial factor in the development of PD. Studies of brain tissue from Parkinson's patients revealed a deficiency in mitochondrial complex I, an essential part of the electron transport chain responsible for cellular energy production. This discovery was among the first to directly associate mitochondrial impairment with PD. Similar deficits in complex I activity have also been observed in skeletal muscle and platelets of individuals with Parkinson's, compared to healthy people (Krige et al. 1992; Moon and Paek 2015).

Further evidence for the importance of mitochondrial dysfunction emerged from cases involving the drug MPTP, which, when abused, leads to persistent Parkinsonian symptoms and loss of dopamine-producing neurons. MPTP is converted in the body to a toxic compound that is taken up by dopamine neurons, where it inhibits complex I, resulting in cell death. Other environmental toxins, such as the pesticides rotenone and paraquat, also block complex I activity and produce Parkinson's-like symptoms and dopamine neuron loss in animal studies and possibly in humans. These findings suggest that defects in mitochondrial complex I play a critical role in the death of dopaminergic neurons by depleting the cell's energy reserves and increasing vulnerability to damage (Langston et al. 1999; Tanner et al. 2011).

Mitochondrial dysfunction is increasingly recognized as a central contributor to PD pathogenesis, supported by genetic and molecular evidence linking familial PD genes to mitochondrial processes. For instance, mutations in PINK1 and PRKN (associated with the PARK6 and PARK2 loci, respectively) disrupt mitochondrial quality control by impairing mitophagy – the selective degradation of damaged mitochondria. These recessive mutations result in the accumulation of dysfunctional organelles, exacerbating oxidative stress and neuronal vulnerability, particularly in dopaminergic cells (Luth et al. 2014).

A key pathological player, α-synuclein, exacerbates mitochondrial dysfunction through direct interactions. Misfolded α-synuclein accumulates on mitochondrial membranes, where it inhibits complex I activity, reducing ATP production and amplifying reactive oxygen species (ROS). Recent studies highlight a toxic interplay between oligomeric α-synuclein and the mitochondrial import machinery. Specifically, oligomers (but not monomers or fibrils) bind to TOM20, a receptor critical for importing nuclear-encoded proteins into mitochondria. This interaction disrupts protein import, compromises respiratory chain function, and perpetuates ROS generation. The resulting energy deficits and oxidative damage create a self-reinforcing cycle, accelerating neuronal degeneration (Di Maio et al. 2016).

These findings underscore a synergistic relationship between genetic susceptibility and protein-mediated toxicity, where mitochondrial impairments – whether inherited or acquired – drive PD progression through disrupted bioenergetics, proteostasis, and redox balance.

Neuroinflammation

Neuroinflammation is a complex process that plays a pivotal role in the pathogenesis of neurodegenerative diseases, including Parkinson's disease. The process involves the activation of immune cells within the CNS, such as

microglia and astrocytes, which release pro-inflammatory cytokines, chemokines, and ROS. Cytokines, such as tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and interferon-gamma (IFN-γ), are also released (Çınar et al. 2022). The neuroinflammation also involves adaptive immunity. Tansey et al. have discussed the significant role of T-cells, particularly CD8+ T Cells, in the SN of PD patients (Tansey et al. 2022). Targeting neuroinflammatory pathways offers promising therapeutic avenues, including the application of anti-inflammatory drugs and inhibitors of inflammatory signaling pathways like the NLRP3 inflammasome and NF-κB (Çınar et al. 2022).

Environmental factors

In addition to genetic and metabolic factors, environmental toxicants have emerged as significant contributors to the increasing incidence of PD. Pesticides, solvents such as trichloroethylene, and air pollution represent some of the most prevalent environmental toxins associated with PD. These toxicants can accumulate in the body through various exposure routes, including inhalation, ingestion, and skin contact. Research has demonstrated that prolonged exposure to these environmental toxins disrupts mitochondrial function and induces neurodegenerative processes. Specifically, the widespread use of agricultural chemicals, alongside urban air pollution, has been identified as a critical environmental risk factor for the development of PD. This underscores the importance of mitigating exposure to these toxicants as a potential strategy for disease prevention. While environmental factors play a pivotal role, other contributors have also been implicated in the rising prevalence of PD. One such factor is the advancement of diagnostic techniques over recent decades. Progress in neuroimaging, biomarker discovery, and refined clinical diagnostic criteria has facilitated the detection of PD, particularly in its early stages. Consequently, these improvements in diagnostic accuracy have led to a greater number of identified cases, including individuals who may have previously been misdiagnosed or underdiagnosed. However, while enhanced diagnostic capabilities and greater awareness have contributed to more precise identification of PD, they alone cannot fully account for the significant rise in its prevalence. Age is another critical factor implicated in this trend, with the incidence of PD increasing exponentially in individuals aged 60 and older. Although the overall incidence of PD correlates with advancing age, it has escalated disproportionately relative to other age-related neurodegenerative diseases, such as Alzheimer's disease. Importantly, while aging is a key risk factor, it does not independently cause PD but likely contributes through age-related physiological changes that may exacerbate the disease process (Dorsey and Bloem 2024).

Overall, the pathogenesis of PD is a complicated process involving a complex interaction of genetic, environmental, and molecular factors. To this day, the aggregation of α-synuclein remains a central factor, forming the hallmark Lewy bodies and Lewy neurites that contribute to the loss of dopaminergic neurons in the substantia nigra (Morris et al. 2024).

Current therapeutic approaches

DA-ergic approaches

The standard therapy for PD is based on the restoration of dopamine (DA, 3,4-dihydroxyphenethylamine) (Fig. 4A) levels in the dopaminergic system and consists of the administration of levodopa (Fig. 4B) (L-DOPA, l-3,4-dihydroxyphenylalanine), which passes through the blood–brain barrier (unlike DA) and is metabolized to DA by aromatic L-amino acid decarboxylase. L-DOPA significantly improves motor symptoms in PD, yet chronic treatment is often associated with a progressive decrease in drug efficacy and the development of complications such as involuntary movements known as levodopa-induced dyskinesia (LID).

Extended use of L-DOPA, a primary treatment for PD, has been linked to neuronal damage stemming from oxidative stress. This occurs when dopamine metabolism via MAO generates ROS within dopamine-producing neurons (Kwon et al. 2022). Laboratory experiments using serotonergic RN46A-B14 cells – which synthesize dopamine when exposed to L-DOPA – demonstrate that prolonged L-DOPA exposure elevates intracellular ROS levels and triggers cell death (Stansley and Yamamoto 2013). However, blocking MAO activity with inhibitors like pargyline substantially mitigates these effects. Such findings imply that high or sustained L-DOPA doses may not only harm dopamine neurons but also disrupt serotonin-producing

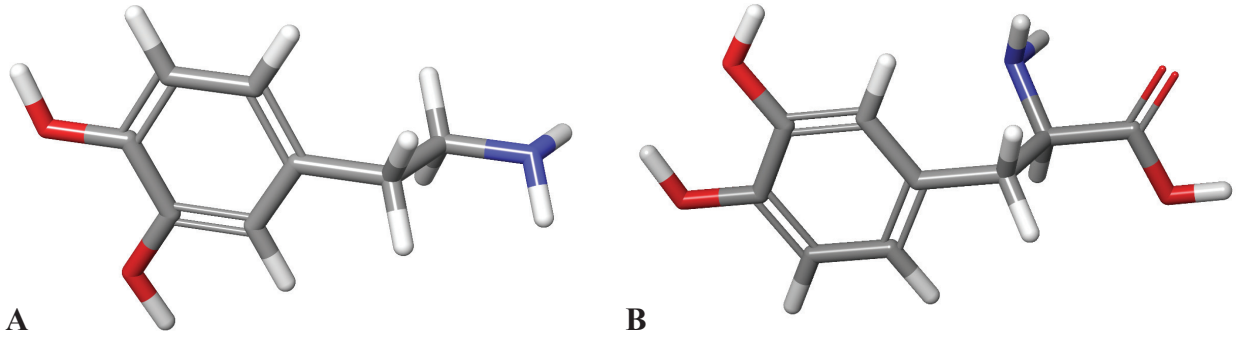

Figure 4. 3D structures of dopamine **(A)** and L-DOPA **(B)**.

cells, potentially explaining psychiatric complications such as depression and anxiety in PD patients. These risks underscore the urgent need to develop alternative therapies that balance efficacy with reduced neurotoxicity.

To maximize clinical benefit and reduce side effects, L-DOPA is routinely administered in combination with other agents. The addition of a peripheral dopa decarboxylase inhibitor (such as carbidopa or benserazide) prevents the premature breakdown of L-DOPA outside the brain, increasing its central bioavailability and reducing peripheral side effects like nausea and cardiovascular disturbances. Dopamine receptor agonists (e.g., pramipexole, ropinirole) are often used alongside or as alternatives to L-DOPA, allowing lower L-DOPA doses, smoothing motor fluctuations, and targeting symptoms not fully controlled by L-DOPA alone. Furthermore, catechol-O-methyltransferase (COMT) inhibitors (such as entacapone or opicapone) are co-administered to prolong L-DOPA's half-life and provide more stable plasma and brain dopamine levels, further minimizing motor complications and fluctuations (Gray et al. 2022; Lee et al. 2024). This combined pharmacological strategy has become a mainstay in modern PD management, as it allows tailoring therapy to both maximize efficacy and limit neurotoxic and neuropsychiatric risks, emphasizing the move toward individualized patient care.

One known mechanism for indirectly increasing DA levels is through the administration of monoamine oxidase inhibitors. The MAO-B isoform predominates in the human brain, where it degrades DA to 3,4-dihydroxyphenylacetic acid and homovanillic acid. MAO-B converts endogenous and exogenous dopamine to hydrogen peroxide. Therefore, it is essential for the processes involved in oxidative stress and oxidative damage that occur in PD.

MAO-B inhibitors, such as selegiline and rasagiline (Fig. 5A, B), work by blocking the breakdown of dopamine in the brain, thereby increasing dopamine levels in the synaptic cleft and enhancing dopaminergic signaling. This inhibition not only improves motor symptoms in PD but also reduces the formation of harmful free radicals that result from dopamine oxidation. Additionally, MAO-B inhibitors prevent the conversion of the neurotoxin MPTP into its active, toxic form MPP+ in animal models, which contributes to their neuroprotective effects (Dezsi and Vecsei 2017).

These medications are effective as monotherapy in the early stages of PD and can also be used alongside L-DOPA to help manage motor fluctuations and extend periods of symptom control. Rasagiline, in particular, is widely prescribed due to its neuroprotective properties and potential to slow disease progression. The clinical benefits of MAO-B inhibitors have been further supported by the approval of safinamide, a selective MAO-B inhibitor, which has been shown to improve both motor and certain non-motor symptoms in people with PD (Dezsi and Vecsei 2017).

Based on the etiology of PD and the role of α-synuclein in its development as a major component of Lewy bodies, a possible therapy for PD is inhibition of α-synuclein protein aggregation by administration of multifunctional small molecules. One such alternative is the MAO-B inhibitor selegiline, which modulates the intracellular clearance of α-synuclein via the ABC transporter-mediated non-classical secretion pathway and temporarily suppresses the formation and transmission of α-synuclein aggregates (Fig. 5) (Pagano et al. 2015).

Levodopa (L-DOPA) is associated with a range of mild side effects, including nausea, vomiting, and hypotension, as well as more severe complications, such as behavioral disturbances and the production of toxic metabolites (Paul and Borah 2016). It has been demonstrated that more than 40% of individuals treated with DA agonists experience impulse control disorders, including pathological gambling, aberrant sexual and eating behaviors, and compulsive medication use (Garcia-Ruiz et al. 2014). Moreover, patients who cease the use of these medications often experience withdrawal symptoms. In addition, young patients presenting with tremor are frequently prescribed anticholinergic agents, such as benztropine, trihexyphenidyl, orphenadrine, procyclidine, and biperiden. However, the prescription of these drugs necessitates careful monitoring due to their potential side effects, particularly those associated with cognitive impairments (Armstrong and Okun 2020).

Non-DAergic approaches – mAChR inhibitors, NMDA blockers

Two additional non-dopaminergic therapeutic strategies are currently employed in clinical practice to alleviate motor deficits in Parkinson's disease. The first strategy involves the inhibition of muscarinic cholinergic receptors (mAChRs), such as through the use of trihexyphenidyl, while the second targets the blockade of ionotropic glutamate receptors (NMDA) within the central nervous system (CNS), exemplified by the use of amantadine (Crosby et al. 2003; Danysz et al. 2021; Rascol et al. 2021). Both NMDA and mAChR receptors are extensively distributed throughout the CNS, and their blockade can significantly modulate neurotransmission, potentially resulting in CNS dysfunction (Bouvier et al. 2015). A deeper understanding of the underlying mechanisms of PD could inform future research and the development of novel therapeutic approaches. For instance, strategies aimed at mitigating oxidative stress – a key factor in the progression of the disease – could be explored by designing pharmacological agents that enhance the body's antioxidant defenses within the substantia nigra. Numerous studies have highlighted the role of antioxidants in the prevention and treatment of PD. For example, a study of 80 patients on the effectiveness of CoQ10 and glutathione found a statistically significant effect on PD symptoms (Weber and Ernst 2006). There are also numerous *in vitro* studies of antioxidants taken with food that inhibit oxidative stress processes. Reducing the negative impact of ROS in patients with PD may be a key element in slowing disease progression and improving quality of life.

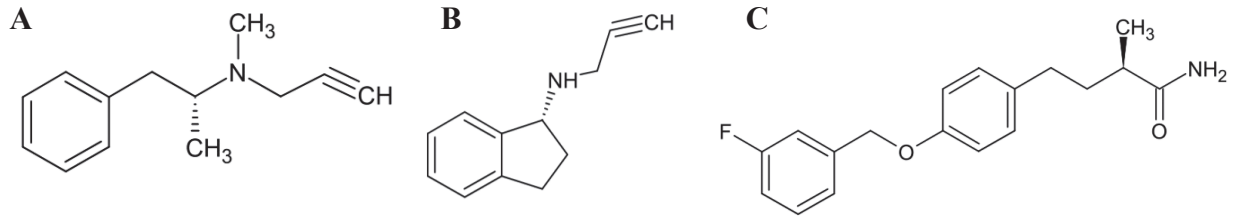

Figure 5. Structures of approved MAO-B inhibitors. **A.** Selegiline; **B.** Rasagiline; **C.** Safinamide.

While treatments aimed at restoring DA levels can help to re-establish extracellular DA concentrations, they do not reverse the functional and anatomical alterations in non-dopaminergic systems. As a result, several alternative, non-DA-based therapeutic strategies have been proposed in recent years (Oertel and Schulz 2016). One such approach is deep brain stimulation (DBS), which has demonstrated both safety and efficacy for certain PD patients, regardless of disease stage. This success is primarily attributed to its ability to modulate specific brain regions, dependent on the targeted stimulation site (Muthuraman et al. 2018). The procedure involves the surgical implantation of unilateral or bilateral leads within the subthalamic nucleus or globus pallidus interna, which are connected to a chest-mounted battery.

In addition, neurotrophic factors, particularly glial cell line-derived neurotrophic factor (GDNF), have emerged as promising candidates for PD therapy. Several strategies have been developed to enhance the stability and retention of GDNF within the brain (Del Rey et al. 2018). Microencapsulated GDNF has been shown to improve motor function and restore DA activity by exerting trophic effects on the nigrostriatal pathway in various PD animal models (Garbayo et al. 2009; Garbayo et al. 2016). Similarly, the administration of basic fibroblast growth factor has been reported to stimulate dopaminergic function in surviving synapses and confer neuroprotection in 6-OHDA hemiparkinsonian rats (Cai et al. 2016).

Another potential strategy involves the neural transplantation of stem cells, which possess self-renewal capacity and the ability to differentiate into dopaminergic neurons. Mesenchymal stem cells, in particular, can differentiate into a range of neuronal phenotypes, including dopaminergic, noradrenergic, serotonergic, and cholinergic cells, making them promising candidates for addressing non-motor symptoms (NMSs) in PD (Romito and Cobellis 2016).

Antioxidant-based therapies have emerged as a complementary strategy in managing PD, targeting oxidative stress – a key contributor to dopaminergic neuron degeneration. While ROS are natural byproducts of metabolic processes, their excessive accumulation in dopamine-producing neurons, driven by enzymatic and non-enzymatic dopamine metabolism, heightens susceptibility to cellular damage (Nakamura et al. 2021). Postmortem analyses of PD patients' brains reveal elevated markers of oxidative damage, such as lipid peroxidation and protein nitration, particularly in the substantia nigra, reinforcing the link between oxidative stress and neurodegeneration (Saito 2017).

Clinical trials evaluating coenzyme Q10 (CoQ10), a mitochondrial antioxidant, demonstrated its safety and potential to slow functional decline in early-stage PD patients, though efficacy varied with dosage and disease progression (Fig. 6A) (Jenner and Olanow 2006). Additionally, studies report reduced plasma levels of exogenous antioxidants, including vitamin C, in PD patients compared to healthy individuals, suggesting a possible role for dietary supplementation (Fig. 6B) (Shults et al. 2002). Experimental models indicate that vitamin C may mitigate levodopa-induced neurotoxicity by scavenging free radicals and stabilizing dopaminergic cells. However, clinical evidence for its therapeutic benefits remains inconsistent, highlighting the need for further research to optimize antioxidant interventions and validate their disease-modifying potential.

Furthermore, the neuroprotective effects of vitamin E in PD have been investigated (Fig. 6C). As a potent free radical scavenger, vitamin E has the potential to reduce oxidative stress – a critical factor in the pathogenesis of PD. Although vitamin E has shown promise in animal models and early clinical trials, the results are inconclusive, and additional preclinical and clinical studies are necessary to fully elucidate its therapeutic potential (Filograna et al. 2016).

Administration of various antioxidants successfully maintains neuronal viability while preserving and improving the activity of their antioxidant system in preclinical models of PD. Unfortunately, when experimental models turn into clinical trials, these therapies are less effective. However, failed clinical trials of non-enzymatic antioxidants in PD do not necessarily preclude the possibility of future success (Foy et al. 1999; Olanow et al. 2024).

Considering the significant contribution of neuroinflammation to the development of PD, targeting the immune system has become a promising strategy for treatment. Certain nonsteroidal anti-inflammatory drugs (NSAIDs) have been shown to protect dopaminergic neurons from damage (Fren et al. 2018). Additionally, recent research suggests that probiotics may offer neuroprotection in various PD models by reducing inflammation (Castelli et al. 2020; Lubomski et al. 2020). Probiotic use has also been associated with improvements in gastrointestinal symptoms such as constipation, bloating, and abdominal discomfort in individuals with PD (Knudsen et al. 2017).

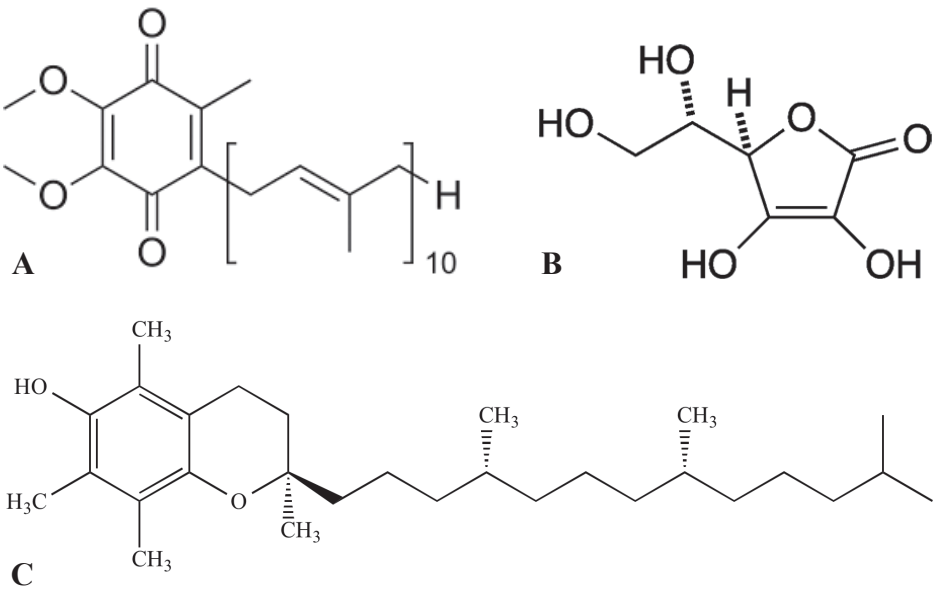

Figure 6. Antioxidants with potential neuroprotective effects in PD. **A.** Coenzyme Q10; **B.** Vitamin C; **C.** α-Tocopherol.

Multi-target treatment

The multitarget-directed ligand (MTDL) design approach represents an innovative paradigm in neurochemistry, focusing on the design and synthesis of dual-acting molecules capable of simultaneously addressing multiple targets within the neurodegenerative cascade. Traditional drug design methodologies – highlighting the "one protein, one target" principle – are often inadequate for addressing the complex, multifactorial nature of neurodegenerative disorders. The efficacy of single-target drugs is frequently compromised by the emergence of resistance, as active sites on target proteins are susceptible to mutations. In contrast, targeting multiple proteins reduces the probability of concurrent mutations across all targets, thereby enhancing therapeutic resilience. This approach has led to the creation of compounds with at least two distinct mechanisms of action, enabling the modulation of multiple pathways implicated in a single disease (Mathew et al. 2019).

MAO and ChE

Reported scientific papers suggest that AChE may influence the apoptosis of dopaminergic neurons, a key factor in PD progression. Moreover, increased AChE expression can induce apoptosis in cell models, while AChE deficiency may protect against dopaminergic neuron loss. Cholinesterase inhibitor drugs can improve cognitive function; however, they may exacerbate motor symptoms and increase tremors (Boos et al. 2021). A recent paper by Pagano et al. (reference 35) discussed that cholinesterase inhibitors (ChIs) demonstrate efficacy in ameliorating cognitive impairment in patients with PD; however, the authors noted that these inhibitors show no significant impact on the reduction of fall risk. Below, we provide recent papers that discuss the synthesis/design, biological evaluation, and molecular docking of compounds targeting MAO-B and ChE enzymes.

A recent paper discussed the synthesis of seventeen N-methyl-piperazine chalcones, which were examined for their MAO-B and AChE inhibiting properties (El-Damasy et al. 2023). Two compounds were identified as potent dual MAO-B and AChE blockers (Fig. 7). The authors noted that disubstituted chalcones exert better enzyme inhibition, and the introduction of a four-halogen moiety adjacent to meta-trifluoromethyl was optimal for MAO-B inhibition. The novel compounds showed a high selectivity index toward MAO-B, which is of great importance. Moreover, the compounds demonstrated low cytotoxicity in a cell-based assay. A molecular docking study was also conducted to explore the active conformations of the lead molecules. Three crystal structures were used: MAO-A (PDB: 2Z5X), MAO-B (PDB: 4A79), and AChE (PDB: 6O4W), and AUTODOCK-VINA was used as the docking software. Interestingly, the trifluoro-based chalcone formed four hydrogen bonds and two π–π interactions with the active site of MAO-B, resulting in a stable complex. Overall, both dual-acting compounds showed moderate binding energies in the target proteins. However, no reference compounds were provided.

Boos et al. (2021) published a paper discussing the synthesis of novel dual inhibitors of MAO-B and AChE, which could be used in the treatment of Parkinson's disease. The main scaffold of the new molecules consisted of a six-membered ring fused with a five-membered ring, comparable to standard MAO-B and AChE inhibitors. The best compound demonstrated IC_{50} values of 16.83 μM against MAO-B and 22.04 μM against AChE (Fig. 8). Moreover, the neuroprotective effects of the compounds were examined. The results showed that the tested molecule, at concentrations of 30 μM, prevented the neurotoxic effects of 6-hydroxydopamine (6-OHDA) in *C. elegans*, protecting dopaminergic

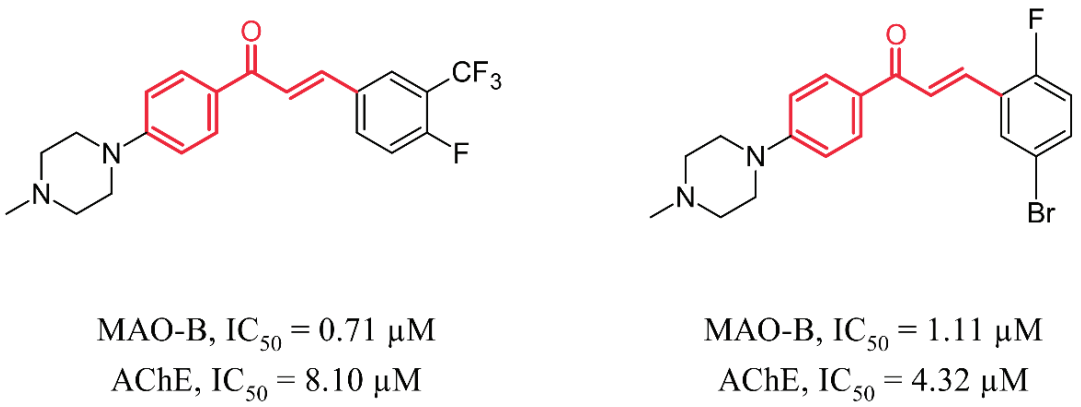

Figure 7. Novel N-methyl-piperazine chalcones as dual-acting MAO-B and AChE inhibitors.

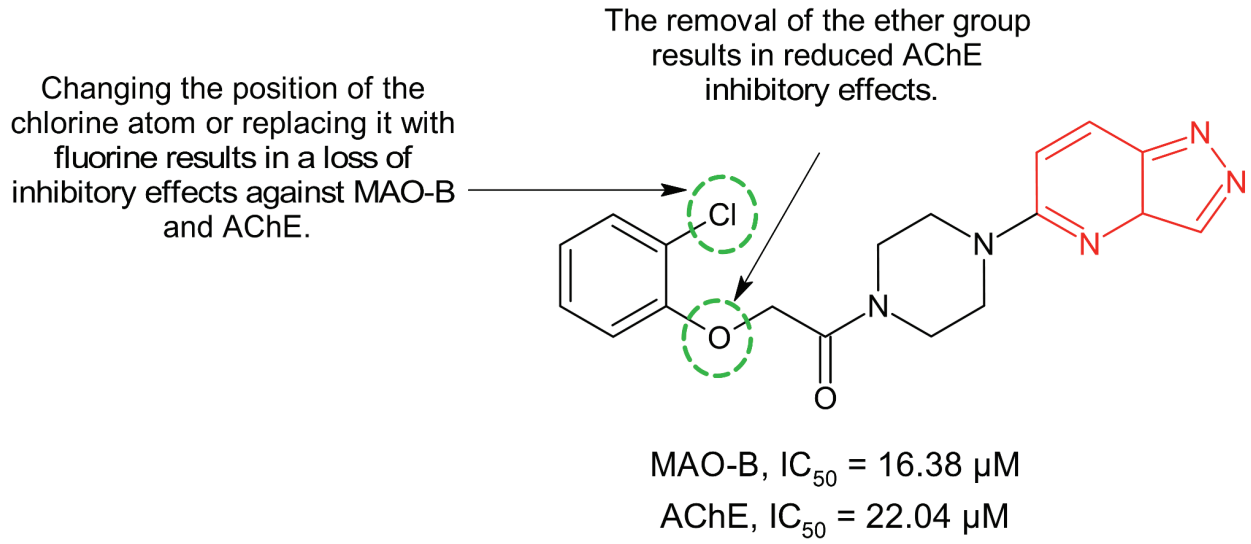

Figure 8. Dual MAO-B/AChE inhibitor containing a common core (depicted in red) found in zonisamide (MAO-B inhibitor) and donepezil (AChE inhibitor).

neurons. Docking studies in the active sites of the enzymes were also carried out. The authors used X-ray structures of MAO-B (PDB: 2V5Z) and AChE (PDB: 4EY7).

Liu et al. developed a novel hybrid compound targeting both monoamine oxidase (MAO) and acetylcholinesterase (AChE) for potential treatment of dementia and depression in PD (Youdim and Weinstock 2022). The compound, with code MT-031 ((S)-3-(1-(methyl(prop-2-yn-1-yl)amino)ethyl)phenyl ethyl(methyl)carbamate) (Fig. 9), was designed by combining structural elements from rasagiline (an MAO inhibitor) and rivastigmine (an AChE inhibitor). The core structure incorporates the propargyl fragment from rasagiline and the carbamate moiety from rivastigmine. *In vitro* assays revealed the following IC_{50} values for MT-031: MAO-A: 0.71 ± 0.04 μM; MAO-B: >1000 μM; AChE: 58.3 ± 6.3 μM. These results demonstrate that MT-031 exhibits selective inhibition of MAO-A over MAO-B, while also showing moderate AChE inhibitory activity. The compound's dual-target approach could potentially address multiple aspects of PD pathology. By inhibiting MAO-A, MT-031 may be particularly effective in managing depression associated with Parkinson's disease, while its AChE inhibitory activity could contribute to cognitive improvements.

Binici et al. found that indole-3-carbinol (I3C) could act as a dual MAO-B and AChE inhibitor at micromolar doses (Venkatesan et al. 2020). The compound demonstrated good MAO-B inhibition properties (IC_{50} = 40.05 μM) and good AChE blocking capacity (IC_{50} = 239.29 μM) (Fig. 10). Furthermore, molecular docking studies on the active sites of these enzymes were carried out. The *in silico* results highly correlated with the *in vitro* experimental results. Based on these findings, the I3C molecule demonstrates considerable promise as a potential therapeutic agent for addressing neurodegenerative disorders. These characteristics suggest that I3C warrants further investigation as a possible intervention for various neurodegenerative diseases, highlighting its potential significance in future medical research and drug development efforts aimed at combating these challenging neurological conditions.

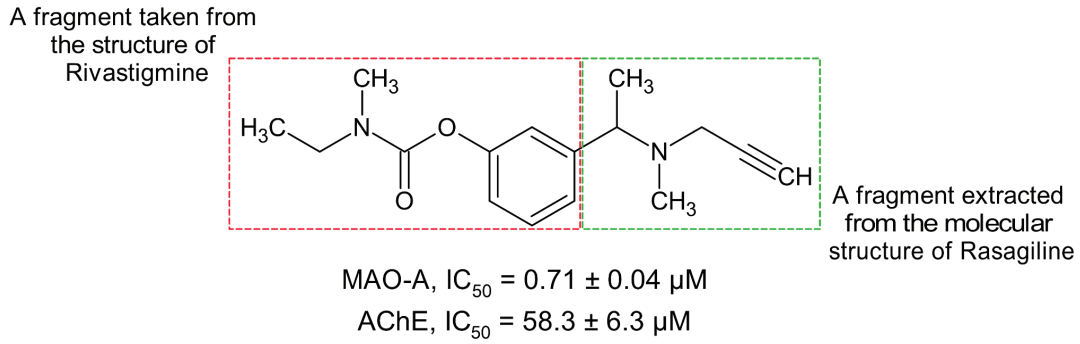

Figure 9. A hybrid structure with fragments extracted from rivastigmine (AChE inhibitor) and rasagiline (MAO-B inhibitor).

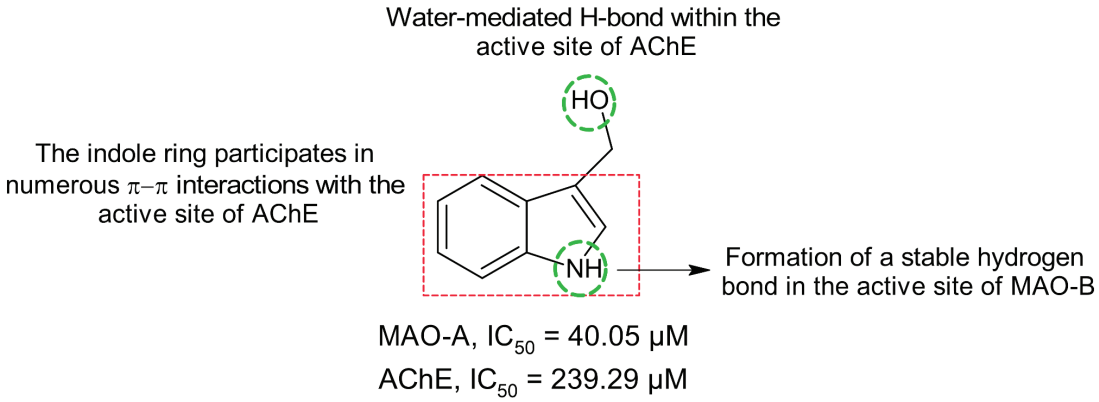

Figure 10. Indole-3-carbinol (I3C) as a dual-acting MAO-B/AChE inhibitor.

Bijo Mathew et al. published a study on the synthesis of novel piperazine-substituted chalcones, which exhibit dual inhibitory activity against MAO-B and AChE (Lee et al. 2021). These compounds represent a new class of potential therapeutic agents for treating neurological disorders – Alzheimer's disease and Parkinson's disease. The most potent molecule in the reported series demonstrated IC_{50} values of 9.91 μM for MAO-B inhibition and 72.1 μM for AChE inhibition (Fig. 11). Molecular docking studies were conducted using the crystal structures of MAO-B (PDB: 2V5Z) and AChE (PDB: 4EY7), revealing that the para-fluorine moiety of the compound was positioned close to the flavin adenine dinucleotide (FAD) cofactor. Additionally, the aromatic rings of the chalcone interacted with the active site amino acids Tyr398 and Tyr326 through π–π interactions. A structure–activity relationship (SAR) analysis was also performed to further understand the molecular basis of these interactions and optimize the design of future compounds.

Our research group recently reported a study on *in silico* drug repurposing of FDA-approved drugs as novel dual MAO-B/AChE inhibitors for the potential treatment of Alzheimer's disease (Mateev et al. 2023). The investigation employed a consensus docking approach utilizing two software packages: Glide and GOLD 5.3. X-ray structures of human MAO-B (PDB: 2V5Z) and AChE (PDB: 4EY6) were obtained from the Protein Data Bank (PDB) for the docking simulations. The highest-ranked approved drugs identified through the *in silico* screening were subsequently evaluated for their inhibitory effects *in vitro*. Among these, the antiretroviral agent dolutegravir demonstrated the most promising results, exhibiting 41% inhibition of hMAO-B at 1 μM concentration and 68% inhibition of AChE at 10 μM concentration (Fig. 12). These findings suggest that dolutegravir may possess dual inhibitory activity against MAO-B and AChE, potentially offering a novel therapeutic approach for Alzheimer's disease. However, to validate these *in vitro* results and further assess the compound's efficacy and safety profile, additional in vivo evaluations are warranted.

A recent study reported by Yamali et al. (2021) explores the development of phenothiazine-based chalcones as multi-target therapeutic agents. The presented compounds were designed to inhibit both cholinesterases and monoamine oxidases. The study highlights the potential of phenothiazine-based structures to serve as dual-target inhibitors, which – as mentioned earlier – could provide a more effective therapeutic approach in the treatment of PD. The authors reported that the most active compound (Fig. 13) shows excellent inhibitory effects against MAO-B and AChE, with IC_{50} values of 0.048 μM for MAO-B and 0.053 μM for AChE. The reported values are comparable with the applied standards – selegiline and donepezil.

A non-selective MAO inhibitor comprising AChE blocking effects was synthesized by Huang et al. (2024) (Fig. 14). The majority of synthesized compounds displayed robust inhibitory activity against cholinesterases (ChEs) and monoamine oxidases (MAOs). Importantly,

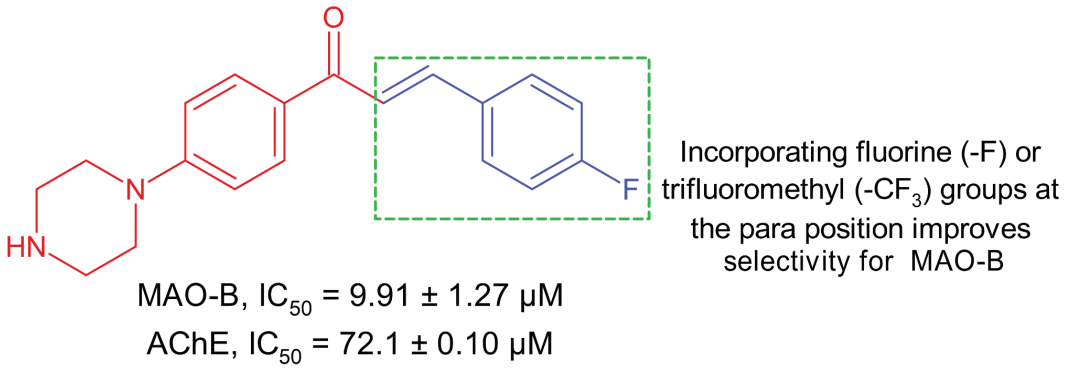

Figure 11. Piperazine-substituted chalcone as a dual-acting MAO-B/AChE inhibitor.

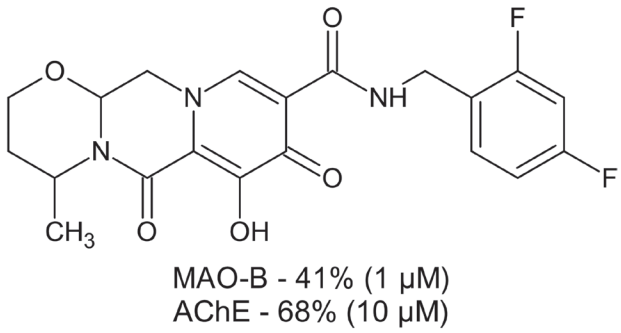

Figure 12. Dolutegravir as a dual-acting MAO-B/AChE inhibitor.

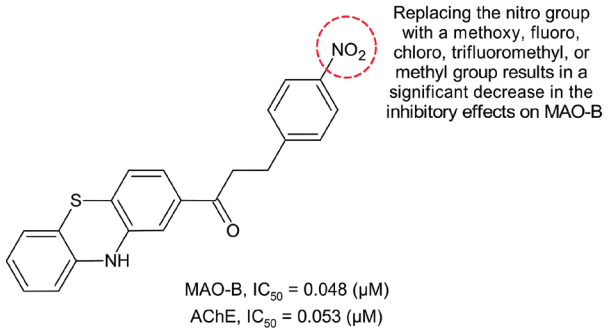

Figure 13. Novel chalcone-based drug with dual-acting properties.

the most active compound depicted in Fig. 14 demonstrated a well-balanced profile of inhibitory activity, with IC_{50} values of 1.57 μM for AChE, 0.43 μM for hBuChE, 2.30 μM for hMAO-A, and 4.75 μM for MAO-B. Moreover, docking studies with the licensed software MOE were carried out in MAO-B (PDB: 2V61), AChE (PDB: 4EY7), and BuChE (PDB: 7QHD). The *in silico* simulations suggested the formation of stable enzyme–ligand complexes. The study highlights the potential of combining cholinesterase and monoamine oxidase inhibitors as a therapeutic strategy for neurodegenerative diseases.

Our research group has successfully developed pyrrole-based compounds with dual MAO-B and AChE inhibitory properties (Mateev et al. 2024; Mateev et al. 2024a). Among the synthesized derivatives, a hydrazide-functionalized pyrrole was identified as a hit compound (Fig. 15), exhibiting significant MAO-B inhibition with an IC_{50} value of 0.665 μM. Additionally, this compound demonstrated notable AChE inhibitory activity, with an IC_{50} value of 4.145 μM, highlighting its potential as a multifunctional agent for neurodegenerative diseases such as AD and PD. To enhance synthetic efficiency, all pyrrole derivatives were prepared using microwave-assisted synthesis, which markedly reduced reaction times and improved final product yields compared to conventional methods. Furthermore, *in silico* molecular docking studies were conducted to investigate the binding interactions of pyrrole-based ligands within the active sites of MAO-B (PDB: 2V5Z) and AChE (PDB: 4EY6). These computational analyses provided valuable insights into the functional groups responsible for stabilizing interactions. The results revealed that the hydrazide moiety plays a key role in enhancing ligand stability within the enzyme active sites, potentially contributing to its high inhibitory activity.

MAO and antioxidants

Dual monoamine oxidase B (MAO-B) inhibitors with antioxidant properties represent an innovative therapeutic strategy for PD, addressing both dopaminergic neurotransmission deficits and oxidative stress mechanisms central to disease progression. Oxidative stress exacerbates PD pathology by generating ROS during dopamine metabolism, damaging mitochondria, and promoting α-synuclein aggregation (Duarte et al. 2022).

A 2022 study explored the synthesis of novel 2-(1H-indol-3-yl)ethan-1-amine derivatives, investigating their dual functionality as Nrf2 inducers and MAO-B inhibitors (Duarte et al. 2022). The authors employed melatonin as a central scaffold, incorporating an alkyne moiety to mimic the primary functional group of the irreversible MAO-B inhibitor selegiline. Significantly, the majority of the synthesized compounds exhibited selective inhibition of MAO-B, with one of the most potent derivatives demonstrating a selectivity index of up to 19.5. The Nrf2 induction potential of these compounds was evaluated using a stable human mammary epithelial cell line, MCF7, as a model system. The compound exhibiting the highest activity as both an MAO-B inhibitor and an Nrf2 inducer is illustrated in Fig. 16.

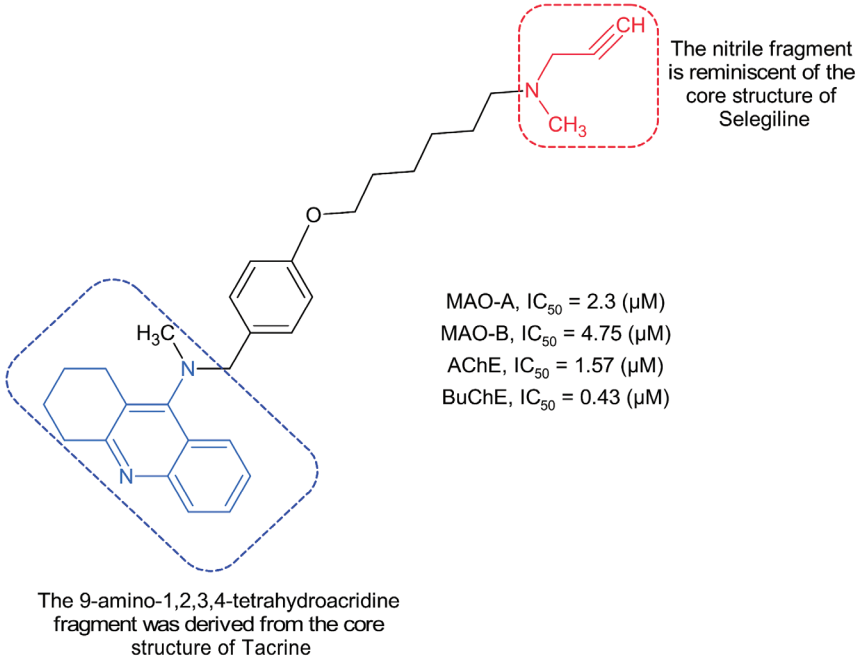

Figure 14. Tacrine–selegiline hybrid molecule with ChE/MAO inhibitory effects.

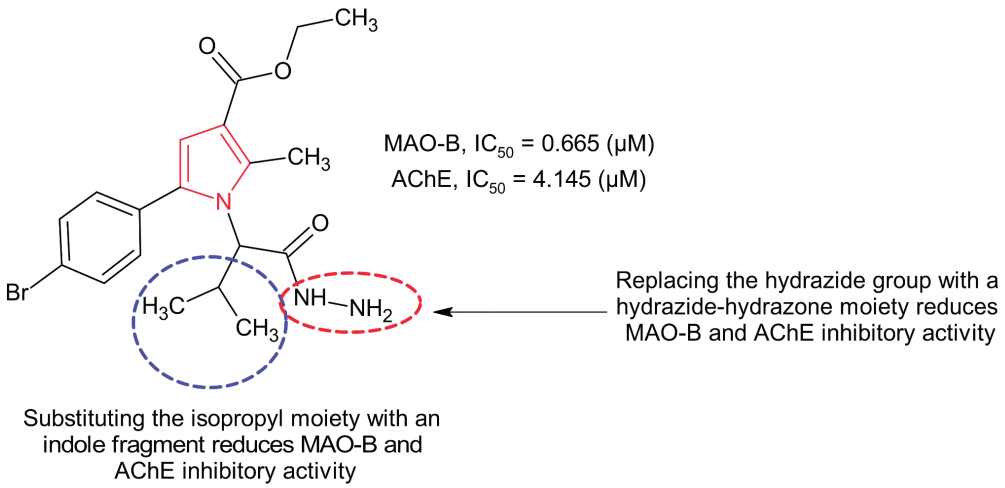

Figure 15. Pyrrole-based compound as a dual-acting MAO-B/AChE inhibitor.

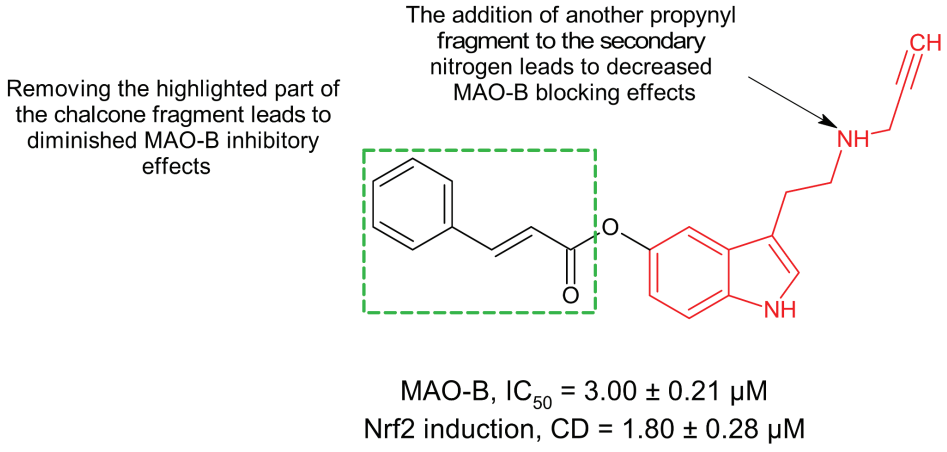

Figure 16. Melatonin-based compound with MAO-B and Nrf2-inducing properties.

A recently published paper by Basagni et al. discussed the synthesis of novel pioglitazone hybrids designed as dual MAO-B inhibitors and Nrf2 translocation inducers (Basagni et al. 2023). The newly synthesized compounds exhibited slightly reduced MAO-B inhibitory activity compared to pioglitazone, with inhibition constants (Ki) ranging from 0.53 ± 0.17 μM to 3.3 ± 1.0 μM for human MAO-B. Molecular docking studies were conducted in the active site of MAO-B (PDB: 4A79), revealing that the most active compound (Fig. 17) was positioned within the substrate cavity, primarily stabilized by hydrophobic interactions. The authors also reported that the aforementioned compound exhibited no cytotoxic effects at concentrations up to 50 μM. Overall, the study demonstrated an effective design strategy for novel pioglitazone-based derivatives, showcasing their enhanced antioxidant properties.

A 2025 study introduced a novel class of dual MAO-B inhibitors and Nrf2 inducers with neuroprotective properties in PD models (Duarte et al. 2025). The authors enhanced the compounds' MAO-B inhibitory potency, selectivity, and Nrf2 induction capacity while maintaining good pharmacokinetic profiles. The indole-based compound depicted in Fig. 18 demonstrated potent anti-inflammatory and neuroprotective activity in oxidative stress-related *in vitro* models, along with high liver microsomal stability and favorable pharmacokinetics in mice – making it a promising candidate for further investigation as a potential PD therapy.

A recent study explores the neuroprotective, radical-scavenging, and MAO-B inhibitory properties of newly synthesized benzimidazole arylhydrazones as potential multi-target drugs for the treatment of PD (Anastassova et al. 2022). The compounds were designed to address the multifactorial nature of PD by combining MAO-B inhibition, antioxidant activity, and neuroprotective effects. Structural modifications – including the incorporation of hydroxy and methoxy groups into the arylhydrazone moieties – were introduced to enhance therapeutic efficacy. Among the tested compounds, a catechol-containing derivative demonstrated strong effects (Fig. 19). It exhibited potent MAO-B inhibition with IC_{50} values comparable to those of clinically used inhibitors. Additionally, in neuroprotection assays using 6-OHDA- and H_2O_2-induced neurotoxicity models, the depicted compound stabilized neuronal membranes and effectively mitigated oxidative stress. The hydrazone moiety was identified as a key structural feature responsible for MAO-B inhibition based on established structure–activity relationships.

MAO-B & MAO-A inhibitors

A paper by Mathew et al. (2021) discussed the synthesis of novel methylthiosemicarbazones as MAO inhibitors. Ten new compounds were synthesized through reactions between methylthiosemicarbazide and substituted methylketones. The most selective inhibitor is depicted in Fig. 20. Notably, this compound did not exhibit AChE inhibitory properties but showed moderate MAO-A blocking effects. The X-ray structure of MAO-B, with the PDB code 2V5Z, was utilized for *in silico* docking simulations. These simulations revealed a π–π interaction between Tyr326 and a benzene fragment. Interestingly, no hydrogen bonds were formed within the active site of MAO-B.

A recent study explores the synthesis and biological evaluation of isatin-based hydrazone derivatives as monoamine oxidase (MAO) inhibitors, which are potential therapeutic agents for neurological disorders such as depression and PD (Maliyakkal et al. 2024). A total of ten compounds were synthesized, divided into two subseries (IA and IB, respectively). The first subseries was based on a combination of isatin and acetophenone, while the second subseries contained an isatin moiety combined with various benzaldehyde derivatives featuring different groups at the para-position of the benzene ring. Structure–activity relationship (SAR) analysis showed that halogenated derivatives from the IB subseries (compounds IB3 and IB4) had the most potent inhibitory effects. Compound IB3 (Fig. 21) was identified as the strongest MAO-B inhibitor, with an IC_{50} value of 0.068 μM. Both IB3 and IB4 were found to be competitive and reversible inhibitors of MAO-A and MAO-B. *In silico* docking studies

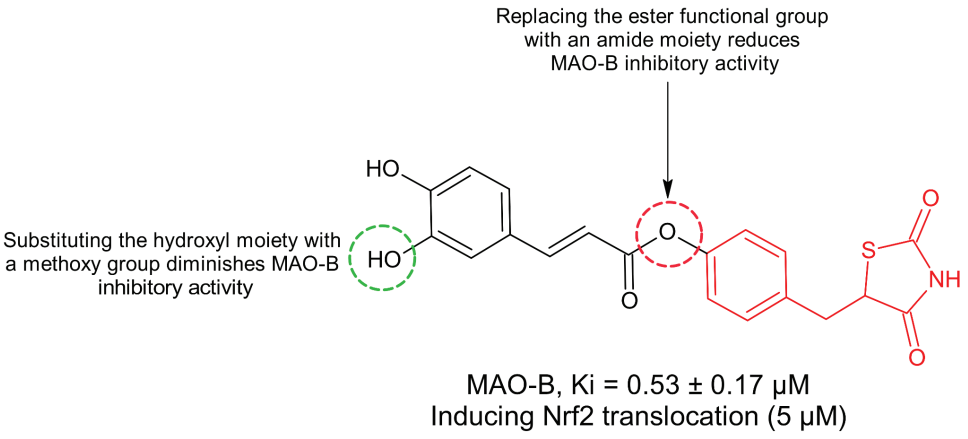

Figure 17. Novel pioglitazone hybrid molecule as an MAO-B inhibitor with Nrf2 translocation effects.

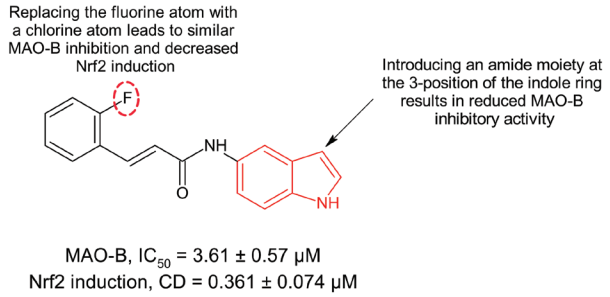

Figure 18. Indole-based compound as MAO-B inhibitor and Nrf2 inducer.

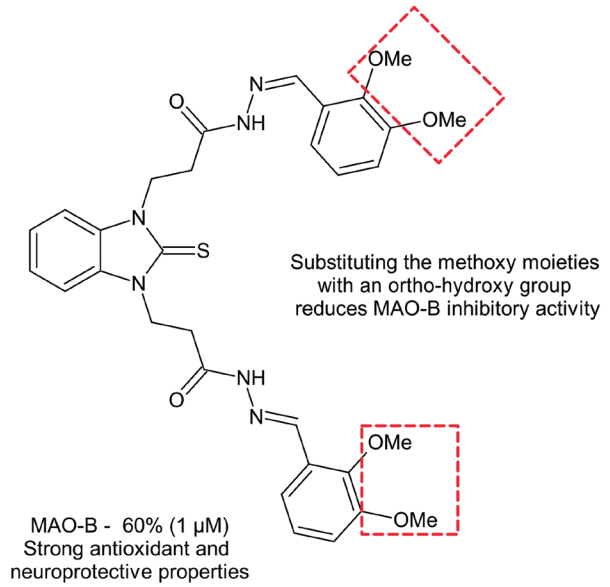

Figure 19. Benzimidazole arylhydrazone as an active MAO-B inhibitor and antioxidant.

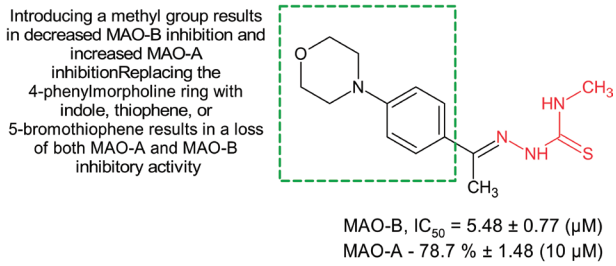

Figure 20. Methylthiosemicarbazones as novel MAO-B and MAO-A inhibitors.

showed that both compounds form stable hydrogen bonds with the Asn181 residue in the enzyme. The study identifies IB3 and IB4 as promising MAO inhibitors with potential applications in treating depression and PD.

MAO inhib and H3 antag

A recent study reported the synthesis of a series of novel compounds based on 1-(3-(4-tert-butylphenoxy)propyl) piperidine with various structural modifications (Łazewska et al. 2022). The synthesized compounds were tested for their binding affinity to H_3R and their inhibitory potency against human MAO-B (hMAO-B). Affinity for

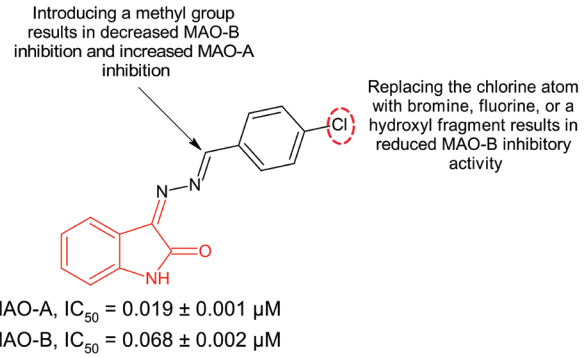

Figure 21. Isatin-based hydrazones as monoamine oxidase inhibitors (MAO-A/MAO-B).

hH_3R was evaluated in a radioligand binding assay using [^{3}H]N-methyl histamine as a radioligand in CHO K1 or HEK293 cells stably expressing hH_3R. The products in discussion, which excelled as the most potent hMAO-B inhibitors and showed strong H_3R affinity, were further analyzed for BBB permeability using the Parallel Artificial Membrane Permeability Assay (PAMPA). As a result, only one compound (Fig. 22) showed a high permeability, as the calculated *Pe* (Pe=16.72 × 10 $^{-6}$ cm/s) was very high and comparable to caffeine (Pe=15.1 × 10 $^{-6}$ cm/s). Regarding its inhibitory potential on the previously stated targets (MAO-B and H_3R), the selected DTL had undergone additional *in vivo* tests. The 4-tert-butylphenoxy derivative showed a positive effect on increasing cerebral DA levels in the rat's brain. The observed result was caused primarily by the blocking of MAO-B activity by the tested compound.

Miscellaneous

A study conducted by Hagenow et al. (2021) takes a look at the development of multi-targeting ligands (MTLs) that simultaneously block adenosine A_1/A_2A receptors (A_1R/A_2AR) and histamine H_3 receptors (H_3R). These ligands are designed to offer a novel therapeutic approach for PD by addressing both motor dysfunction and non-motor symptoms like sleep disturbances. As for the design of the synthesized molecules – a piperidino-/pyrrolidino(propyloxy)phenyl H_3R pharmacophore was merged with an adenosine antagonist arylindenopyrimidine core. Two lead compounds were identified; however, one of them possessed moderate MAO-B inhibitor effects – ST-1992 (Fig. 23). Receptor binding assays confirmed high affinity for A_1R, A_2AR, and H_3R. In addition, high selectivity was identified for the target receptors, with low affinity for dopamine D_1/D_5 receptors, reducing side effects. Furthermore, *in vivo* studies showed that ST-1992 (2 mg/kg, p.o.) increased wakefulness and reduced slow-wave sleep (SWS). In conclusion, the analyzed compounds (ST-2001 and ST-1992) show promise as multi-targeting ligands for PD, potentially reducing dyskinesia while also addressing non-motor symptoms like sleep disturbances.

A recent study highlights the potential of ethyl ferulate (Fig. 24) as a dual-acting compound with both MAO-B

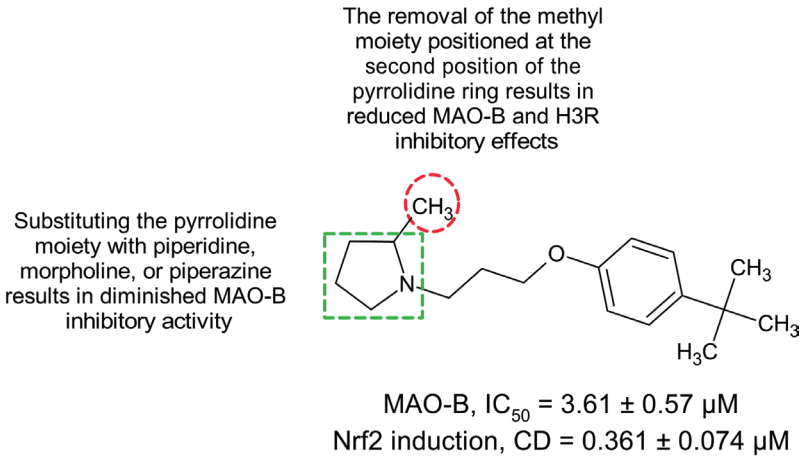

Figure 22. Pyrrolidine-based compounds as dual-acting *h*H3R ligands and MAO-B inhibitors.

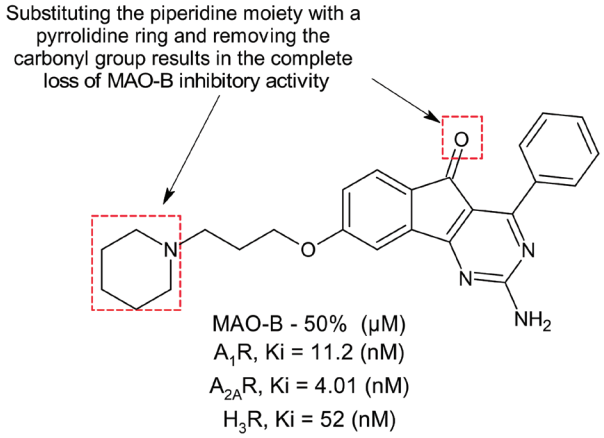

Figure 23. Multi-target MAO-B, A1R/A2AR/H3R ligand – ST1992.

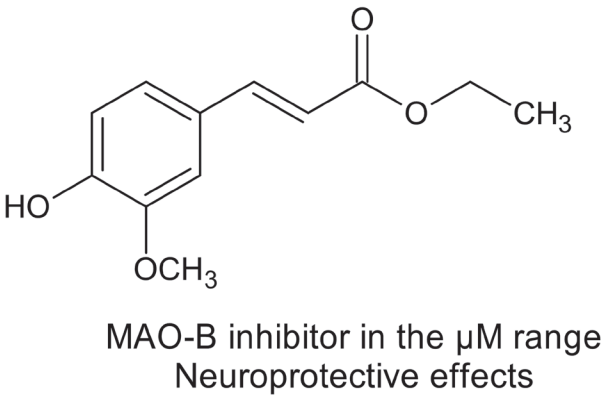

Figure 24. Structure of Ethyl ferulate (EF) - MAO-B inhibitor and neuroprotective agent.

and neuroprotective properties, making it a candidate for further research in neurodegenerative diseases (Zou et al. 2022). The authors stated that the EF is blood-brain barrier (BBB) permeable with low toxicity even at concentrations up to 100 μmol. Moreover, EF reduces the expression of pro-inflammatory mediators such as IL-1β, IL-6, TNF-α, COX-2, and iNOS. Overall, EF demonstrated good MAO-B inhibitory effects and neuroprotective capacity.

A recently published article discussed the synthesis of 19 novel xanthine-based molecules with multi-target actions against MAO-B, the A2A adenosine receptor, and phosphodiesterase-4 and -10 (PDE4/10) (Załuski et al. 2023). Additional agonist effects towards the dopamine D2 receptor (D2R) were also tested. The authors synthesized the desired compounds by reacting different xanthine derivatives with a dopamine-based fragment. The hydroxyl functional groups in the latter molecule were protected with methyl moieties in some of the novel ligands. Importantly, the observed hybrid compounds exerted excellent IC50 values against the MAO-B enzyme in the nanomolar range – 44 to 205 nM. Most of the ligands were non-selective against A1 (rA1) ARs and A2A (rA2A) ARs sourced from rats' brains. The most active compound (Fig. 25) expressed a Ki value of 0.370 ± 0.063 in micromolar concentrations. Furthermore, the authors reported the radical-scavenging capacities of the synthesized compound through the 2,2-diphenyl-1-picrylhydrazyl (DPPH) assay and *in vitro* model of oxidative-stress-induced neuroblastoma cell death.

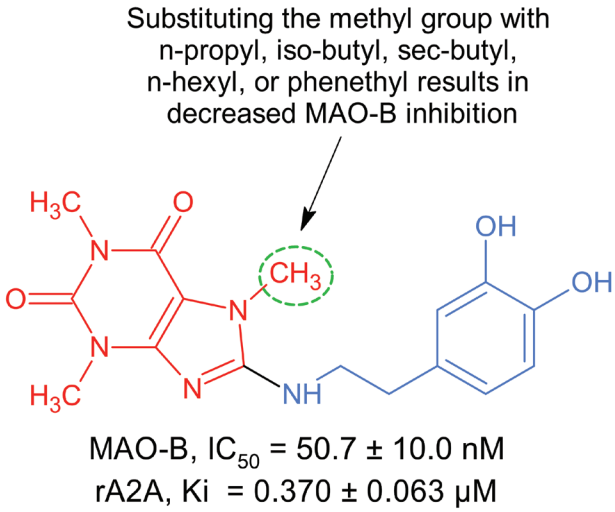

Figure 25. Novel xanthine-dopamine hybrid molecule as an MAO-B inhibitor and A2A adenosine receptor antagonist.

Drawbacks of multi-target MAO-B inhibitor development

Despite significant advances in the design and preclinical evaluation of multi-target MAO-B inhibitors, several challenges and limitations remain, which have limited their clinical impact in the treatment of PD. Although MAO-B inhibitors such as selegiline, rasagiline, and safinamide are well established in PD management, meta-analyses indicate that their symptomatic benefits are often modest in magnitude. Furthermore, some clinical trials have produced conflicting results regarding their ability to slow disease progression, emphasizing the need for more rigorous, long-term studies.

Many multi-target ligands demonstrate potent enzyme inhibition, neuroprotective effects, and favorable pharmacokinetic profiles *in vitro* or in animal models. However, these promising findings frequently fail to translate into substantial clinical benefits in human trials. The complexity of human PD pathology, compensatory mechanisms, and the limitations of current animal models all contribute to this discrepancy. For example, antioxidant-based therapies and dual MAO-B/AChE inhibitors often show neuroprotection in preclinical studies, yet clinical trials have yielded inconclusive or negative outcomes. Moreover, achieving balanced affinity and selectivity for multiple targets while maintaining favorable pharmacokinetic and drug-like properties is a significant challenge. Drug design strategies, such as pharmacophore merging or linking, can result in large, lipophilic molecules with poor bioavailability or unintended off-target activity.

Addressing these challenges will require improved translational models, advanced medicinal chemistry approaches, comprehensive clinical trials, and close attention to safety and regulatory requirements to fully realize the therapeutic potential of these agents.

Future perspectives

Numerous studies have demonstrated that MAO-B inhibitors are both effective and safe for managing early and advanced stages of PD. These agents significantly alleviate motor and non-motor symptoms, reduce "OFF" periods, and exhibit potential neuroprotective properties. Furthermore, they address the need for long-term, standardized therapeutic strategies and expand the options available for comprehensive management throughout the disease course. Additionally, novel MAO-B inhibitors with enhanced selectivity, safety profiles, and neuroprotective effects are currently under development. With continued research, these inhibitors are anticipated to offer greater therapeutic advantages for patients with neurodegenerative disorders such as PD.

Future perspectives in MAO-B inhibitor therapy include the integration of precision medicine approaches to tailor treatments based on individual genetic and disease profiles, maximizing therapeutic benefits while minimizing adverse effects. The design and synthesis of MTDLs represent a promising direction, potentially enhancing efficacy and reducing drug resistance compared to single-target therapies. Continued interdisciplinary research and clinical trials are crucial to validate these strategies, with the ultimate goal of achieving more effective, disease-modifying treatments for PD.

Additional information

Conflict of interest

The authors have declared that no competing interests exist.

Ethical statements

The authors declared that no clinical trials were used in the present study.

The authors declared that no experiments on humans or human tissues were performed for the present study.

The authors declared that no informed consent was obtained from the humans, donors or donors' representatives participating in the study.

The authors declared that no experiments on animals were performed for the present study.

The authors declared that no commercially available immortalised human and animal cell lines were used in the present study.

Use of AI

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Data availability

All of the data that support the findings of this study are available in the main text.

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