

Therapeutic Potential of Heterocyclic Compounds Targeting Mitochondrial Calcium Homeostasis and Signaling in Alzheimer's disease and Parkinson's disease

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Abstract: The brain is a complex organ that controls body functions and homeostasis through the action of neuronal and glial cells. Neuronal activity is highly energy-dependent and requires large numbers of functional mitochondria to provide substantial amount of energy via mitochondrial oxidative phosphorylation (OXPHOS), the most efficient metabolic process to generate adenosine triphosphate (ATP). Under stress conditions, neurons are particularly vulnerable to mitochondrial dysfunction, leading to decreased ATP synthesis, excessive generation of reactive oxygen species (ROS) and reactive nitrogen species (RNS), and intracellular Ca^{2+} dyshomeostasis, although not necessarily in this order. Alzheimer's disease (AD) and Parkinson's disease (PD) are the two most common neurodegenerative diseases in elderly and are characterized by the presence of abnormal protein aggregates and the progressive and irreversible loss of neurons in specific brain regions. The exact mechanisms underlying the etiopathogenesis of AD or PD remain unknown, but there is extensive evidence indicating that compromised mitochondrial energy metabolism along with a depleted antioxidant system play a vital role in the pathophysiology of these neurological disorders. Toxic accumulation of proteins such as amyloid β peptides ($\text{A}\beta$) or amyloid precursor protein (APP) in AD and α -synuclein (α -syn) or leucine-rich repeat kinase 2 (LRRK2) in PD cause mitochondrial deficits through direct inhibition of electron transport chain (ETC) assembly and function, thereby resulting in further generation of ROS/RNS and disturbance of Ca^{2+} influx. Due to the improvement in life expectancy, the incidence of age-related neurodegenerative diseases has significantly increased. There is no effective protective treatment or therapy available but rather only very limited palliative treatment. There is an urgent need for the development of preventive strategies and disease-modifying therapies (both neuroprotective and neurorestorative interventions) to treat AD/PD. Here, we review the capability of some heterocyclic compounds to modulate Ca^{2+} homeostasis and signaling with a potential role in regulating mitochondrial function and associated free radical production during the development and onset of AD or PD. Moreover, we have included the chemical synthesis of a series of heterocycles and their derivatives.

Keywords: Alzheimer's disease; Parkinson's disease; mitochondria; oxidative stress; calcium; heterocyclic compounds

Introduction

The brain is particularly prone to oxidative insult due to a complex interconnected myriad of reasons, such as a high metabolic activity, neurotransmitter autooxidation, elevated content of redox active transition metals, modest antioxidant defense, glutamate excitotoxicity, and altered calcium (Ca^{2+}) influx and signaling processes.^[1] An impaired antioxidant system or aberrant and sustained free radical formation can result in redox balance variations and concomitant alteration in redox-sensitive signaling pathways, leading to significant changes in the state or activity of a neuron. At physiological levels, brain

reactive oxygen species (ROS) and reactive nitrogen species (RNS) are second messengers involved in intracellular signaling but an elevated concentration of free radicals causes harmful effects to biological macromolecules that contribute to the aging process and the pathogenesis of neurodegenerative diseases.^[2-5] Lipid peroxidation (LPO) consists in the abstraction of allylic hydrogen atoms from side chains of polyunsaturated fatty acids (PUFAs) by ROS and RNS. A major deleterious outcome of LPO is the generation of a variety of reactive aldehyde species, such as malondialdehyde (MDA) and 4-hydroxy-2-nonenal (4-HNE). The reaction between $O_2^{\bullet-}$ and $NO^{\bullet}$ leads to the formation of peroxynitrite, which targets tyrosine residues in proteins via free radical addition to generate 3-nitrotyrosine (3-NT). Protein carbonylation is an oxidative stress-driven non-enzymatic and irreversible post-translational modification (PTM). The synthesis of protein carbonyls normally responds to the oxidative deamination of alkaline amino acids such as arginine, lysine, and histidine. Advanced glycation end products (AGEs) are formed in a non-enzymatic reaction among lipids, proteins or nucleic acids and reducing sugars. The interaction of AGEs with their receptors RAGEs elicits oxidative stress. ROS/RNS may also interact with nucleobases of the DNA (e.g., guanine) to form 8-hydroxy-2-deoxyguanosine (8-OHdG) while oxidative RNA damage induces the production of 8-hydroxyguanosine (8-OHG).

Compelling evidence has demonstrated that mitochondrial electron transport chain (ETC) is the major endogenous source of ROS/RNS generation, although the endoplasmic reticulum (ER) and peroxisomes can be also an important site of free radical formation, showing a redox interplay between these organelles.^[6] Specifically, respiratory chain complexes I (NADH: ubiquinone oxidoreductase) and III (ubiquinol: cytochrome c oxidoreductase) produce high rates of $O_2^{\bullet-}$. The ETC also comprises membrane-embedded proteins in the inner mitochondrial membrane that shuttle electrons from NADH and $FADH_2$ to molecular oxygen. Simultaneously, protons are pumped from the mitochondrial matrix to the intermembrane space, thereby resulting in the reduction of oxygen to water. The energy released from these redox reactions is stored as a mitochondrial potential used to drive the phosphorylation of adenosine diphosphate (ADP) to form adenosine triphosphate (ATP). Moreover, PTMs involve enzyme-mediated covalent addition of specific functional groups (such as phosphorylation, ubiquitination, glycosylation, nitration, and methylation) to proteins after their synthesis. Redox-related PTMs can modulate the activity of proteins implicated in a variety of cellular signaling pathways, such as protein folding and degradation, transcription factor expression and activity, and energy metabolism by regulating the tricarboxylic acid cycle (TCA) and glycolytic enzymes, fatty acid metabolism, and protein cysteine thiol nitrosation, sulfenylation or glutathionylation of the mitochondrial ETC complexes.^[7-10] Oxidative DNA damage of the gene promoter encoding subunits of the F1 and F0 domains of ATP synthase has also been observed during aging and neurodegeneration.^[11] Mitochondria along with the ER play an important role in controlling intracellular Ca^{2+} homeostasis, which regulates several vital neuronal processes, including synaptic plasticity, metabolic regulation, proliferation, gene expression, and apoptosis through modulation of a number of enzymes such as phospholipases, proteases, and nucleases. During aging and in neurodegenerative diseases, Ca^{2+} can be converted from a physiological signal into a pathological effector. Cytosolic and organelle Ca^{2+} overload promotes Ca^{2+} mitochondrial accumulation, which triggers the opening of the mitochondrial permeability transition pore (mPTP) and the disruption of the mitochondrial membrane potential ($\Delta\Psi_m$). Sustained mPTP opening leads to Ca^{2+} release, mitochondrial depolarization, OXPHOS disruption, compromised structural and functional integrity of the inner mitochondrial membrane, and release of cytochrome c and other apoptogenic proteins from the outer mitochondrial membrane.^[12]

AD and PD are neurodegenerative diseases that share common pathological features, including protein misfolding and aggregation, synaptic impairment, mitochondrial deficits, axonopathy, and aberrant free radical production. In addition, altered Ca^{2+} homeostasis and signaling may contribute to accelerating the pathogenesis of AD/PD. Ca^{2+} overload is mainly mediated by A β and tau in AD and α -synuclein (α -syn) and leucine-rich

repeat kinase 2 (LRRK2) in PD.^[13-16] Modifications in neuronal Ca^{2+} influx via voltage-gated Ca^{2+} channels (VOCCs) and glutamate receptors promote excitotoxic Ca^{2+} accumulation and concomitant defective neurotransmission, impaired synaptic plasticity and damaged mitochondrial function, including increased ROS/RNS production, activation of mitochondrial permeability transition, stimulation of mitophagy and decreased ATP synthesis.^[16] Therefore, targeting aberrant Ca^{2+} homeostasis may represent a plausible option for the prevention and therapy of neurodegenerative diseases. We have reviewed a number of heterocyclic compounds that modulate Ca^{2+} signaling and homeostasis and can serve as a therapeutic target in both AD and PD.

Mitochondrial deficits and oxidative stress as close partners in Alzheimer's disease brain damage

AD is the most common neurodegenerative disorder characterized by brain atrophy and impaired cognitive performance. Neuropathological studies have observed an extracellular accumulation of amyloid beta ($\text{A}\beta$) and an intraneuronal deposition of insoluble neurofibrillary tangles (NFTs) containing hyperphosphorylated tau protein.^[17] A large body of research has demonstrated that impaired mitochondrial function (and associated energy failure) is a causative factor of AD and occurs before development of $\text{A}\beta$ plaques and NFTs, indicating this is an early event in the pathogenesis of the disease. Mitochondrial pathological changes drive disease progression, leading to an increased oxidative burden, synaptic degeneration, dysregulated Ca^{2+} homeostasis, and neuronal loss. This is consistent with the "mitochondrial cascade hypothesis" that postulates that bioenergetic deficits mediate AD.^[18-20] Brain metabolic variations would be primarily responsible for mitochondrial dysfunction in AD. Glucose deprivation leads to reduced activity in the default mode network, an area that includes the posterior cingulate cortex, the precuneus, the medial prefrontal cortex, the inferior parietal cortex, and the medial temporal lobe and that preferentially associated with atrophy and amyloid and tau deposition in AD.^[21-23] Positron emission tomography (PET) with [^{18}F]-fluro-2-deoxyglucose analyses have shown a progressive decline in cerebral glucose metabolism in AD patients.^[24-26] Glucose metabolism is connected to thiamine-dependent pathways, including the Krebs cycle and the pentose phosphate pathway, which are compromised in AD.^[27-29] In addition, oxidation of glucose by substrate-level and oxidative phosphorylation produces ATP molecules and results in a synergistic effect with mitochondria in metabolic pathways.

Another specific event linked to mitochondrial failure in AD is the development of phenotypic changes in these organelles. Defective mitochondrial function is characterized by the abnormal formation of a subset of swollen mitochondria with distorted cristae. Indeed, ultrastructural examination confirmed the presence of mitochondrial morphometric abnormalities in postmortem brain specimens from individuals with AD.^[30,31] Postmortem examination of AD patients revealed a significant decrease in the numbers of intact mitochondria.^[30] Furthermore, mitochondrial dysfunction correlates with certain enzyme deficiencies, such as the α -ketoglutarate dehydrogenase complex (α -KGDH), pyruvate dehydrogenase complex (PDHC), and transketolase.^[29,32-35] There is a direct relationship between reduced brain regional glucose metabolism and downregulated thiamine-dependent enzyme activities (such as α -KGDH).^[27,34] The most common feature found in AD is a deficiency in complex IV (cytochrome c oxidase, COX), which has been reported in the cortical and hippocampal brain regions^[36-40] and platelets^[36,41-43] of patients. Downregulated complex IV activity has been also detected in AD cybrid cells.^[44] Cognitively normal subjects with a parental history of late-onset AD exhibited COX decreased activity in platelet mitochondria, suggesting a role for mitochondrial DNA (mtDNA) in maternal transmission, since no differences in COX activity were seen between paternal history of late-onset AD and controls.^[45] All these empirical observations undeniably implicate mitochondrial damage in the pathophysiology of AD.

Together with mitophagy, mitochondrial dynamics – a specialized type of mitochondrial autophagy – serves as a quality control mechanism for the maintenance of mitochondrial integrity and functionality and is crucial for neuronal homeostasis and survival. Mitochondrial dynamics are tightly regulated by the fusion-fission machinery that promotes the generation or degradation of a mitochondrial syncytium. The molecular process of fusion is driven by the GTPases optic atrophy type 1 (Opa1) and mitofusin 1 (Mfn1) and mitofusin 2 (Mfn2) whereas dynamin-related protein (Drp1) interacts with the mitochondrial fission 1 protein (Fis1), the mitochondrial fission factor (Mff), and the mitochondrial dynamics proteins of 49 and 51 kDa (MiD49/51) to mediate mitochondrial fission.^[46–48] Axonal transport is a cellular mechanism that controls the active trafficking of proteins, lipids, organelles, and neurotransmitters, and is critical for the maintenance of the neuronal network function and viability. Kinesin motor proteins are responsible for the anterograde transport, which carries new synthesized material from the cell body to distal axons. Retrograde transport is required for efficient distribution of cargoes from the axon terminals toward the soma and is mediated by dynein. It has been described a crosstalk between mitochondrial fusion and fission events and axonal transport integrity.^[5,49,50] Mitochondrial deficits and free radical production, changes in redox homeostasis, and apoptosis correlate with abnormalities in mitochondrial dynamics and axonal transport.^[5,51] An imbalance between mitochondrial fusion and fission rates has been documented in AD. Mitochondrial axonal transport is tightly interconnected with mitochondrial dynamics and play a prominent role in preserving mitochondrial morphology and quality control. mRNA and protein levels of Opa1, Mfn1 and Mfn2 were reduced while gene expression and protein content of Drp1 and Fis1 were upregulated in postmortem brain samples from individuals with different Braak AD stages.^[52] In primary neurons from A β PP mice, mRNA levels of genes involved in mitochondrial fusion were downregulated while the expression of mitochondrial fission-related genes were augmented, suggesting an excessive mitochondrial fragmentation.^[53] In the same study, A β PP neurons exhibited decreased mitochondrial anterograde axonal transport although retrograde mitochondrial motility remained unchanged in axonal projections. Mitochondrial axonal trafficking deficits, abnormal mitochondrial distribution, and increased content of 4-HNE and Ca²⁺-induced H₂O₂ were detected in transgenic mice overexpressing human APP/A β (Tg mAPP mice).^[54]

A β aggregation may also determine mitochondrial function. Enhanced A β burden has been detected in mitochondria from autopsy specimens of late onset AD as in transgenic mice overexpressing mutant amyloid precursor protein (APP).^[55,56] A β _{1–40} and A β _{1–42} mitochondrial internalization is mediated by the receptor components TOM20, TOM40 and TOM70 of the translocase of the outer membrane (TOM) complex and this translocation is independent of the $\Delta\Psi_m$.^[57] The APP N-terminal fragment contains a mitochondrial targeting sequence that creates stable intermediate complexes with TOM and TIM complexes.^[56] Moreover, A β can interact with A β -binding alcohol dehydrogenase (ABAD) in cerebral cortex mitochondria of sporadic individuals with AD and in cultured neurons from transgenic mice overexpressing ABAD and exposed to A β , resulting in a leakage of ROS.^[58] A β (mainly oligomeric A β and A β ₄₂) can interact with cyclophilin D, a regulatory component of the mitochondrial mPTP, leading to synaptic pathology, mitochondrial stress and neuronal death in both the temporal cortex of AD patients and transgenic APP mice.^[59] A β /cyclophilin D-mediated toxicity might involve a Ca²⁺ signaling mechanism.

The A β _{25–35} peptide induced a rapid, specific and dose-dependent downregulation of COX activity in non-synaptic mitochondria isolated from rat brain.^[60] Impaired energy metabolism, including inhibition of COX and several dehydrogenase activities together with deficiencies in mitochondrial respiration were reported in A β -treated non-synaptic rat brain mitochondria.^[61] Synaptic mitochondria exhibited a larger age-dependent accumulation of A β and mitochondrial abnormalities compared with non-synaptic mitochondria, indicating that synaptic mitochondria are more prone to A β pathology.^[54] Several familial and amyloid-based animal models of AD, including triple transgenic AD, APP,

Thy1, and COXd/AD mice display systemic mitochondrial dysfunction, including down-regulated COX activity, impaired mitochondrial respiration, augmented glycolysis and marked oxidative insult.^[62-65] Apolipoprotein E (APOE), the major genetic risk factor for late-onset AD, may directly interact with mitochondria, affecting its function, dynamics and motility. COX immunoreactivity was significantly depleted in post-mortem cortical samples and posterior cingulate cortex of young-adult APOE ϵ 4 carriers.^[66,67] In addition, proteins involved in the regulation of ketone and glucose metabolism were also affected.^[67] A β -induced persistent mitochondrial fission causes deleterious effects. Exposure to A β or overexpression of APP resulted in excessive mitochondrial fragmentation and abnormal mitochondrial distribution of in neuronal cultures.^[68-70] Similar results were obtained when crossing Drp1^{+/-} mice with APP transgenic mice; partial reduction of Drp1 protected against APP/A β -induced mitochondrial and synaptic impairment.^[71] In addition, A β can induce S-nitrosylation of Drp1, which increases its translocation into mitochondria.^[72] Ca²⁺ signaling and oxidative stress are important contributors to A β -induced mitochondrial fragmentation. A β promotes mitochondrial Ca²⁺ influx and Ca²⁺/calmodulin-dependent protein kinase II (CAMKII)-mediated protein kinase B (Akt) activation, thereby causing Drp1 phosphorylation and increasing its mitochondrial translocation.^[73]

Tandem mass tag multiplexed quantitative mass spectrometry revealed that tau protein can interact with a subset of mitochondrial proteins.^[74] Intracellular accumulation of tau can disrupt mitochondrial function by downregulating complex I activity, diminishing ATP synthesis and interrupting mitochondrial dynamics.^[75] P301S tau mice exhibited reduced complex I (NADH: ubiquinone oxidoreductase), α -KGDHC and transketolase enzyme activity accompanied of lower mtDNA copy number and increased mitochondrial fission in the cerebral cortex.^[35] The same study demonstrated that advanced glycation end products were attenuated in tau mice, which showed an important oxidative and nitrosative damage. Tau can also cooperate with A β to induce a synergistic detrimental effect on mitochondria. Indeed, tau and A β interaction can exacerbate respiratory capacity abnormalities, inhibit both complex I and 4 activities, and disturb energy metabolism on isolated mitochondria from the cerebral cortex of triple transgenic AD mice.^[76] The interplay between the NH₂-truncated tau peptide and A β mediated mitochondrial dysfunction through the impairment of the adenine nucleotide translocator type 1 (ANT-1), located in the inner mitochondrial membrane and responsible to catalyze the adenosine diphosphate-adenosine triphosphate (ADP/ATP) exchange.^[77]

Pathological p-tau exhibits lower affinity for the microtubule network, resulting in increased fission events. It has been shown that transgenic P301L tau mice display an unbalanced concentration of mitochondrial dynamics-associated proteins in the hippocampi, with a diminished immunoreactivity of fusion proteins and elevated fluorescence signal of fission proteins.^[78] Moreover, ablation of tau ameliorates mitochondrial function by preserving mitochondrial dynamics and structure and reducing oxidative insult. In particular, genetic deletion of tau caused a shift of mitochondrial dynamics towards fusion and upregulated both 4-HNE and Nrf2 mRNA levels in the mouse hippocampus.^[79] In addition, genetic tau ablation blocks A β -mediated activation of glycogen synthase kinase 3 β (GSK3 β) – a kinase responsible for tau phosphorylation – which leads to an improvement of the anterograde axonal transport of mitochondria in primary hippocampal neuron cultures from transgenic hAPP mice.^[80] Tau mice expressing the R406W mutation showed axonal transport deficits that causes an accumulation of insoluble tau in the neuronal perikarya and subsequent development of NFTs.^[81] Diverse pathogenic isoforms of tau inhibited kinesin-based fast axonal transport by activating the PP1-GSK3 signaling pathway in isolated squid axoplasm.^[82]

Sustained mitochondrial dysfunction is a primary cause of an excessive generation of ROS/RNS in AD brains and leads to A β aggregation and toxicity.^[83] Aggregation of A β or tau within mitochondria not only compromises the function of crucial mitochondrial proteins but also instigates oxidative stress. ROS/RNS promote A β and tau pathology via activation of p38 mitogen-activated protein kinase (MAPK).^[84] The connection between A β ₁₋₄₀ and A β ₁₋₄₂ and mitochondrion interfered with its function and led to mitochondrial

oxidative damage in N2a cells overexpressing human wild-type APP and Tg2576 AD mice, which showed a downregulation in COX enzymatic activity and elevated content of H₂O₂ before A β plaque formation.^[68] A β attenuated mitochondrial respiration and $\Delta\Psi$ generation induced by various substrates of complexes I and IV. The A β _{1–42} peptide enhanced the levels of ROS by inhibiting complex I activity and membrane LPO associated with complex IV deficiencies. Furthermore, a sharp increase in the GSSG/GSH ratio was observed in postmortem AD specimens, indicating a defective antioxidant defense system.^[85]

Free radical-mediated chain of reactions that results in an oxidative deterioration of PUFAs is a key feature of AD. The LPO product malondialdehyde (MDA) is robustly increased in the cerebral cortex and hippocampus of AD patients.^[86,87] Levels of 4-HNE have been reported in different AD brain regions, including the temporal and entorhinal cortex and the hippocampus compared with age-matched controls.^[88,89] Increased immunoreactivity of 4-HNE parallel to reduced levels of antioxidant proteins and enzymes such as catalase, glutathione peroxidase, superoxide dismutase and peroxiredoxin were described in the superior temporal gyrus from APOE ϵ 4 cases.^[90] Moreover, high levels of the LPO markers 4-hydroxy-2-nonenal (4-HNE), F2-isoprostanes, and 8,12-iso-iPF₂ α -VI were found in the cerebral spinal fluid (CSF) specimens of AD patients.^[91–93] Redox proteomic analyses revealed a significant lipoxidation and nitration of several key mitochondrial enzymes, including the ATP synthase in the hippocampus of AD subjects.^[94,95] ROS-induced functional variations in the F1Fo-ATP synthase may represent a potential mechanism of OXPHOS deficiency in AD.^[96] A large body of literature has shown that protein nitration is a feature of AD. The number of 3-NT-positive neurons was robustly enhanced in post-mortem brain samples from AD cases.^[97–100] Protein carbonyls are also upregulated in subjects with AD though the expression pattern varies between different brain regions.^[101] Carbonylation of proteins and AGEs plasma levels were specifically elevated in male AD patients.^[102] The content of DNA strand breaks was higher in cerebral cortex and hippocampus specimens from individuals with AD compared to controls.^[103,104] HPLC analysis revealed a prominent increase in 8-OHdG levels in DNA isolated from the brains of idiopathic AD cases while elevated 8-OHG immunoreactivity was described in temporal cortex neurons of preclinical early-onset individuals with AD.^[105,106]

Impaired mitochondrial function and associated oxidative damage in Parkinson's disease

PD is a chronic neurodegenerative disease characterized by the loss of DA neurons in the substantia nigra (SN) and their axonal projections to the striatum. A histopathological hallmark of the disease is the presence of neuronal cytoplasmic inclusions termed Lewy bodies (LB), which are predominantly composed of α -syn and, to a lesser extent, ubiquitin.^[107] α -Syn can undergo PTMs, including nitration, ubiquitination, glycosylation and phosphorylation (serine 129 (pS129) is the dominant pathological modification of α -syn).^[5] SNCA gene point mutations or multiplications cause familial dominant PD. Based on PET and single photon emission computed tomography studies, a significant glucose hypometabolism was detected in the cerebral cortex of individuals with early-stage PD.^[108] Using [¹⁸F]-fluro-2-deoxyglucose PET imaging, a robust attenuation in glucose metabolism was found in the hippocampus and in the temporo-parietal and occipital regions of PD dementia (PDD) patients.^[109] An independent study confirmed that PD subjects have decreased glucose metabolism in the occipital and inferior parietal lobes in comparison to the control group.^[110] There is a correlation between cerebral glucose intake and synaptic density in individuals with LB disease, but progressive glucose hypometabolism cannot be fully explained by synaptic degeneration.^[111] Neurons metabolize glucose predominantly through the pentose phosphate pathway (instead of using glycolysis) to preserve their redox status. Assessment of the levels of nicotinamide adenine dinucleotide phosphate (NADPH), an enzyme produced by the glucose-6-phosphate dehydrogenase, was performed in brain biopsy samples of mild PD cases (with low LB deposition) and moderate-to-severe PD cases (with an important LB pathology). The findings suggested that

perturbed glucose metabolism is an early event in idiopathic PD.^[112] Interestingly, *in vitro* and *in vivo* studies revealed that α -syn may play a central role in glucose uptake through the activation of the LPAR2/Gab1/PI3K/Akt signaling pathway.^[113]

Mitochondrial defects in PD also involve morphologically abnormal mitochondria, evidenced by organelle swelling and reduced cristae size and number. In SN neurons of patients with PD, around 80% of total mitochondria exhibited an irregular shape and swollen morphology with deranged cristae patterns.^[114] Using electron microscopy, subsets of mitochondria appeared swollen and rounded or enlarged in cybrid cell cultures prepared from platelet-derived mtDNA of sporadic PD cases.^[115] Thiamine is an important cofactor for various critical enzymes involved in brain oxidative metabolism, including α -KGDH, PDHC, and transketolase. In contrast to AD, the levels of thiamine remain unchanged in the plasma of PD cases.^[116] Nevertheless, free thiamine content was significantly reduced in lumbar CSF specimens of PD subjects.^[117] The cerebellar enzymatic activity (but no protein concentration) of α -KGDH declined by 50% in PD patients and was independent of an overall decrease in mitochondrial numbers.^[118] However, Mizuno and colleagues found an increased α -KGDH immunoreactivity in the SN of patients with idiopathic PD that correlates with disease severity.^[119] Pyruvate dehydrogenase E1 subunit alpha 1 (PDHA1) regulates PDHC through reversible phosphorylation. Individuals with sporadic PD displayed lower PDHA1 fluorescence in both the putamen and SN relative to the control group.^[120] The activity of α -KGDH, PDHC, and succinate dehydrogenase (SDH) and the respiratory function were inhibited in PC12 cells overexpressing monoamine oxidase B (MAO B).^[121]

Systemic deficiencies in complex I assembly and decreased activity might result in impaired oxidative capacity, ensuing ROS/RNS overproduction, and progressive mitochondrial deficiencies, a major culprit in the degenerative process of DA neurons. Disturbances in mitochondrial complex I were initially seen in SN tissue of postmortem human samples.^[122,123] Noteworthy, inhibition of complex I was detected in the SN pars compacta (but not in SN reticulata).^[124] Impaired catalytic activity of complex I has been found in the frontal cortex and in peripheral tissues such as, skeletal muscle, platelets and lymphocytes of late-onset PD subjects.^[122,125-128] Nevertheless, a significant downregulation in the enzymatic activity of complex I/III was also reported in untreated patients with early-onset PD.^[129] Progressive and permanent loss of complex I in mouse DA neurons resulted in impaired behavioral outcome and early axonal damage, which diminishes retrograde transport of striatal trophic factors and induces bioenergetic failure.^[130]

Mounting evidence supports the notion that defects in mitochondrial dynamics are likely a common mechanism leading to mitochondrial dysfunction and neurodegenerative process in PD.^[131] Perturbations in mitochondrial dynamics and disrupted motor-cargo interactions have been observed in individuals with PD. Indeed, SN tissue from patients with sporadic PD displayed a significant immunoreactivity attenuation of both the short and long OPA1 isoforms, though no changes were noticed in MFN1 protein concentration.^[114] p.A495V and p.G488R heterozygous OPA1 missense mutations were identified in individuals with parkinsonism and subclinical optic neuropathy.^[132] OPA1 is further linked to non-syndromic, idiopathic PD associated with aberrant changes in cristae structure and disrupted mitochondrial networks.^[133] Altered trafficking along axons may represent a slow but steady feature disrupting mitochondrial homeostasis, since mitochondria undergo bidirectional transport along microtubule and actin filaments. Impaired axonal transport has been reported in clinical PD. In particular, SN DA neurons displayed low levels of kinesin heavy chain (KHC) and kinase light chain (KLC1) in subjects with early-onset PD while DYNLT3 immunoreactivity was markedly diminished in patients with late-onset PD.^[134] Moreover, parkinsonized rats exhibited decreased content in mitochondrial fusion proteins (OPA1 and MFN2), increased levels of mitochondrial fission proteins (DRP1) and attenuated anterograde (KHC and KLC1) retrograde (DYNLT3) axonal transport.^[2,135] Mitochondrial quality control also includes mitophagy, a mitochondrial-selective autophagic process to degrade dysfunctional or defective mitochondria.^[136,137]

α -Syn not only localizes in the cytosol but also at or in mitochondria of DA neurons in different systems, including cell cultures, rodent midbrain, and human subjects with PD.^[5,138] Tom40 is an essential protein-conducting pore that directly interacts with α -syn for its import into mitochondria.^[138] Protein levels of Tom40 (but not TOM20) were significantly attenuated in PD brains and transgenic mice overexpressing wild-type human α -syn. In addition, depletion of TOM40 promoted α -syn accumulation, oxidative insult, and DNA damage but stereotaxic delivery of TOM40 reversed α -syn-induced pathological events.^[139] The data suggest that α -syn interaction with the mitochondrial protein import machinery might be an upstream effect in α -syn-mediated toxicity. A specific association between wild-type α -syn and mitochondria-associated ER membranes was found in cells and transgenic mice expressing α -syn, a finding supported by the fact that α -syn predominantly binds to lipid rafts and acidic phospholipid-rich membrane domains.^[140] Di Maio *et al.* revealed a high-affinity binding between specific post-translationally modified α -syn and TOM20 in midbrain DA neurons of PD cases and rotenone-injected rats.^[141] Such association was not detected with TOM22, TOM40 or the component of the translocase of the inner membrane TIM23.

Mitochondria-targeted α -syn may cause structural damage to the organelle. Differentiated DA cells transduced with α -syn exhibited compromised mitochondrial structural integrity, including massive swelling, abnormal morphology, and distorted cristae.^[142] Inhibition of complex I activity and altered levels of complex I-related proteins also occur as a consequence of α -syn mitochondrial import, which can further increase endogenous content of α -syn, thereby initiating a feed-forward cycle. Thus, accumulation of α -syn led to 3-fold decrement in complex I activity in the SN of postmortem PD brains.^[138] Selective reduction in complex I immunoreactivity was observed in midbrain homogenates of AAV-A53T α -syn-transduced rats.^[2] The fluorescence intensity of Ndufs3, a subunit of complex I, arose downstream α -syn-TOM20 association in cultured cells.^[141] A significant decrease of the complex I subunit NDUF8 was reported in α -syn transgenic mice.^[139]

α -Syn plays an important role in controlling mitochondrial integrity by regulating dynamics, transport, and clearance. A53T and A30P mutations in α -syn elicited mitochondrial fragmentation via a DRP1-independent pathway and increased OPA1 cleavage in crude mitochondrial fractions from M17 cells.^[140] Mitochondrial fragmentation mediated by α -syn can occur in either a Drp1-independent or -dependent mechanism in HeLa cells.^[143] The authors also showed that overexpression of MFN1 or MFN2 fusion proteins did not prevent fragmentation, supporting the idea that α -syn plays a selective role in fission events. α -Syn-induced mitochondrial fragmentation precedes OXPHOS disturbances, including mitochondrial respiration and $\Delta\Psi_m$.^[143] Preformed α -syn fibrils perturbed mitochondrial fission-fusion cycle by attenuating OPA1 levels and increasing DRP1 immunoreactivity in cultured rat ventral midbrain DA neurons.^[5] Combined exposure to α -syn fibrils and rotenone resulted in an additive toxicity. Human neural stem cells overexpressing A53T mutant α -syn increased the amount of short round-shaped (fragmented) mitochondria despite the concentration of both MFN and Drp1 remained unchanged, supporting a physiological role for α -syn in regulating mitochondrial morphology probably linked to an association between the N-terminal region and the mitochondrial membrane.^[144] Furthermore, the C-terminal domain of α -syn triggered mitochondrial fragmentation and oxidation.^[145] α -Syn-induced fragmented mitochondrial phenotype was reversed following co-expression of DJ-1, PINK1 or parkin.^[146]

Primary ventral midbrain neuronal cultures incubated with synthetic α -syn fibrils displayed axonal transport deficiencies, with variations in kinesin and dynein markers.^[5] Live-imaging analyses revealed no differences in anterograde and retrograde mitochondrial content between wild-type or mutated α -syn and the control group.^[144] Nevertheless, overexpression of α -syn (especially A53T α -syn) in embryonic stem cells led to alterations in mitochondrial flux, suggesting an imbalance in mitochondrial distribution along axons. AAV delivery of human α -syn in the medulla oblongata gradually spread to more rostral brain regions – following a stereotypical pattern that may reflect neuron-to-neuron transmission – and accumulated in dystrophic axons, where was distributed and propagated

in both ipsilateral and contralateral sides via axonal transport.^[147] Inhibition of LRRK2 kinase activity promoted α -syn movement toward the presynaptic terminal in primary hippocampal neuron cultures transfected with α -syn.^[148] Reduced levels of pS935 LRRK2 (an indirect assessment of LRRK2 kinase activity) mediated α -syn accumulation in presynaptic terminals of the mouse SN and striatum.^[148] The C-terminal truncation of α -syn is responsible for retrograde motility of mitochondria.^[145] In addition, membrane potential is required for α -syn transport, a process dependent on the mitochondrial ATP pool.^[138] Cells transfected with α -syn promoted Ca^{2+} trafficking from the ER to the mitochondria via mitochondria-associated ER membranes.^[149] However, α -syn depletion inhibits agonist-stimulated Ca^{2+} entry into mitochondrial matrix.

Higher $\text{OH}^\bullet$ concentration was detected in isolated mitochondrial fractions from primary DA neuron cultures transfected with α -syn relative to the control group.^[138] Protein thiol oxidation was a feature of cell cultures incubated in the presence of oligomeric, pS129, or DA-modified α -syn.^[141] Moreover, knockdown of endogenous α -syn expression resulted in a robust reduction of protein thiol oxidation in SN DA neurons. Elevated MitoSox-red fluorescence was observed in cell lines expressing α -syn, which was mitigated by SIRT3.^[150] Exposure to exogenous α -syn fibrils augmented ROS/RNS production by increasing the MitoSox ($\text{O}_2^{\bullet-}$) signal and the levels of 3-NT in primary midbrain neuronal cultures.^[5] AAV-driven overexpression of human mutated A53T α -syn into the rat SN elicited systemic oxidative insult, including LPO and protein nitration in the ipsilateral hemisphere.^[2] Either wild-type or A53T α -syn accumulation in isolated mitochondria from human neuroblastoma cells induced peroxidation of lipids and $\text{NO}^\bullet$ formation, the later sensitive to intramitochondrial ionized Ca^{2+} .^[151] Cells expressing α -syn displayed an aberrant content of mtDNA deletions and oxidative DNA lesions.^[139] In summary, specific derangements in complex I are responsible for α -syn conformational changes, impaired mitochondrial function and biogenesis, exacerbated oxidative stress and Ca^{2+} dysregulation, leading to DA neuron degeneration.

Ca^{2+} dysregulation and downstream effects in Alzheimer's disease

Ca^{2+} signaling in neurons is often started by activation of plasma membrane channels including voltage-gated Ca^{2+} channels (VOCCs), receptor-operated Ca^{2+} channels (ROCCs) as, for instance, NMDA receptors or other Ca^{2+} -permeable such as transient receptor channels (TRP) or store-operated channels (SOCs) driven by Stim and Orai protein family members (**Figure 1**) whose opening induces Ca^{2+} influx into cells due to the large electrochemical gradient for Ca^{2+} . Ca^{2+} signaling also starts following activation of Ca^{2+} release channels in the ER such as IP_3 receptors after G protein-coupled receptor mediated phospholipase C activation induced mainly by glutamate metabotropic receptors or acetylcholine muscarinic receptors. Ca^{2+} release also takes place through ryanodine receptor channels activated by different messengers, including Ca^{2+} itself, which is responsible of the Ca^{2+} -induced, Ca^{2+} release (CICR) mechanism, a process known to be primed by chemicals like caffeine. Ca^{2+} influx and Ca^{2+} release mechanisms enhance the cytosolic free intracellular Ca^{2+} concentration ($[\text{Ca}^{2+}]_{\text{cyt}}$) leading to neuron cell activation as stated above. This process is limited by endogenous Ca^{2+} buffers, particularly Ca^{2+} binding proteins such as calbindin, and Ca^{2+} extrusion systems, including plasma membrane Ca^{2+} ATPases (PMCA), sarcoplasmic and ER Ca^{2+} ATPases (SERCA), and $\text{Na}^+/\text{Ca}^{2+}$ exchangers (NCXs) that remove Ca^{2+} from cytosol back to the extracellular space and/or to intracellular organelles, principally, the ER. Mitochondria also work as Ca^{2+} removing organelles. In this case, Ca^{2+} is not pumped in or exchanged but enters the mitochondrial matrix through the mitochondrial Ca^{2+} uniporter (MCU) complex, containing an activated Ca^{2+} channel that promotes mitochondrial Ca^{2+} uptake in favor of a massive electromotive force, the $\Delta\Psi_m$ (**Figure 1**). In fact, subtle modifications in $\Delta\Psi_m$ may considerably influence mitochondrial Ca^{2+} uptake ability.^[152] Ca^{2+} uptake by mitochondria activated the Krebs cycle and energy production but excess leading to mitochondrial Ca^{2+} overload may enhance oxidant stress and mPTP, leading to apoptosis. In contrast to other organelles, mitochondria are not Ca^{2+}

stores and accordingly, mitochondrial Ca^{2+} excess returns to the cytosol in a substantially slow fashion, in exchange for Na^{+} through mitochondrial $\text{Na}^{+}\text{-Li}^{+}/\text{Ca}^{2+}$ exchangers (NCLX).

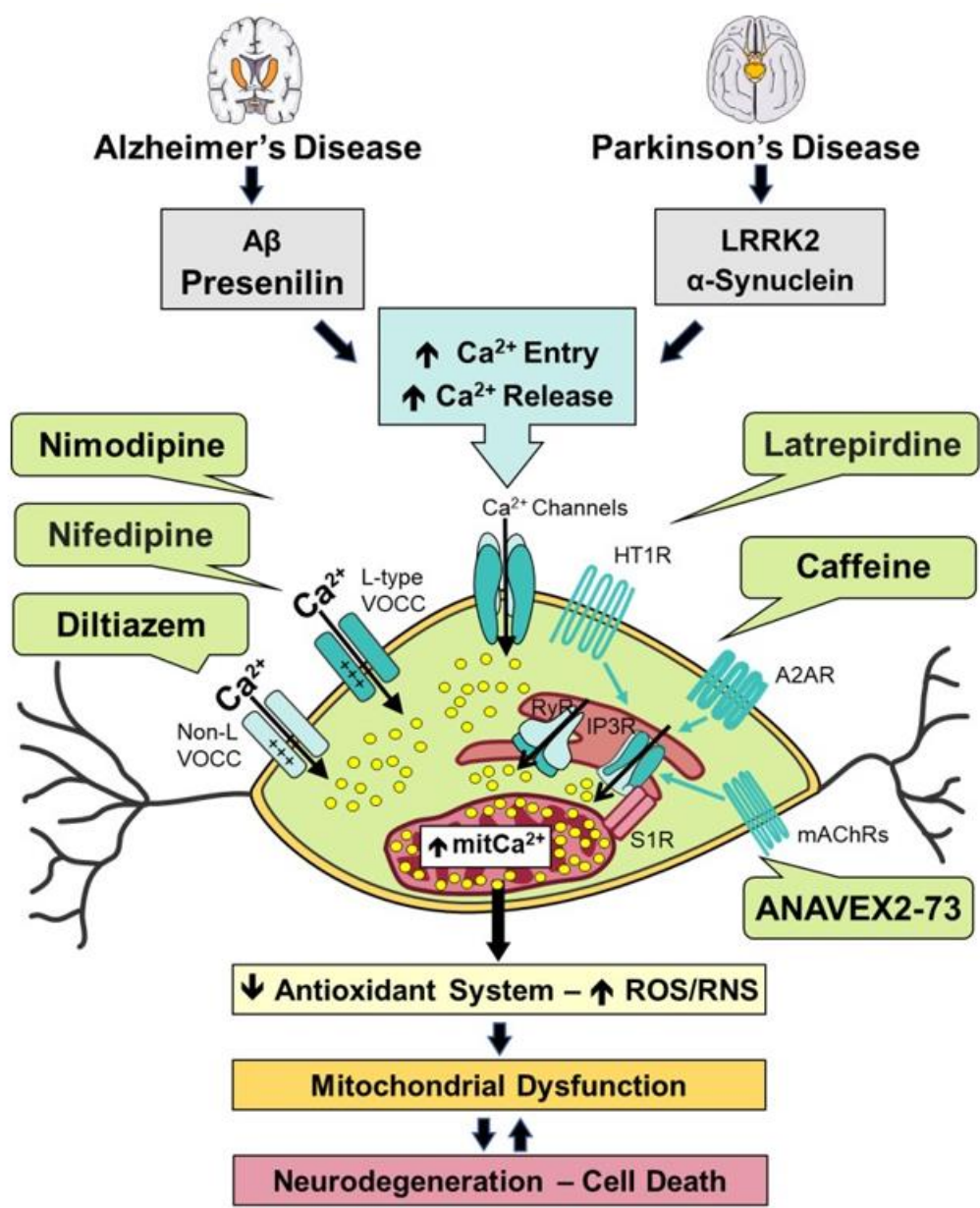


Figure 1. Heterocycles target Ca^{2+} dyshomeostasis leading to mitochondrial Ca^{2+} overload, oxidative damage and neuronal degeneration in AD and PD.

The MCU is a low affinity Ca^{2+} channel. Therefore, only very high Ca^{2+} concentrations limited in time and space (Ca^{2+} hot spots or microdomains) efficiently activate MCU and mitochondrial Ca^{2+} uptake. As a consequence, only those mitochondria closely located to sites of generation of these Ca^{2+} microdomains such as IP_3 receptor channels at the ER and some Ca^{2+} channels at the plasma are able to efficiently take up Ca^{2+} .^[153] We used mitochondria-targeted aequorin to monitor, for the first time, the coupling of Ca^{2+} release and mitochondrial Ca^{2+} uptake in the soma and neurites of neurons in primary cultures.^[154,155] This configuration limits mitochondrial Ca^{2+} overload involved in mPTP. However, if Ca^{2+} influx or Ca^{2+} release mechanisms are enhanced and/or sustained, or Ca^{2+} buffers or extrusion systems are saturated, then mitochondrial Ca^{2+} overload may occur leading to neuron cell death. In the last few years, a large body of evidence indicates that changes in intracellular Ca^{2+} homeostasis may contribute to neuron damage in AD and PD.^[156]

Early evidence suggested that neurons obtained from mouse models of AD displayed changes in intracellular Ca^{2+} homeostasis, including alterations in resting levels of intracellular Ca^{2+} and Ca^{2+} stores.^[157] These changes could be associated to the effects of mutations in the APP and presenilins PS1 and PS2, which process APP either directly or indirectly via excessive production of $\text{A}\beta$ species. Mounting evidence indicates that presenilins may work as ER leak channels, so presenilin mutations involved in familial AD cases would lead to variations in Ca^{2+} store content and Ca^{2+} release.^[158] In addition, elevated generation of $\text{A}\beta$ species tend to oligomerize and eventually aggregate, thereby resulting in the formation of toxic $\text{A}\beta$ species. The mechanism by which $\text{A}\beta$ species promote neuron damage is not totally understood. First indications suggested that $\text{A}\beta$ proteins could integrate in lipid bilayers and form Ca^{2+} -permeable pores termed amyloid channels.^[159] We showed that $\text{A}\beta_{1-42}$ oligomers, the assembly state that probably correlates better with cognitive deficits in AD, increase Ca^{2+} influx in rat cerebellar and hippocampal neurons, followed by mitochondrial Ca^{2+} overload as monitored by bioluminescence imaging in individual neurons expressing mitochondria-targeted aequorin.^[160,161] Mitochondrial Ca^{2+} overload induced by $\text{A}\beta_{1-42}$ oligomers promote mPTP opening followed by release of cytochrome c and apoptosis. Importantly, prevention of mitochondrial Ca^{2+} uptake without affecting the rise in cytosolic Ca^{2+} protected neurons. For instance, small mitochondrial depolarization – that reduces the driving force for mitochondrial Ca^{2+} uptake – diminishes the mitochondrial Ca^{2+} overload and the ensuing release of cytochrome c and apoptosis.^[160]

Interestingly, a number of non-steroidal anti-inflammatory drugs (NSAIDs), such as the aspirin metabolite salicylate, and over the counter NSAIDs such as sulindac sulfide, indomethacin, ibuprofen and its enantiomer *R*-flurbiprofen (that partially depolarize mitochondria at low concentrations) resulted in the inhibition of both the mitochondrial Ca^{2+} overload and the resulting apoptosis. Thus, $\text{A}\beta$ neurotoxicity depends largely on mitochondrial Ca^{2+} overload and any compound targeting MCU, or $\Delta\Psi\text{m}$ may protect against $\text{A}\beta$ oligomer-induced pathology. Therefore, mitochondrial Ca^{2+} emerged as a potential new target to prevent AD^[162] that could be targeted by different compounds, like the antibiotic minocycline, able to prevent neurotoxicity^[163] or drugs like methadone that promote neurotoxicity.^[164] Interestingly, clinical data suggested that some of these compounds, particularly several NSAIDs, showed a neuroprotective effect in several animal models of AD. *R*-Flurbiprofen, an enantiomeric form of flurbiprofen lacking anti-inflammatory activity was selected for a large AD clinical trial. Unfortunately, this trial failed probably because selected patients undergo large neuron cell death at the time of recruitment. The question remains whether NSAIDs and mitochondria are still good candidates for developing new drugs against AD.^[165] Overall, data suggest a critical role for intracellular Ca^{2+} dyshomeostasis in AD that is amenable for the development of novel pharmacological agents to be tested in further clinical trials.^[166]

In addition to the contribution of excitotoxicity, mutations in APP and/or presenilins and the overproduction of $\text{A}\beta$ oligomers, a critical component that is often overlooked is the critical influence of aging. We have developed an *in vitro* model of neuronal aging based on long-term culture of rat hippocampal neurons that, under specific conditions, acquire an aging phenotype. We reported that Ca^{2+} responses induced by activation of VOCCs after plasma membrane depolarization and neurotoxins, including the glutamate receptor agonist NMDA and $\text{A}\beta$ oligomeric forms, were significantly elevated in aged neurons compared to young neurons.^[167,168] These functional changes were associated to changes in the expression of NMDA receptor subunits. Interestingly, NMDA and $\text{A}\beta$ oligomers increased mitochondrial Ca^{2+} overload and apoptosis only in aged neurons but not in young cells, possibly because the cytosolic Ca^{2+} responses evoked by the neurotoxins were high enough to induce mitochondrial Ca^{2+} overload only in aged neurons, thus implying a critical role of mitochondrial Ca^{2+} in cell death induced by these agonists.

Neuroinflammation also plays a pivotal role in the etiopathogenesis of AD. A critical component of inflammation is the activation of Toll-like receptors (TLRs), transmembrane

pattern-recognition receptors of the innate immune system that recognize diverse pathogen-derived and tissue damage-related ligands and induce the corresponding immune response in specific cells. Recent data suggest that TLR signaling contributes to the pathogenesis of AD and other age-related, neurodegenerative diseases.^[169] Consistently, we recently demonstrated that the TLR4 agonist lipopolysaccharide (LPS) induces Ca^{2+} responses and apoptosis in hippocampal aged neurons *in vitro* while no effects were observed on young neurons.^[170] These effects were prevented by administration of TLR4 antagonists. Consistently, TLR4 expression is significantly increased in aged neurons relative to young cells. Treatment of aged neurons with $\text{A}\beta$ oligomers enhanced TLR4 expression as well as LPS-mediated Ca^{2+} responses and neuron cell loss. These data indicate that both aging and $\text{A}\beta$ oligomers may contribute to increase the susceptibility to neuroinflammation in rat hippocampal neurons.^[171]

The data also suggest that aging neurons undergo significant changes in expression and/or activity of molecular players involved in Ca^{2+} transport that renders them more vulnerable to damage. We reported that long-term cultures of rat hippocampal neurons underwent such Ca^{2+} remodeling.^[172] Specifically, aged neurons show enhanced resting $[\text{Ca}^{2+}]_{\text{cyt}}$ and Ca^{2+} store content and release from ER, together with increased Ca^{2+} transfer from the ER into mitochondria. Moreover, aged neurons exhibited a significant decrease in the so-called store-operated Ca^{2+} entry (SOCE), a pathway that has been related to dendritic spine stability and memory storage. Therefore, these changes in Ca^{2+} homeostasis found in aging neurons may favor energy production at the risk of increased susceptibility to mitochondrial Ca^{2+} overload and cell death as well as reduced spine stability. These functional changes correlated with altered expression of the ER IP_3 receptor, mitochondrial MCU, NMDA and TLR4 receptors, and the plasma membrane molecular players involved in SOCE.^[173] Interestingly, treatment of aged neurons with $\text{A}\beta$ oligomers further exacerbated most of the changes involved in Ca^{2+} remodeling associated to aging and the susceptibility to cell death, including resting Ca^{2+} , Ca^{2+} store content, and Ca^{2+} responses to NMDA and TLR4.^[173] Administration of $\text{A}\beta$ oligomers also decreases further SOCE in aged neurons. We proposed that neuronal aging is associated to Ca^{2+} remodeling that favors energy production at the expense of increased susceptibility to damage and decreased ability for memory formation. In addition, this process is exacerbated by the generation of $\text{A}\beta$ oligomers, leading to pathological aging that contributes to the development of AD.^[174]

The mechanism by which $\text{A}\beta$ peptide species, particularly oligomers, promote neuron damage is not totally understood. The proposal that $\text{A}\beta$ species form Ca^{2+} permeable pores or channels responsible for Ca^{2+} entry is not widely accepted.^[166] Alternatively, it has been proposed that $\text{A}\beta$ oligomers bind and activate plasma membrane Ca^{2+} channels, particularly NMDA receptor channels.^[175] We have recently shown that Ca^{2+} responses to $\text{A}\beta$ oligomers were highly dependent on synaptic networking.^[176] In particular, we demonstrated that generation of spontaneous, synchronous $[\text{Ca}^{2+}]_{\text{cyt}}$ oscillations in neurons are abolished by many different blockers of synaptic transmission (such as NMDA receptor antagonists) and blockers of action potential propagation (tetrodotoxin). In the absence of networking activity, Ca^{2+} responses to the $\text{A}\beta$ oligomers are smaller and are inhibited only by NMDA receptor antagonists and blockers of the formation of amyloid channels (such as NA7). In addition, combination of these two blockers essentially abolished Ca^{2+} responses induced by $\text{A}\beta$ oligomers.^[176] These findings suggest the involvement of both NMDA receptors and the amyloid channels in the primary response to $\text{A}\beta$ oligomers that are further enhanced by networking activity. In support of this notion, we also showed that non-neuronal cells expressing NMDA receptors exhibited Ca^{2+} responses to oligomers, in contrast to cells lacking NMDA. Expression of NMDA receptor subunits NR1/NR2A and NR1/NR2B in these cells restored Ca^{2+} responses to NMDA but not to $\text{A}\beta$ oligomers. These data suggest that $\text{A}\beta$ oligomers may promote Ca^{2+} entry via both amyloid channels and NMDA receptors. Thus, NMDA receptors appear necessary but not sufficient for Ca^{2+} responses to oligomers. Furthermore, $\text{A}\beta$ oligomers may activate distant neurons intertwined by synaptic connections, thus favoring the spreading of excitation

by the recruiting of further NMDA receptors and specific VOCCs, leading to massive Ca^{2+} entry, excitotoxicity, and neuron degeneration in AD.^[176]

Accordingly, intracellular Ca^{2+} homeostasis and its dysregulation play a pivotal role in the susceptibility to neuron damage during aging, neuroinflammation, excessive production of amyloid peptides, excitotoxicity, and mutated presenilins, all of them processes involved in AD. We are currently working on the development of novel drugs targeting these pathways, for example, the synthesis of marine heterocyclic compounds.^[177]

Altered Ca^{2+} homeostasis and concomitant neurotoxicity in Parkinson's disease

Damage of SN DA is considered a main mechanism responsible for PD. These neurons are under extreme bioenergetic demand because of three particular features: (i) the maintenance of a giant axonal tree that requires anterograde/retrograde transport of cytosolic metabolites and organelles, (ii) the maintenance and propagation of action potentials (APs) and the restoring of ionic gradients, and (iii) the large number of synaptic vesicles cycling. Related to the elevated energy requirement, SN DA neurons display large $[\text{Ca}^{2+}]_{\text{cyt}}$ oscillations that can boost mitochondrial OXPHOS activity, which may render them vulnerable to damage when neurons are challenged by different stressors like genetic mutations, mitochondrial toxins or defective aging (Figure 1).

In 2007, Surmeier and cols. proposed for the first time that reliance of DA neurons on L-type VOCCs sensitive to dihydropyridines or Cav1.3 channels, for rhythmic pacemaking rendered them vulnerable to different stressors known to promote PD. These authors demonstrated that reliance of pacemaking activity on these VOCCs increased in a time-dependent manner and differed from young SN DA neurons, that apparently, use alternative mechanisms for pacemaking activity common to other neuron types unaffected in PD.^[178] Interestingly, it appears that these juvenile mechanisms remain latent in aged neurons, such that inhibition of Cav1.3 turn on the pacemaking mechanism to the juvenile form, thus protecting DA neurons from damage. Specifically, treatment with isradipine, a blocker of Cav1.3 channels, reversed the pacemaking phenotype and protected against different PD toxins. Data prompted the consideration of dihydropyridines, used for decades as hypertensive treatment, could be a novel approach for PD.^[179] The present view is that spike-activated Ca^{2+} influx mediated by Cav1.3 channels may trigger Ca^{2+} release from the ER that is transferred to mitochondria to stimulate mitochondrial OXPHOS by two Ca^{2+} -dependent mechanisms: a mechanism mediated by the MCU-dependent Ca^{2+} uptake and enhanced Krebs cycle and mitochondrial respiration, and another mechanism dependent of the malate-aspartate shuttle. The disruption of any of the two mechanisms results in the impairment of the ability of DA neurons to sustain a spike activity. Thus, although this feedforward mechanism attends DA neurons bioenergetic demands linked to sustained spiking, it also underlies the increased oxidative stress and damage with aging or disease.^[180]

Whether targeting mitochondria oxidant stress is enough to prevent PD progression has been extensively examined. Unfortunately, these attempts have failed so far to show efficacy. Recent epidemiological studies provided evidence of a significant correlation between low PD risk and the use of Cav1 channel inhibitors such as dihydropyridines. A recent Phase III clinical trial using isradipine did not show beneficial effects on PD patients. The reasons for the trial failure may be associated to the extensive damage of DA neurons in patients already at the time of diagnosis and/or recruitment, and/or the low level of isradipine concentration achieved *in vivo* in the central nervous system due to large drug clearance.^[181] Despite this failure, there is still a substantial interest in developing novel drugs selectively targeting Ca^{2+} signaling in DA neurons.

For instance, cyclic α -aryl β -dicarbonyl derivatives are important scaffolds in medicinal chemistry that have been used for developing new candidate agents for treating PD. Specifically, a palladium-catalyzed coupling reactions of haloarenes were conducted recently with diverse five- to seven-membered cyclic β -dicarbonyl derivatives that include barbiturate, pyrazolidine-3,5-dione, and 1,4-diazepane-5,7-dione. The coupling reactions

of different *para*- or *meta*-substituted aryl halides were efficient when Pd(*t*Bu₃P)₂, Xphos, and Cs₂CO₃ are used in 1,4-dioxane reflux conditions. Consequently, several 5-aryl barbiturates were synthesized to be used as new scaffolds of Cav1.3 channel inhibitors with an IC₅₀ at 1.42 μM.^[182]

Modulation of calcium signaling and homeostasis by heterocyclic compounds in Alzheimer’s disease and Parkinson’s disease

Extensive evidence has demonstrated that dysregulation of Ca²⁺ homeostasis and signaling are mechanisms that play an essential role in the etiopathogenesis of AD and PD. Aβ peptides are involved in the excessive accumulation of intracellular Ca²⁺ through the formation of Ca²⁺-permeable pores in the plasma membrane or by increasing Ca²⁺ influx via activation of L-type VOCCs and NMDA or AMPA receptors.^[14,15] On the other hand, genetic mutations in presenilin or activation of inositol 1,4,5-trisphosphate (IP₃) and ryanodine receptors promote Ca²⁺ leak in the ER, which produces an elevation of both cytosolic and mitochondrial Ca²⁺ concentration.^[183-185] Mutations in the gene encoding for LRRK2, which are associated with both familial and sporadic PD, elicited transcriptional upregulation of the mitochondrial Ca²⁺ uniporter and the mitochondrial Ca²⁺ uptake 1 protein in post-mortem human brain, fibroblasts, and primary mouse cortical neurons.^[16] Pathological mutant LRRK2 enhanced mitochondrial Ca²⁺ uptake and dendritic injury but increased mitochondrial Ca²⁺ release restored Ca²⁺ homeostasis and was neuroprotective. These findings demonstrated that LRRK2-driven neurodegeneration raises susceptibility to mitochondrial Ca²⁺ overload and implicates mitochondrial Ca²⁺ dyshomeostasis in the pathogenesis of PD. Moreover, knockdown or inhibition of IP₃ kinase B led to α-syn aggregation and phosphorylation in primary cortical neurons from mice incubated with α-syn fibrils, which increases (i) Ca²⁺ release from the ER, (ii) mitochondrial Ca²⁺ content, and (iii) mitochondrial respiration.^[13] We have found some heterocyclic compounds with the capability of modulating Ca²⁺ uptake that can be considered as promising pharmacological agents for the treatment of AD and PD (Table 1).

Table 1. Summary of heterocycle compounds effects on AD and PD. Status: <https://clinicaltrials.gov/>.

eterocyclic Com- pound	Chemical Name	Target	Proposed Mechanism	Effect on Neurodegener- ative Diseases. Status of Clinical Trials
1. ANAVEX2-73 (Blarcamesine)	Tetrahydro- <i>N,N</i> - dimethyl-2,2-di- phenyl-3-fu- ranmethana- mine hydrochlo- ride	mAChRs S1R	• ↓ Ca²⁺ release • ↓ Mitochondrial stress • Activated antioxidant response pathway • Limited apoptosis	Memory improvement and neuroprotective ef- fects in AD and PD. • AD (Phase 2/3) • PD Dementia (Phase 2) • PD (Phase 1)
2. Caffeine (Mateine)	1,3,7-Trimethyl- 3,7-dihydro-1 <i>H</i> - purine-2,6-di- one	A2AR RyR (+)	• ↓ Oxidative damage • ↓ Aβ levels • ↓ α-Synuclein aggre- gates • Restored AChE and Na⁺/K⁺ ATPase activity	Reduced risk of develop- ing AD and PD Epidemiological studies: PD, possible motor bene- fits
3. Diltiazem (Cardizem)	(2 <i>S</i> ,3 <i>S</i>)-5-(2-(Di- methyla- mino)ethyl)-2- (4-methoxy- phenyl)-4-oxo- 2,3,4,5-tetrahy- dro- benzo[<i>b</i>][1,4]thi	Non-dihy- dro-pyri- dine VOCC	• ↓ Ca²⁺ entry • ↓ Oxidative damage • ↓ Inflammatory re- sponse	Reduced risk of develop- ing AD and PD Epidemiological & Ran- domization Studys

azepin-3-yl ace- tate				
4. Latrepirdine (Dimebon)	3,6-Dimethyl-9-(2-methyl-pyridyl-5)-ethyl-1,2,3,4-tetrahydro-γ-carboline dihydrochloride	H1R Other Ca2+ Chan- nels	• ↓ Ca2+ release and en-try • ↓ Aβ levels • ↓ Oxidative damage to lipids • Inhibitor AChE • ↓ α-Synuclein	Cognitive and psychiatric benefit in AD Improvement in cognitive decline in HD Status: • AD (Discontin-ued) • HD (Discontin-ued)
5. Nifedipine (Procardia)	3,5-Dimethyl 2,6-dimethyl-4-(2-nitrophenyl)-1,4-dihydro-pyridine-3,5-di-carboxylate	L-Type VOCC	• ↓ Ca2+ entry • ↓ Secreted Aβ • ↓ Oxidative damage	Reducing risk developing AD and PD Epidemiological & Ran-domization Studies
6. Nimodipine (Nimotop)	3-isopropyl 5-(2-methoxyethyl) 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydro-pyridine-3,5-di-carboxylate	L-Type VOCC	• ↓ Ca2+ entry • Neuroprotection • ↓ Aβ toxicity • ↓ Oxidative damage • Abolished pacemaking activity in DA neurons	Reducing risk developing AD and PD Epidemiological & Ran-domization Studies

1. ANAVEX2-73

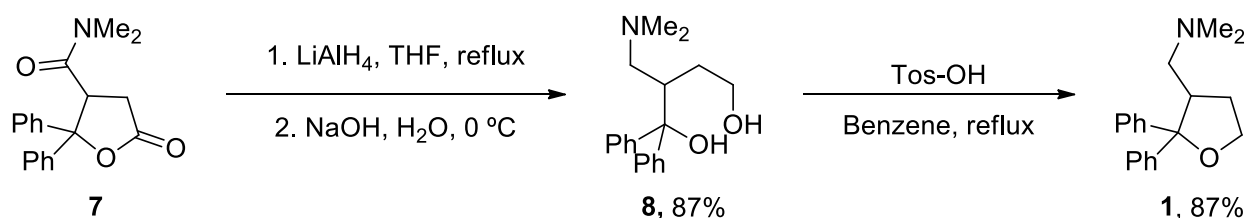
ANAVEX2-73 (Blarcamesine) is a non-selective muscarinic acetylcholine receptor (mAChR) and alfa-1 receptor (S1R) ligand that exhibits an important affinity for its pharmacological targets at micromolar concentration.^[186] σ1 Receptors are ubiquitously expressed in the central nervous system (CNS) and are located at mitochondria-associated ER membranes, where they interact with IP3 receptors to regulate Ca²⁺ exchange between the ER and mitochondria, thereby resulting in reduced mitochondrial stress, regulation of ion channels, activation of the nuclear erythroid 2-related factor 2 (NRF2) / antioxidant response element (ARE) pathway, and limited apoptosis.^[187,188] IP₃ receptor-mediated Ca²⁺ release correlates with variations in the availability of mitochondrial Ca²⁺ and ATP synthesis.^[189] A formal concept analysis (FCA) combined with the Knowledge Extraction and Management (KEM) environment was able to identify ANAVEX2-73 (tetrahydro-*N,N*-dimethyl-2,2-diphenyl-3-furanmethanamine hydrochloride) as a potential genomic biomarker of disease and therapeutic response in a phase IIa clinical trial.^[190] An ongoing randomized, double-blind phase III trial of this compound is evaluating the bioavailability, safety, tolerability, and effectiveness of the treatment in patients with AD (NCT03790709), PD with dementia (NCT03774459) and Rett syndrome (NCT03758924).

Intraperitoneal administration of ANAVEX2-73 (0.3-1 mg/kg) reversed scopolamine- and dizocilpine-induced learning impairments one week after intracerebroventricular injection of the neurotoxic Aβ₂₅₋₃₅ peptide in mice.^[191] Using the same mouse model, treatment with ANAVEX2-73 inhibited the phosphatidyl-inositol 3-kinase (PI3K)/Akt pathway, thereby resulting in the activation of GSK-3β, improvement of behavioral deficits, and limitation of Aβ seeding and tau-induced pathology.^[192] Moreover, the drug preserved mitochondrial integrity and function in isolated mitochondria from the hippocampal brain region of Aβ₂₅₋₃₅ injected mice by increasing the activity of complex IV and oxygen consumption at all states.^[193] Exposure to ANAVEX2-73 also decreased the peroxidation of lipids, Bax/Bcl-2 ratio (that determines the cell susceptibility to apoptosis) and cytochrome c release. In an independent study, ANAVEX2-73 restored the respiratory control ratio and preserved complex IV levels from Aβ toxicity in a Ca²⁺-dependent fashion that regulates several tricarboxylic acid cycle (TCA) enzymes including α-ketoglutarate

dehydrogenase complex and isocitrate dehydrogenase, responsible for NADH production, a substrate for complex I.^[194] ANAVEX2-73 displayed a synergic effect with donepezil (but not with memantine) and restored spontaneous alternation and passive avoidance response in a non-transgenic mouse model of AD.^[195] Incubation with ANAVEX2-73 elicited the accumulation of LC3-II-positive puncta and succeeding autophagic flux in cell cultures. *C. elegans* expressing GFP-LGG-1 (a marker of autophagy) treated with ANAVEX2-73 exhibit increased autophagic activity. In addition, administration of ANAVEX2-73 to A β ₄₂-expressing nematodes upregulated proteostasis capacity, ultimately resulting in a dissociation and clearance of A β ₄₂ aggregates.^[196]

In summary, ANAVEX2-73 modulates Ca²⁺ release after its interaction with IP₃ receptors and prevents mitochondrial failure in multiple ways, including through the activation of the NRF2/ARE pathway that directly controls the expression of several antioxidant and anti-inflammatory genes. In addition, the molecule promotes autophagosome biogenesis and autophagic flux to degrade aggregated proteins and damaged organelles (such as mitochondria).

ANAVEX2-73 (1-(2,2-diphenyltetrahydro-3-furanyl)-*N,N*-dimethylmethanamine hydrochloride) **1** unique total synthesis was reported by Foscolos and co-workers.^[197] The key step during the synthesis is the reduction-opening of lactone **7** to provide 1,4-diol **8**, which was subsequently converted by acid-catalyzed cyclodehydration to ANAVEX2-73 **1** (Scheme 1).



Scheme 1. Unique total synthesis of ANAVEX2-73 **1** reported by Foscolos and co-workers.

2. Caffeine

Caffeine (Mateine), a purine alkaloid present in several plants (*Coffea*, *Camellia*, *Cola*, *Cirus*, *Ilex*, *Paullinia*, and *Theobroma*), is the most consumed psychoactive substance in the world.^[198] Coffee contains a variety of compounds such as caffeine, chlorogenic acid, cafestol, diterpenes and kahweol.^[199] Moreover, coffee is a rich source of bioactive components that contribute to its biological activity, including potassium (K⁺), magnesium (Mg²⁺), niacin and potent antioxidants (chlorogenic acid and tocopherol).^[200] Research studies have established a strong relationship between frequent caffeine consumption and reduced risk of developing AD and PD, with no detectable adverse effects in the CNS in an exposed population. A large body of literature has shown that mutations in presenilins are linked with Ca²⁺ signaling dysregulation and elevated Ca²⁺ release from the ER in neuronal cultures expressing mutant PS,^[201-203] transgenic mice engineered to overexpress mutant PS1,^[204,205] and fibroblasts from subjects with AD.^[206-208] PS induces excessive Ca²⁺ accumulation and release in part via its biochemical interaction with the IP₃ receptor Ca²⁺ release channel, thereby resulting in an anomalous regulation of Ca²⁺ signaling pathways and stimulation of APP processing and A β synthesis,^[209-211] even prior the formation of plaques and NFTs.^[212] Ca²⁺ storage content is higher in mutant presenilin-1 (PS1) knock-in neurons primary cortical neurons from a triple transgenic mouse model of AD (3xTg-AD) compared to non-transgenic cells.^[213] Caffeine exposure altered Ca²⁺ signaling and promoted its release, which was independent of extrusion mechanisms or variations in the steady-state concentration of specific Ca²⁺-binding proteins. However, this effect was attributed to the activation of the ryanodine receptors (RyRs) that become sensitized to so-called process of Ca²⁺-induced release by caffeine.

The CAIDE longitudinal epidemiological study suggested an association between mid-life moderate coffee (but no tea) consumption and late-life reduced risk of dementia

and AD.^[214] Specifically, caffeine intake (3-5 cups per day) reversed cognitive impairment (assessed by Mini-Mental State Examination) in a gender-specific manner (women age 65 and older). A recent mendelian randomization study found that genetically predicted higher caffeine content in the plasma correlates with diminished risk of AD.^[215] Following confounding adjustment, it has been described that long-term coffee consumption (≥ 2 cups/day) was associated with a significant cognitive decline decrease in pathological A β deposition. Nevertheless, no changes were observed in cortical thickness, cerebral white matter hyperintensities or cerebral glucose metabolism, which are features also related to the neurodegenerative process.^[216] The Honolulu Heart Program provided the first evidence showing a potential beneficial effect of caffeine intake in PD patients. Coffee drinkers (28 oz or more per day) had 5-fold lower incidence of developing PD compared to non-caffeine drinkers following an adjustment for both age and pack-years of cigarette smoking.^[217] This study was further supported by Ascherio and colleagues.^[218] In addition, consumption of decaffeinated coffee was not associated with decreased risk of PD, suggesting that caffeine, rather than other coffee components, accounts for the inverse association observed. The findings showed a significant negative correlation between caffeine intake and risk of developing PD in men but a U-shaped relationship among women. The risk of PD was similar in women using hormones and women who never used hormones. Interestingly, caffeine diminished the risk of PD in menopausal women that did not take hormone replacement but there is a higher risk (4-fold) among hormone users with high caffeine.^[219] The risk of PD was even lower when coffee intake is combined with cigarette smoking and nonsteroidal anti-inflammatory drug use, resulting in a cumulative effect.^[220]

A different clinical trial confirmed that caffeine consumption mitigates the risk of PD, but its neuroprotective properties may vary depending on its interaction with other factors, such as obesity and low serum cholesterol levels, which can modify the risk of having PD.^[221] A meta-analysis involving a large number of participants found a non-linear relationship between coffee consumption and the incidence of PD that achieves the maximum protective effect at 3 cups per day.^[222] However, the authors described a linear dose relationship of reduced risk of PD with both tea and caffeine consumption, especially in men compared to women and in European and Asian population relative to USA residents. Based on an open-label, dose-escalation study, caffeine had potential motor and non-motor benefits in subjects with PD, with the maximum tolerated dose of 100-200 mg/day bis in die (BID) without affecting sleep quality.^[223] In a randomized controlled trial, administration of 200 mg caffeine BID for six weeks did not improve daytime somnolence in PD patients but possessed the potential to reverse motor symptoms.^[224] Transgenic mice over-expressing the human APP gene carrying the Swedish mutation (APP^{sw}) treated with 0.3 mg/mL caffeine in the drinking water for 5 months exhibited an improvement in multiple behavioral measurements.^[225] In addition, enzyme-linked immunosorbent assay showed a significant downregulation of both A β ₄₀ and A β ₄₂ levels and decreased PS1 and β -secretase (BACE) protein concentration in the hippocampus of these AD mice. Oral supplementation with caffeine for 4 months restored motor performance, anxiety and memory deficits, prevented neuronal death in the CA1 pyramidal layer of the hippocampus, and promoted neurogenesis in the absence of detectable pathological effects on the A β pathology in transgenic Tg4-42 and 5xFAD mouse models of AD.^[226] Caffeine did not alter the optical density or mRNA expression levels of A1 or A2A receptors in the mouse cerebral cortex or hippocampus.

A β burden was reduced in both brain and plasma of APP^{sw} and APP/PS1 mice (which contain human transgenes for both APP bearing the Swedish mutation and *PSEN1* containing a L166P mutation) following either acute or chronic caffeine administration.^[227] However, amyloid plasma levels were not correlated with (i) A β brain content, (ii) cognitive impairment, and (iii) pro-inflammatory cytokine levels in aged mice. Animals receiving caffeine also display an enhanced memory performance. It has been also demonstrated that long-term administration of caffeine is protective in the THY-Tau22 transgenic mouse model of progressive AD-like tau pathology by limitation of spatial memory abnormalities, tau phosphorylation, oxidative stress, and inflammation.^[228] Since persistent (but not

acute) administration of caffeine increases cerebrospinal fluid (CSF) secretion in rats in comparison to the control-treated group, it has been proposed that chronic caffeine intake can promote CSF production combined with an elevated cerebral blood flow velocity and Na^+/K^+ -ATPase levels.^[229] Protein kinase A (PKA) is a heterotetrametric enzyme comprised of two regulatory and two catalytic subunits that plays an essential role in cell proliferation with an anti-apoptotic activity. The cyclic adenosine monophosphate (cAMP)-response element binding protein (CREB) is a transcription factor that modulates a subset of genes implicated in cognition and neuron survival. c-Jun N-terminal kinase (JNK) and extracellular signal-regulated kinase (ERK) are mitogen-activated protein kinases that can trigger apoptotic signaling by the upregulation of pro-apoptotic genes through the activation of specific transcription factors or directly, by catalyzing protein phosphorylation. Administration of caffeine upregulated PKA activity, induced CREB phosphorylation, and reduced the levels of phosphorylated JNK and ERK in the striatum (but no frontal cortex) of APPsw mice, suggesting that caffeine pro-apoptotic signaling.^[230] Caffeine intake resulted in memory capacity improvement and increased hippocampal brain neurotrophic derived factor (BDNF) and tyrosine receptor kinase B (TrkB) immunoreactivity in PS1/APP double transgenic mice and rats treated with aluminum chloride.^[231,232]

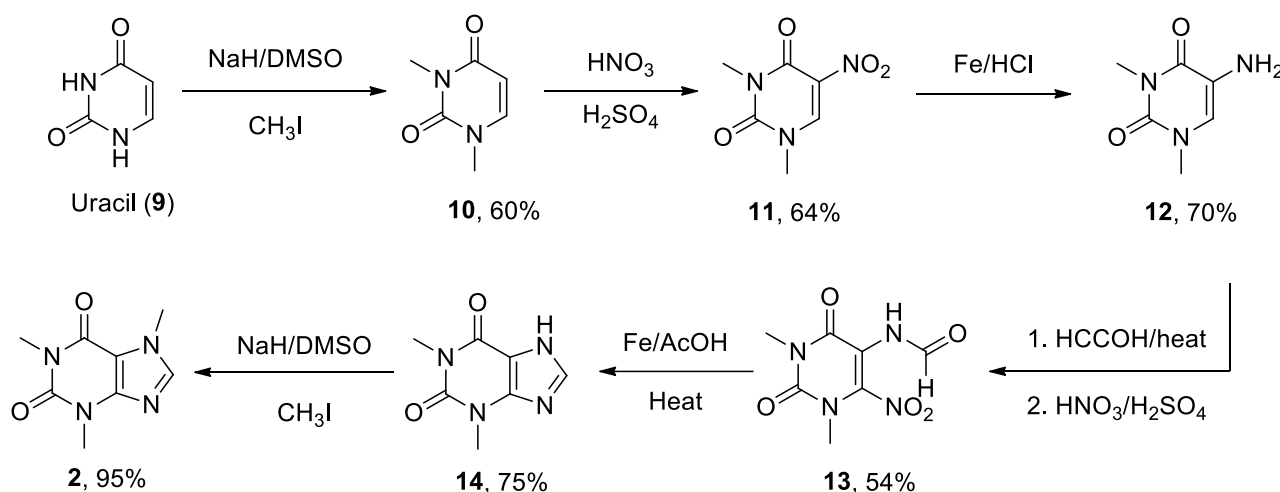
Caffeine also has a neuroprotective role in PD. Exposure to caffeine preserved the degeneration of the nigrostriatal DAergic pathway in neurotoxin-based animal models of PD, such as rotenone, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), and 6-hydroxydopamine (6-OHDA). Histopathological and immunohistochemical characterization of brain tissue from rotenone-exposed rats show a significant degeneration of SN DA neurons and their projections into the striatum. However, administration of caffeine provided a dose-dependent therapeutic effect against rotenone-mediated neurotoxicity.^[233] Injection of caffeine through a peritoneal route improved the behavioral phenotype, normalized brain enzymatic activities of both acetylcholinesterase (AChE) and Na^+/K^+ -ATPase (which play an important role in memory and learning) and mitigated neuroinflammation and oxidative damage in rotenone-treated rats.^[234] Caffeine modulated striatal protein content and catalytic activity of cytochrome P450 (a membrane-bound hemoprotein that plays a central role in the detoxification of xenobiotics), glutathione-S-transferases (a family of phase II detoxification enzymes involved in the protection of macromolecules from attack by ROS, reactive electrophiles, environmental carcinogens, and chemotherapeutic agents) and vesicular monoamine transporter-2 (VMAT-2, an integral presynaptic protein that controls the packaging and release of DA and other neurotransmitters from synaptic vesicles) in mice receiving MPTP for 4 weeks.^[235] Using *ex vivo* ^1H - ^{13}C -NMR spectroscopy, Bagga *et al.* found that pretreatment with caffeine increased neuronal glutamatergic and GABAergic metabolic activity, and neurotransmission in MPTP-injected mice.^[236] Oral supplementation with the coffee component eicosanoyl-5-hydroxytryptamide attenuated MPTP-induced nigrostriatal DAergic cell loss in mice, displayed both antioxidant and anti-inflammatory properties and normalized phosphoprotein phosphatase 2A (PP2A) methylation and activity.^[237]

Intraperitoneal injection of 10-20 mg/kg day of caffeine improved motor dysfunction and increased catecholamine levels in a rat model of 6-OHDA-induced striatal lesion.^[238] Striatal injection of 6-OHDA elicited apomorphine-induced rotation and impaired locomotor activity in parallel with a loss of DA immunoreactivity and an inflammatory response, but administration of caffeine ameliorated the behavioral and pathological PD-like phenotype. Moreover, it has been also reported that administration of caffeine in the drinking water can exert neuroprotective effects by decreasing the number of inclusions positive for pS129 α -syn, content of TUNEL-stained apoptotic cells, LC3-mediated macroautophagy, and lysosome-associated membrane protein type 2A (LAMP2A) chaperone-related autophagy in mice that received an intracerebral injection of synthetic α -syn fibrils with the A53T missense mutation.^[239] Regarding its potential mechanism of action, caffeine is an antagonist of the adenosine-2A receptor (A2AR), which are predominantly localized in the GABAergic striatopallidal neurons projecting from the caudate nucleus and the putamen to the external segment of the globus pallidus (indirect pathway).^[240] A2ARs

colocalize with DA2 receptors to form heteromeric complexes that mediate the allosteric antagonism between adenosinergic and DAergic transmission.^[241] Noteworthy, a double-blind, randomized, crossover study showed that treatment with caffeine improved the pharmacokinetic profile of levodopa by reducing its plasma concentration-time profile and by prolonging its effect.^[242]

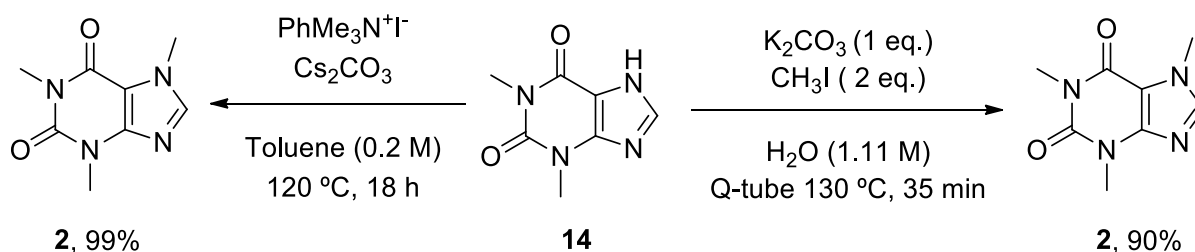
In summary, while caffeine has complex biological and pharmacological profiles, experimental evidence indicates that caffeine readily crosses the blood-brain barrier and exerts its action by antagonizing A2ARs and confers neuroprotection by stimulating mitochondrial function and by attenuating excitatory neurotransmitter release, oxidative insult, and neuroinflammation. Clinical trials have shown that caffeine significantly enhances AD-related memory loss and improves motor symptoms in PD patients. In addition, caffeine has a well-established long-term safety profile. Together with its low cost and high availability, caffeine is a promising therapeutic agent for the treatment of neurodegenerative diseases.

The most recent total caffeine (1,3,7-trimethyl-3,7-dihydro-1*H*-purine-2,6-dione) **2** synthesis was reported by Narayan in 2003 from uracil **9**.^[243] *N*-Methylation in the presence of a strong base such as sodium hydride in dimethylsulfoxide (DMSO) produced 1,3-dimethyluracil **10**, which was nitrated and subsequently reduced to 5-amino-1,3-dimethyluracil **12**, using iron and hydrochloric acid. Compound **13** was obtained following two conventional steps and resulted in the formation of theophylline **14** after a reduction process and an intramolecular heterocyclization reaction with iron and acetic acid. The final methylation at position 7 led to the generation of caffeine **2**. Therefore, synthesis of caffeine needed seven reaction steps with an ~10% overall yield (Scheme 2).



Scheme 2. Synthesis of caffeine **2** reported by Narayan in 2003 from uracil **9**.

In recent years, new and improved methodologies for the *N*-methylation of theophylline **14** have been published. A novel technique uses the Q-tube apparatus in water at over boiling temperature as a green solvent.^[244] In a different study, Schnürch's group optimized the employment of quaternary ammonium salts as monoselective *N*-methylation reagents (Scheme 3).^[245]



Scheme 3. New methodologies applied for the *N*-methylation of theophylline **14**.

3. Diltiazem

Diltiazem (Cardizem) is a non-dihydropyridine Ca^{2+} channel blocker with antihypertensive, antiarrhythmic and vasodilation properties. The drug selectively targets the VOCCs, which are the primary mediators of Ca^{2+} influx into neurons in response to membrane depolarization. P/Q- and N-type VOCCs regulate neurotransmitter release upon arrival of the action potential to the axon terminal in the presynaptic neuron. Glutamate release promotes postsynaptic Ca^{2+} trafficking by activation of NMDA receptors (NMDAR) or through an indirect pathway involving L-type VOCCs.^[246] Reduced Ca^{2+} transient at presynaptic or postsynaptic sites can mitigate glutamate-induced excitotoxicity. Therefore, administration of Ca^{2+} channel blockers has become an interesting approach for the treatment of neurodegenerative diseases. PET and postmortem analyses of different brain regions (such as cerebral cortex and amygdala) from AD subjects revealed a marked inhibition of AChE enzymatic activity, responsible for the hydrolytic metabolism of the neurotransmitter acetylcholine into acetate and choline.^[247-249] In contrast, administration of $\text{A}\beta_{25-35}$ peptide upregulated the activity of AChE through modulation of the L-type VOCCs (increasing intracellular Ca^{2+} concentration) in embryonal carcinoma P19 cells.^[250] When cultures were incubated in the presence of diltiazem, the authors found a 75% loss of AChE enzyme activity.

Epidemiological data obtained from individuals with PD indicate that long-term treatment with Ca^{2+} channel blockers targeting Ca^{2+} channels of DA neurons may represent a potential therapeutic strategy, reducing the risk for developing the disease.^[251-253] A larger study involving 65,001 patients, reinforced the connection between Ca^{2+} channel blockers and diminished incidence of PD.^[254] In addition, centrally acting Ca^{2+} channel blockers prevent nigrostriatal DAergic degeneration in parkinsonian mice and non-human primates and improve survival rate in vitro.^[178,255,256] There is evidence supporting a beneficial effect of diltiazem against DA toxicity in human neuroblastoma cells.^[257] Cav1.2 and Cav1.3 are L-type VOCCs regulate DAergic neuron spontaneous firing activity in the SN region of the brain. DA neurons fire either in a low frequency single-spike pattern or transiently, in a high-frequency so-called burst mode. Data from animal models support clinical observations showing that diltiazem has positive effects on AD-induced pathology. Ca^{2+} channel blockers, such as diltiazem, protect neurons from $\text{A}\beta$ -induced influx of Ca^{2+} ions and downstream toxicity as well as decrease the amyloid content by facilitating the clearance rate.^[258,259] Excessive neuronal Ca^{2+} influx contributes to neuronal dysfunction and degeneration that underlies cognitive disturbances in AD. Neuronal cultures incubated with $\text{A}\beta$ peptides led to an enhanced Ca^{2+} entry.^[260] Furthermore, endogenous accumulation of oligomeric $\text{A}\beta$ led to an upregulated expression of L-type VOCCs (Cav1.2).^[259] Diltiazem improved survival rate and decreased Ca^{2+} intracellular concentration by blocking L-type Ca^{2+} channels in vitro. Diltiazem protected MC65 neuroblastoma cells from the toxicity mediated by the APP C-terminal fragment by improving cell survival.^[261]

In addition, the $\text{A}\beta_{25-35}$ fragment decreased both secreted APP and $\text{A}\beta$ while promoted cell-associated APP in chick sympathetic neurons. Enhanced APP secretion with no variations in the amount of cell-associated APP occurred in response to diltiazem.^[262] The accumulation of exogenous $\text{A}\beta$ significantly attenuated cell viability and proliferation (determined by using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide, MTT) in primary hippocampal neuronal cultures, which was reversed by exposure to diltiazem.^[13] This study also provided evidence supporting that $\text{A}\beta$ toxicity shows an early Ca^{2+} -independent phase and a late Ca^{2+} -dependent phase. Spontaneous alternation behavior, a reliable measure of short-term of spatial working memory, was significantly increased in mice treated with diltiazem.^[263] Chronic exposure to aluminum or any other of its forms in the drinking water has been associated with higher risk of developing AD.^[264-266] Aluminum accumulation has been detected in the brain of AD cases, where causes neurofibrillary degeneration in neurons.^[267] Bouras *et al.* found a specific increased content of aluminum within NFTs in both the inferior temporal cortex and hippocampus of indi-

viduals with AD.^[268] Aluminum induces A β protein conformational modifications and aggregation (including amyloid fibrillation) either in vitro or in vivo.^[269-272] Aluminum chloride has been reported to cause dementia (AD accounts for the ~70% of cases) but administration of diltiazem reversed learning and memory deficits, AChE upregulation, and oxidative damage in mice.^[273] Ginkgo biloba augmented the bioavailability of diltiazem by modulating cytochrome P450 3A activity in both the rat liver and small intestine.^[274]

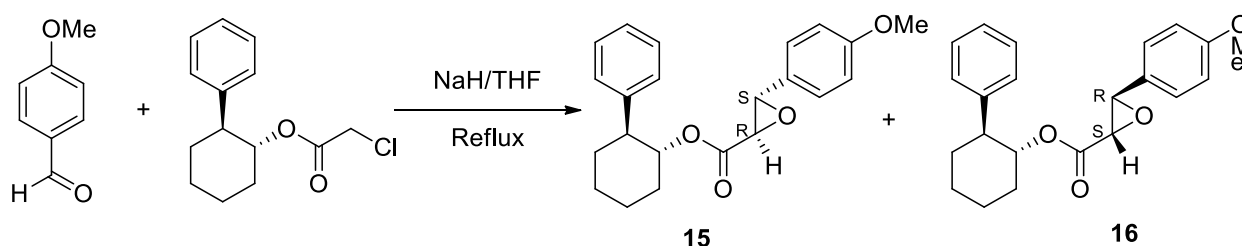
It has been reported that Cav1.2 and Cav1.3 L-type VOCCs are susceptible of degeneration during the progression of PD.^[275-277] During spontaneous action potentials, L-type VOCCs contribute to Ca²⁺ oscillations in the soma and dendrites of constantly active mid-brain DA neurons. The extended opening of L-type VOCCs throughout autonomous pacemaking induces prolonged cytoplasmic Ca²⁺ trafficking and its overload in SN DA neurons, leading to mitochondrial oxidative stress.^[275,277] L-type VOCCs-mediated alteration of the steady-state of DA levels is responsible for causing downstream oxidative stress and α -syn-induced toxicity.^[278] In contrast, some studies suggest that administration of Ca²⁺ channel blockers (including diltiazem) could be associated with the development of parkinsonian symptoms, particularly, in subjects that already had subclinical idiopathic PD pathology.^[279,280] Despite there is a lack of research investigating the potential antioxidant effect of diltiazem in AD or PD, it has been found that its intraperitoneal injection decreased the levels of nitrite (an indirect assessment of nitric oxide) and MDA (a lipid peroxidation marker) and upregulated the activity of several antioxidant enzymes such as reduced glutathione, catalase, and superoxide dismutase in a streptozotocin-induced rat model of diabetes.^[281] High-performance liquid chromatography analysis showed a significant decline of MDA content in perfused rabbit hearts treated with diltiazem.^[282] Oral supplementation with diltiazem for two weeks reduced thiobarbituric acid-reactive species (TBARS, a by-product of LPO) and nitrite content and upregulated superoxide dismutase (SOD) and reduced glutathione enzymatic activities in an aluminum chloride mouse model of AD.^[273] Because of their autonomous pacemaking activity coupled to action potentials, SN DA neurons have particularly high energetic (ATP) demands and may be subjected to elevated levels of basal oxidative stress.^[283]

Likewise, the anti-inflammatory effect of diltiazem in patients with AD or PD has not yet been examined. Diltiazem produced a dose-dependent inhibitory effect on T-cell proliferation.^[284] Individuals undergoing cardiopulmonary bypass surgery displayed an increase in IL-6 content, which was significantly attenuated following diltiazem administration.^[285] Enhanced levels of the anti-inflammatory cytokine IL10 were observed in subjects with unstable angina receiving diltiazem.^[286] Moreover, intraperitoneally injected diltiazem reduced IL-10 and TNF- α (but no nitrite/nitrate and IL-6) plasma concentration in BALB/c mice injected with bacterial lipopolysaccharide (LPS).^[287] Synthetic A β ₂₅₋₃₅ fragments added to human fetal brain cell cultures activate microglia and increase the levels of intracellular Ca²⁺ in a time-dependent fashion.^[288] Treatment with the L-type VSCCs antagonist diltiazem resulted in a transmembrane diminished Ca²⁺ influx that abolishes microglial stimulation. Cav1.2 VOCCs (particularly α 1 subunit) are highly expressed in reactive astrocytes of mice overexpressing A β protein precursor (A β PP), which is specifically linked to an A β plaque deposition.^[289] Cav1.2 channels are also expressed in microglia. Variations in the balance between M1 (pro-inflammatory) and M2 (anti-inflammatory) microglial phenotypes are related to PD. It has been demonstrated that diltiazem-induced blockade of L-type VOCCs promotes pro-inflammatory M1 transition and decreases anti-inflammatory M2 macrophage polarization in mouse microglia-derived MG6 cells, resulting in an upregulated iNOS mRNA expression and downregulated arginase levels.^[290] In addition, knockdown of microglial Cav1.2 led to behavioral impairment, DA neuron degeneration in the SN of MPTP-injected mice compared to control group, and reduce polarization toward the M1 phenotype.

In summary, the L-type VOCC diltiazem is a Ca²⁺ antagonist that can be used to treat dementia and dementia-related diseases due to its capability of improving cognitive deficits, such as learning and memory capacity. The drug also improves neuron survival and exhibits both antioxidant and anti-inflammatory properties. Diltiazem can cause nausea

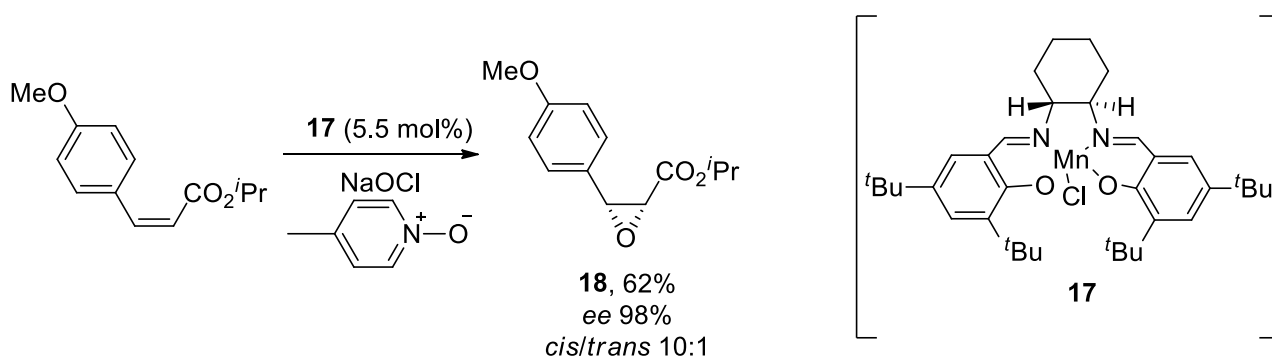
and vomiting, pulmonary oedema, and renal failure. Diltiazem, together with verapamil, are the most toxic Ca^{2+} channel blockers in overdose and their toxicity is associated with significant cardiovascular collapse, metabolic problems (e.g., hyperglycemia) and vascular smooth muscle tone deficits.

The first racemic synthesis of diltiazem (2-(2-dimethylaminoethyl)-5-(4-methoxyphenyl)-3-oxo-6-thia-2-azabicyclo[5.4.0]undeca-7,9,11-trien-4-yl]ethanoate) **3** was described in 1990.^[291] The first asymmetric total synthesis of (+)-diltiazem was reported by Naito and co-workers, using a diastereoface differentiating nucleophilic addition as the key step to create the two contiguous stereogenic centers.^[292] Schwartz used the separation of diastereomeric glycidic esters (**15** and **16**) by direct crystallization as the key step, based on their marked difference in solubility.^[293] Enantiomerically pure glycidic ester **15**, the required isomer for the synthesis of (+)-diltiazem **3**, was the major product obtained (54% yield) (Scheme 4).



Scheme 4. Schwartz's strategy for the synthesis of (+)-diltiazem **3**.

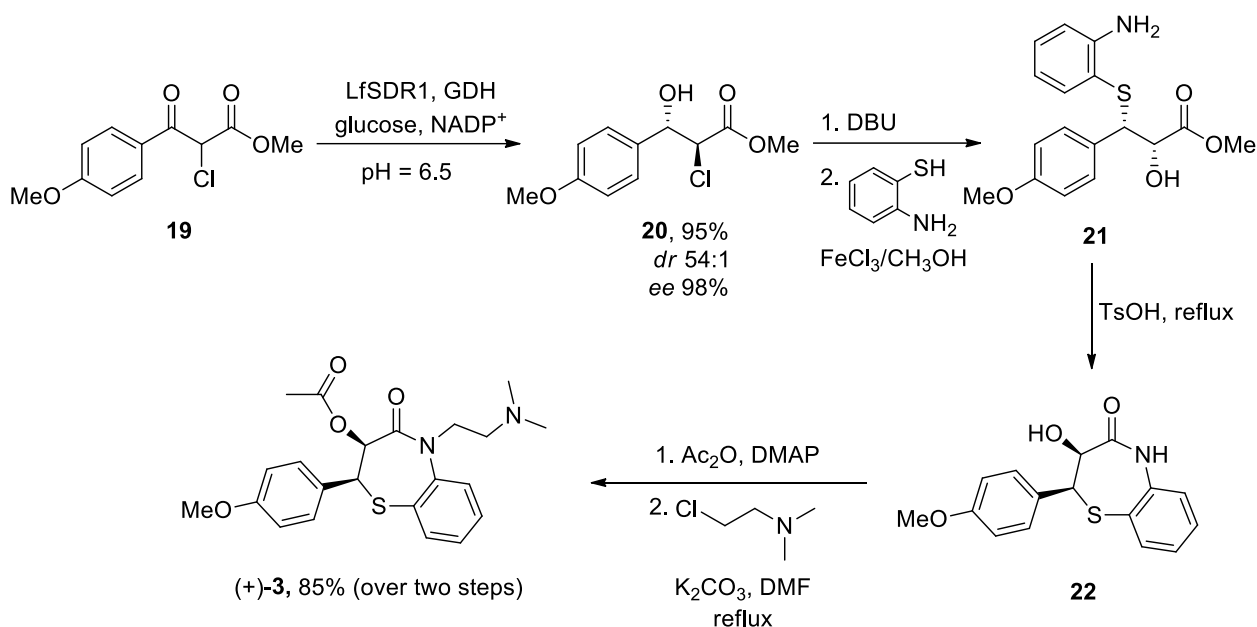
In 1994, Jacobsen *et al.* used a manganese-catalyzed asymmetric epoxidation of cinnamate esters for the preparation of an enantiomerically pure key intermediate **18** in the synthesis of **3** (Scheme 5).^[294]



Scheme 5. Preparation of the enantiomerically pure key intermediate **18** for the synthesis of (+)-diltiazem **3**.

To date, more synthetic routes to prepare (+)-diltiazem **3** from a chiral epoxide intermediate have been reported. The enantiomerically pure epoxide has been obtained by the introduction of a chiral auxiliary in the reaction^[295,296], utilization of Yang's catalyst^[297], addition of metal complexes^[298] or by direct acquisition.^[299]

A useful synthetic methodology employed to induce chirality in the product is the utilization of lipase^[300,301] or baker's yeast catalysed reactions.^[302] The most recent approach employed for total synthesis of (+)-diltiazem **3** was reported by Chen and colleagues in 2022.^[303] Racemic keto ester **19**, obtained in two steps from commercially available reagents, is converted into enantiomerically pure hydroxy ester **20** by ketoreductase-catalyzed dynamic reductive kinetic resolution. Two conventional steps (ring closure and ring opening) are further taken to produce an intermediate **21**, which is readily subjected to intramolecular acid-catalyzed amidation. Two additional steps from intermediate benzothiazepinone **22** are required to obtain (+)-diltiazem **3**. This chemoenzymatic synthesis involves eight steps to obtain (+)-diltiazem **3** in ~45% overall yield (Scheme 6).



Scheme 6. Chemoenzymatic synthesis of (+)-diltiazem 3 proposed by Chen and colleagues in 2022.

4. Latrepirdine

Latrepirdine (Dimebon) is a carboline that blocks H1 histamine receptor (H1R) activity. A broad spectrum of effects on neurologically relevant targets was proposed based on various cell- and animal-based studies. The compound is a potent reversible and competitive inhibitor of both AChE and butyrylcholinesterase, which leads to elevated acetylcholine content and concomitant boosting of cognitive performance.^[304,305] Besides its anti-histaminic properties, latrepirdine can modulate a wide range of other neurotransmitter receptors (such as DA, serotonin, glutamate, α -adrenergic, and imidazole).^[306,307] Studies carried out in rat cerebral neurons confirmed the inhibitory effect of latrepirdine on NMDA receptors and involve the polyamine site of the NMDA NR2B subunit (the target for histamine) as a potential binding site.^[304,308] Latrepirdine has also been shown to interact with Ca^{2+} channels; for example, its administration effectively blocked the activity of L-type VOCCs ($IC_{50} = 57 \mu M$) in cerebellar granule neurons.^[309] A pilot clinical trial carried out in patients with mild-to-moderate AD given latrepirdine for 8 weeks showed an important reduction of neuropsychiatric symptoms (depression) and a significant cognitive function enhancement together with a lack of hematological and biochemical disturbances.^[304] Drug safety and efficacy were also examined in moderate-to-severe AD subjects (NCT00912288). Data from a phase II randomized, double-blind, placebo-controlled clinical study showed a significant improvement in cognition, function, and behavioral outcome following 60 mg/day latrepirdine for 26 and 52 weeks (6 months extension phase) in individuals with mild-to-moderate AD with no adverse effects recorded.^[310] CONNECTION and CONTACT phase III trials (NCT00838110) failed to show significant improvement in any primary or secondary outcome measures of cognition in patients treated with latrepirdine.^[311] A phase II randomized, placebo-controlled trial of latrepirdine showed a protective effect against cognitive impairment in subjects with mild-to-moderate Huntington's disease.^[312] Results from the double-blind, placebo-controlled Phase III HORIZON trial (NCT00920946) revealed that latrepirdine failed to achieve statistical significance for co-primary endpoints in individuals with mild-to-moderate Huntington's disease. A meta-analysis study revealed that latrepirdine did not ameliorate overall cognition, but the molecule enhanced the neuropsychiatric inventory scale, used to assess psychopathology in dementia patients.^[306]

Cerebellar granule neurons incubated with the $A\beta_{25-35}$ peptide displayed morphological alterations, cell loss, and dysregulated intracellular Ca^{2+} homeostasis.^[309] Nevertheless,

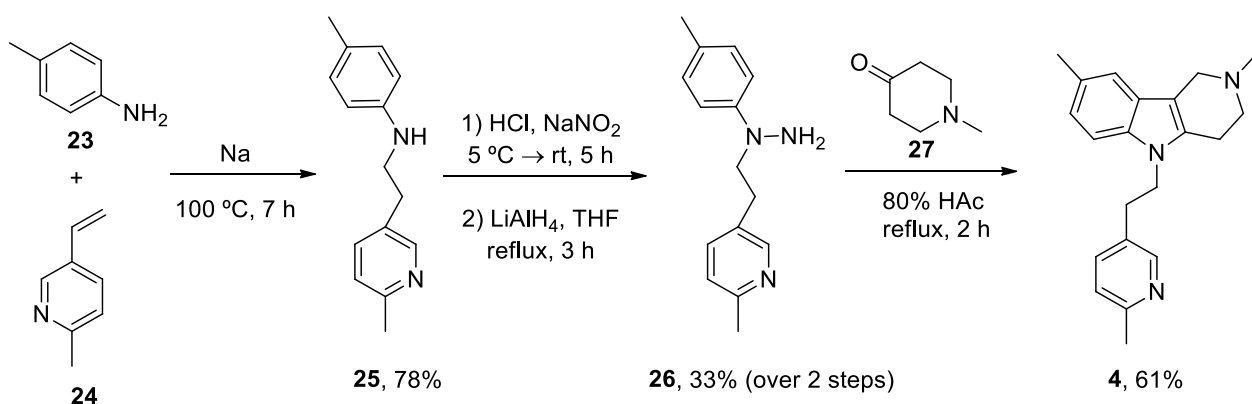
exposure to latrepirdine preserved neurons against A β -mediated toxicity through inhibition of the L-type VOCCs current. Intraperitoneal administration of latrepirdine reversed learning and memory loss following chronic partial deprivation of cerebral cholinergic functions, which causes dementia in rats.^[305] Latrepirdine had the capability of modulating cognitive ability in 5xFAD mice, though it was unable to mitigate A β -associated pathology.^[313] P301S tau mice consistently performed better on both the inverted grid and accelerating rotarod tests after latrepirdine treatment, suggesting that the molecule is associated with enhanced motor performance.^[314] Treatment with latrepirdine 15 min prior to scopolamine-induced memory impairment significantly ameliorated delayed matching-to-sample task accuracy (to assess memory) in young adult and aged Rhesus macaques.^[315] Treatment with latrepirdine in the drinking water for 4 months resulted in improved cognitive function in TgCRND8 mice although did not modify neither A β ₄₀ or A β ₄₂ content, suggesting APP processing as a direct target of the drug.^[316] FDG-PET studies revealed an increased cerebral glucose utilization in aged mice in response to latrepirdine exposure.^[317] Augmented succinate dehydrogenase activity, $\Delta\Psi_m$, and ATP synthesis were normalized following latrepirdine administration in differentiated SH-SY5Y cells and primary neuron cultures from mouse cerebral cortex with no differences in the mtDNA copy number, thereby suggesting a restoration of mitochondrial function.^[318] Preservation of mitochondrial shape, mass, and respiratory chain complex activities were seen following latrepirdine treatment in cells incubated with A β .^[319] The compound can also preserve mitochondrial function by targeting the mPTP opening induced by the A β ₂₅₋₃₅ peptide and MPP⁺ (1-methyl-4-phenylpyridinium).^[320] Mitochondrial accumulation of Ca²⁺ induces depolarization of the mitochondrial membrane and, if large and sustained enough, a subsequent irreversible opening of the mPTP. Moreover, no changes were observed in pivotal metabolic enzymes, suggesting that latrepirdine's neuroprotective effect is independent of promoting mitochondrial energy metabolic pathways.^[309]

It has been shown that short-term exposure to latrepirdine causes: (i) A β accumulation and increased secretion of APP metabolites in mouse N2a neuroblastoma cells overexpressing APPsw; (ii) higher levels of A β ₄₂ in isolated cortical synaptoneurosome preparations from TgCRND8 mice; and (iii) enhanced A β ₄₀ levels in the hippocampal interstitial fluid of Tg2576 AD mice.^[321] Either Ca²⁺ or A β ₂₅₋₃₅ toxic fragment promoted mitochondrial LPO but administration of latrepirdine inhibited oxidative damage to lipids.^[320,322] In addition, the molecule has been shown to prevent LPO induced by tert-butyl hydroperoxide in rat brain mitochondrial homogenates.^[323] In addition, administration of the drug diminished the content of hyperphosphorylated tau-positive dystrophic neurons in the mouse spinal cord while no changes in the levels of inflammatory markers were detected. Latrepirdine can also have a pro-autophagic activity, with a selective autophagic elimination of protein aggregates. Latrepirdine induces MTOR- and ATG5-dependent autophagy, which results in decreased levels of intracellular APP metabolites, including A β in the neocortex and hippocampus of TgCRND8 AD mice.^[324] Latrepirdine can also stimulate autophagy-mediated degradation of α -syn in differentiated SH-SY5Y neurons and in the mouse brain.^[325] Immunohistochemical analyses found a significant decrease in the number of TDP-43-like inclusions in cells transfected with TDP-43.^[326] α -Syn pathogenic and toxic effect was markedly reduced in *S. cerevisiae*, SH-SY5Y cells, and the mouse brain through a selective autophagic protein degradation.^[325] Administration of latrepirdine attenuated methamphetamine- (but not MPTP) induced cytotoxicity in mice in a body temperature-independent manner, suggesting a neurotoxin-specific protective effect.^[13] However, the authors only measured the concentration of DA in the mouse striatum, with a lack of assessment of other additional key factors associated with neurodegenerative processes. Increased lifespan and motor performance parallel to reduced γ -syn aggregation, number of proteinaceous inclusions, and the inflammatory response were observed in transgenic mice overexpressing γ -syn treated with latrepirdine in the drinking water.^[314] In contrast, exposure to the drug failed to protect DAergic neurons in *C. elegans* and mouse models of PD.^[327] Fourteen-old-month α -syn transgenic mice receiving latrepirdine did

not exhibit neurochemical, behavioral, or histopathological variations relative to the control group. Noteworthy, these mice recapitulate some pathological features typically manifested at the early onset of the disease.^[328]

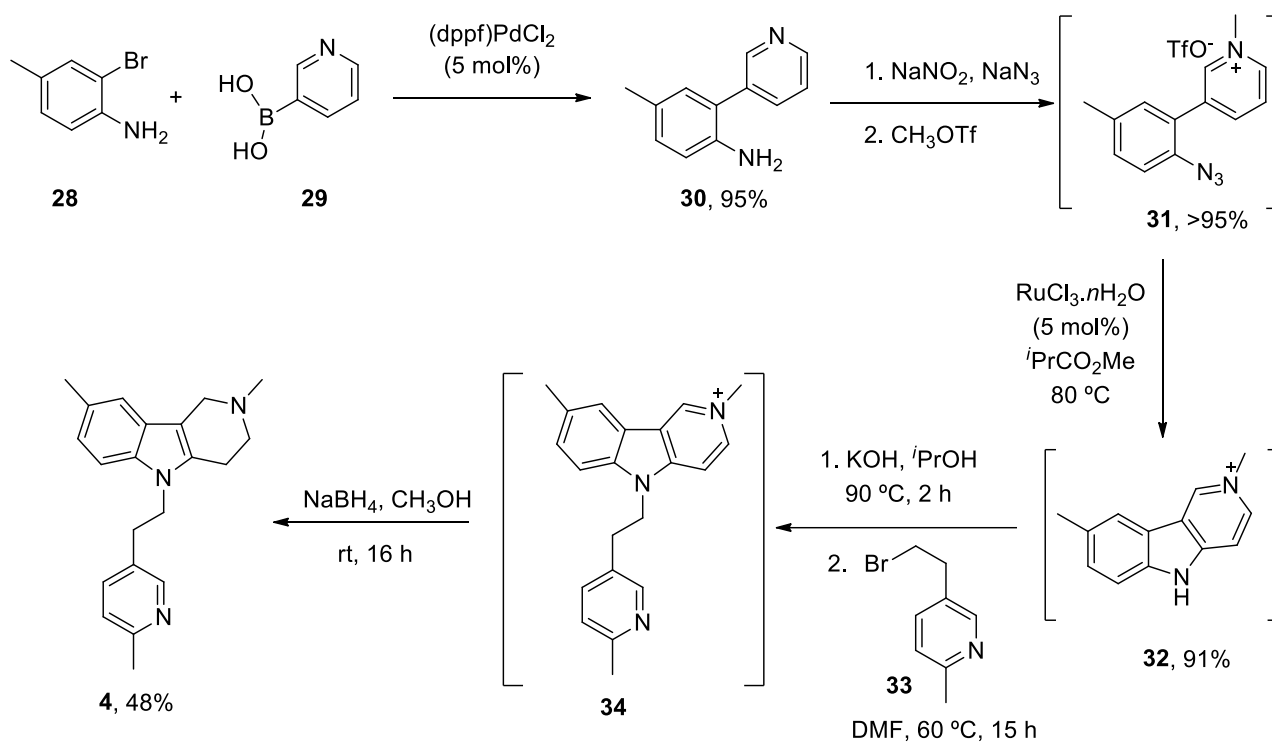
In summary, psychiatric symptoms (such as depression) and learning and cognitive measures were restored in AD patients undergoing latrepirdine treatment, in part due to its ability to increase acetylcholine concentration by inhibition of either AChE or histamine receptors. Latrepirdine may elicit neuroprotective activity by promoting mitochondrial function and clearance of a range of intracellular inclusions through the stimulation of autophagy. The molecule may also regulate several targets involved in AD pathology, such as neurotransmitter receptor activity, stabilization of Ca^{2+} signaling, and LPO. Toxicological studies have shown that latrepirdine is safe and a well-tolerated drug. A dosage exceeding the therapeutic range by 100 times for a period of 2 months did not cause any physiological changes or pathology in guinea pigs, rats, or dogs.^[304,329]

Latrepirdine (2,3,4,5-tetrahydro-2,8-dimethyl-5-[2-(6-methyl-3-pyridinyl)ethyl]-1H-pyrido[4,3-b]indole) **4** was originally synthesized using the Fischer-indole reaction.^[330] A more recent synthesis reported by Zheng *et al.* employed *p*-toluidine **23** and 2-methyl-5-vinylpyridine **24** as commercial starting materials and achieved the desired product **4** in 16% yield over four reactions steps.^[331] Moreover, cyclization of compound **26** and 1-methylpiperidin-4-one **27** was carried out with 80% HAc in a one-pot two steps reaction instead of using benzene and HCl/EtOH (Scheme 7).



Scheme 7. Synthesis of latrepirdine **4** reported by Zheng *et al.* 2022.

The synthesis of latrepirdine **4** has also been performed using the chemistry of ruthenium (III) catalysts in a concise and efficient manner.^[332] The reaction comprised six steps, which required three purification processes only with an ~47% overall yield. The key step involved the stereoselective formation of γ -carboline **32** from ortho-substituted aryl azide **31** catalysed by RuCl₃·*n*H₂O (Scheme 8).



Scheme 8. Ruthenium (III) catalysis used in the synthesis of latrepirdine 4.

5. Nifedipine

Nifedipine (Procardia) is a first-generation dihydropyridine Ca^{2+} channel blocker used to treat hypertension and to control angina pectoris. Nifedipine is a selective antagonist of the L-type VOCCs that plays an essential role in neuronal processes triggered by membrane depolarization, thereby contributing to Ca^{2+} -mediated events activated by signaling pathways and diverse stimuli, including neurotransmitter release, rhythmic firing, gene expression, etc.^[333] There is growing evidence that nifedipine may be an effective therapeutic agent for the treatment of neurodegenerative diseases, including AD and PD. APOE $\epsilon 4$ peptide-induced increase in the concentration of intracellular Ca^{2+} and transcriptional activity of cAMP-response element-binding protein (CREB) in rat hippocampal neuronal cultures was reduced after administration of nifedipine, suggesting that L-type VOCCs are involved in neuron responses to APOE $\epsilon 4$.^[334] In culture of primary mouse hippocampal neurons, A β enhanced the content of cytosolic Ca^{2+} and concomitant phosphorylation of serine-880 in the AMPA-selective glutamate receptor 2 (GluR2), which leads to attenuated synaptic activity.^[335] In contrast, exposure to nifedipine diminished Ca^{2+} levels and GluR2 phosphorylation and increased cell surface GluR2. It has been reported that A β -mediated toxicity promotes the activation of the Ca^{2+} -calmodulin kinase II (CaMKII)/AMP-activated protein kinase (AMPK) pathway.^[336,337] Exposure to nifedipine mitigated A β toxicity by preserving cell viability in SH-SY5Y cells stably transfected with an empty vector or expressing the cellular prion protein, indicating that Ca^{2+} influx via L-type VOCCs is involved in A β -induced neurotoxicity.^[338] Administration of nifedipine significantly diminished the content of secreted A β_{1-42} and key components of the gamma secretase complex (e.g., PS-1) in H4 neuroglioma cells overexpressing APP, without triggering cell death.^[339] Primary CNS neurons cultured from PS1-deficient mice showed higher susceptibility to oxidative stress but exposure to nifedipine increased the survival rate, suggesting that L-type VOCCs-mediated Ca^{2+} influx via was responsible for the neuronal loss.^[340]

It has been suggested that deficits in APP^{-/-} mice are associated with alterations in Ca^{2+} homeostasis. Treatment with nifedipine (but not the NMDAR blocker 2-amino-5-phosphonovaleric acid) restored post-hypoxic related damage, leading to an improve-

ment of neuron functional deficiencies such as population spike amplitude and depolarized resting $\Delta\Psi_m$ in hippocampal slices from mice lacking APP.^[341] To determine the specific pathways involved in altered Ca^{2+} homeostasis, primary cortical neuron cultures from 3xTg-AD or APPsw mice were incubated with intracellular $\text{A}\beta$.^[342] Quantitative measurements displayed a marked boost in resting $[\text{Ca}^{2+}]_{\text{cyt}}$ concentration (further enhanced by extracellular Ca^{2+} efflux) that was blocked by nifedipine, suggesting that elevated Ca^{2+} influx occurs through L-type VOCCs. An age-dependent increase of L-type VOCC amplitude was described in CA1 pyramidal neurons (but not CA3 or dentate granule neurons) in 3xTgAD mice relative to wild-type mice, consistent with the notion that CA1 neurons are prone to p-tau/NFT pathology due to an excessive Ca^{2+} trafficking. Nevertheless, Ca^{2+} current was limited by nifedipine, which attributes to the L-type VOCCs the enhanced intracellular Ca^{2+} pool.^[343] The stromal interaction molecule 1 (STIM1) is a type I transmembrane protein that plays a pivotal role in Ca^{2+} influx. Stim1 positively modulates Orai1 channels for store-operated Ca^{2+} entry and negatively modulates L-type VOCCs. STIM1 protein levels were decreased in the medium frontal gyrus of patients diagnosed with AD.^[344] STIM1-KO differentiated cells displayed an elevated Ca^{2+} entry in response to membrane depolarization, which was nifedipine-sensitive. Primary hippocampal neuronal cultures from 5xFAD mice exposed to nifedipine inhibit abnormal VOCC and store operated Ca^{2+} (SOC) entry, a process regulated mainly by STIM1. In contrast, STIM2 was responsible to modulate depolarization-mediated Ca^{2+} entry through VOCCs into cells with full Ca^{2+} stores.^[345] Intracellular Ca^{2+} responses to membrane depolarization were potentiated by the V337M mutant tau in diverse cell cultures, which were inhibited following administration of nifedipine. These findings suggest that upregulation of L-type VOCC-mediated Ca^{2+} influx results from destabilization of microtubules triggered by tau mutations.^[346] Late insoluble (but not soluble or early insoluble) tau aggregates activated sensitive Ca^{2+} channels, thereby increasing Ca^{2+} signaling, cell loss, and oxidative damage ($\text{O}_2^{\bullet-}$ levels) in primary cultures of rat cortical neurons and astrocytes.^[347] The rate of ROS production was significantly diminished in the presence of the NADPH oxidase inhibitor AEBSE (2-aminoethyl) benzenesulfonyl fluoride hydrochloride), indicating that ROS formation was NADPH oxidase-dependent. In addition, administration of nifedipine limited tau-mediated Ca^{2+} influx, generation of ROS, and overall toxicity. The data demonstrated that: (i) tau effect depends on its aggregation state, and (ii) late insoluble aggregates incorporate into the membranes, resulting in an ionic current alteration and VOCC stimulation.

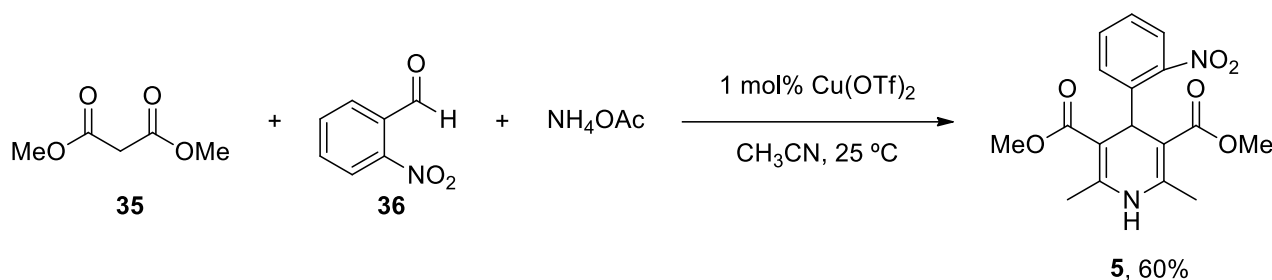
The subthalamic nucleus (STN) has been proposed to play a central role in the disrupted function of the basal ganglia circuitry associated with PD. Distinct activity patterns, such as increased burst firings, have been observed in STN neurons and represent a pathognomonic electrophysiological feature linked to PD. High-frequency stimulation of the STN or pharmacological blockade of the subthalamopallidal network in monkeys and rats improved motor symptoms.^[348-350] Patch-clamp studies performed in rat brain slices showed that around 50% of STN neurons display the intrinsic property of switching from single-spike activity to burst-firing mode.^[351] Treatment with nifedipine caused an irreversible reduction in burst frequency and abolished burst firing. Furthermore, the role of VOCCs was investigated in STN neurons. Based on nifedipine effects on the frequency and current curve, it was established that both short- and long-duration rebound bursting neurons contain nifedipine-sensitive Cav1.2-1.3 channels, which only contribute to rebound activity in STN neurons with long-lasting rebounds.^[352] High-frequency stimulation-induced oscillations in the STN resulted at least in part from Ca^{2+} entry through the high-threshold potential nifedipine-sensitive L-type VOCCs.^[353] Pasternak *et al.* reported that nifedipine was not linked to significantly lower risk of developing PD, but the small sample size undermined the findings.^[354] Nifedipine exposure did not have a significant effect on DA neuron survival but exhibited a stimulatory impact on neurite length. The actions of cholinesterases such as AChE and butyrylcholinesterase on Ca^{2+} conductance may be responsible for the trophic effect on neurite outgrowth in embryonic ventral mid-brain cultures.^[355] Nifedipine limited both glutamate- and NMDA-related CREB phosphorylation. Stimulation of D1 receptors or cAMP pathway in primary striatal neuron

cultures produced cytosolic accumulation of Ca^{2+} that interacted with nifedipine, resulting in Ca^{2+} -mediated CREB phosphorylation and c-fos gene expression.^[356]

Injection of nifedipine into the dorsal striatum did not affect apomorphine-induced rotational behavior, indicating that it had no effect on DAergic transmission.^[357] In a different study, microinjection of 6-OHDA resulted in a significant upregulation of mRNA levels of the Cav1.2 Ca^{2+} channel $\alpha 1$ subunit in the ipsilateral SN.^[358] Subcutaneous injection of 3.5 mg/kg nifedipine significantly decreased apomorphine-induced rotation and partially restored striatal DA concentration in 6-OHDA-lesioned rats. These findings imply that L-type VOCCs are directly connected with DA neurodegeneration. Nifedipine prevented nobiletin- (a natural polymethoxy flavonoid extracted from the fruit peel of citrus) induced DA release in the CA1 region of the hippocampus of MPTP-injected mice.^[359] The high-threshold Ca^{2+} spike (HTS) and the slow oscillatory potential (SOP) are diverse Ca^{2+} conductances that play an important role in the generation of action potentials in SN DA neurons. While nifedipine showed a slight inhibitory effect on HTS, the molecule was able to block SOP. Moreover, nifedipine steadily abolished the spontaneous firing pattern.^[360] Quinpirole is a D2 receptor agonist that inhibits Ca^{2+} current in both 6-OHDA-lesioned and reserpine-injected rats.^[361] However, quinpirole inhibitory effect was reversed by nifedipine. These data suggest that DA-depletion leads to a rearrangement of the high voltage-activated (HVA) Ca^{2+} current profile, an outcome also observed in monogenic forms of PD (DJ1 mice). Rotenone-treated SH-SY5Y cells incubated with nifedipine showed a concentration-dependent decrease in Ca^{2+} trafficking, suggesting that the neurotoxin activates the L-type VOCCs opening.^[362] The results also demonstrated that Ca^{2+} is involved in rotenone-mediated apoptosis and ROS production. Pretreatment with nifedipine increased cell survival, synaptic vesicle exocytosis, and neurite outgrowth as well as mitigated DA release and generation of ROS (using the dichlorodihydrofluorescein diacetate (DCFH-DA) probe) in PC12 treated with rotenone.^[363] These results indicated that intracellular Ca^{2+} plays an important role in rotenone-induced DA toxicity. Quantitative assessment in organotypic sagittal vibrosections from p10 rat brain, showed that L-type VOCC inhibitor nifedipine do not exert a neurotoxic activity on DAergic or cholinergic neurons.^[364] Even though nifedipine did not protect cholinergic neurons, the drug counteracted axotomy-mediated DA neuron degeneration in the SN but not in the ventral tegmental area, possibly by regulating proinflammatory cytokine release.

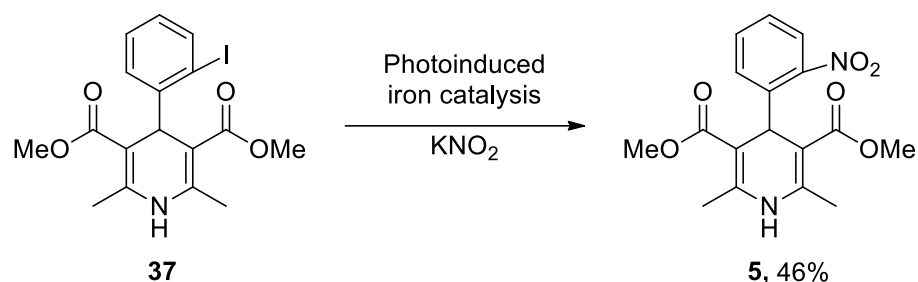
In summary, nifedipine is an antagonist of L-type VOCCs antagonist involved in $\text{A}\beta$ and tau pathology, neurotoxin-induced DA degeneration, Ca^{2+} homeostasis and signaling, synaptic function, oxidative insult, and apoptotic cell death. The primary manifestation of nifedipine-related toxicity is hypotension secondary to loss of systemic vascular resistance. Subacute and subchronic toxicity studies indicated that oral administration of nifedipine has a safety profile at doses of up to 50 mg/kg in rats over a period of thirteen weeks. In dogs, no damage was detected up to 100 mg/kg dosage for a period of four weeks. Rats tolerated daily intravenous administration of 2.5 mg/kg nifedipine over a period of three weeks while dogs tolerated up to 0.1 mg/kg nifedipine for six days. An overdose of nifedipine can induce severe hypotension, systemic vasodilation, and reflex tachycardia.

The first total synthesis of nifedipine **5** was reported in 1989 by Singh, who used an acid-catalyzed reaction of an enamine with two perhydro-heterocycles.^[365] Other synthetic procedures were reported in the following years using different methodologies.^[366-370] Solid phase synthesis was also applied^[371,372] as well as one-pot solvent-free synthesis.^[373-375] The most common synthetic procedure to obtain pyridines is using the Hantzsch reaction.^[376-383] The preparation of 1,4-dihydropyridines requires two equivalents of β -keto ester, an aldehyde and nitrogen donor. Sudalai and co-workers utilized dimethylmalonate **35** as the β -keto ester, 2-nitro-benzaldehyde **36** for the aldehyde and ammonium acetate as the nitrogen donor (**Scheme 9**).^[384]



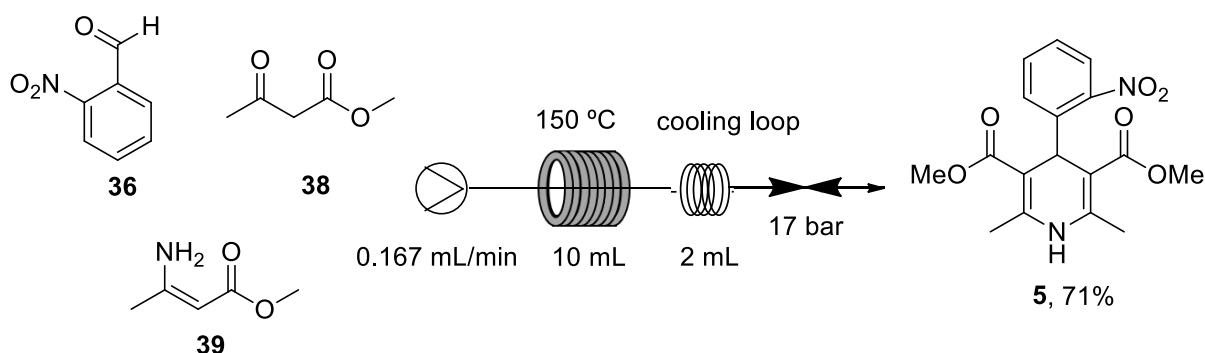
Scheme 9. Hantzsch reaction used in the preparation of nifedipine **5**.

This reaction has a great number of modifications, such as the utilization of different homogeneous^[385-388] or heterogeneous^[389-391] catalysts, and the variation of the solvent.^[392] In 2021, nifedipine (3,5-dimethyl 2,6-dimethyl-4-(2-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate) **5** was synthesised through a photoinduced iron-catalysed *ipso*-nitration via single-electron transfer.^[393] Aryl iodide **37** changed the iodine to nitro substituent to obtain **5** with good yield induced by photocatalysis (**Scheme 10**).



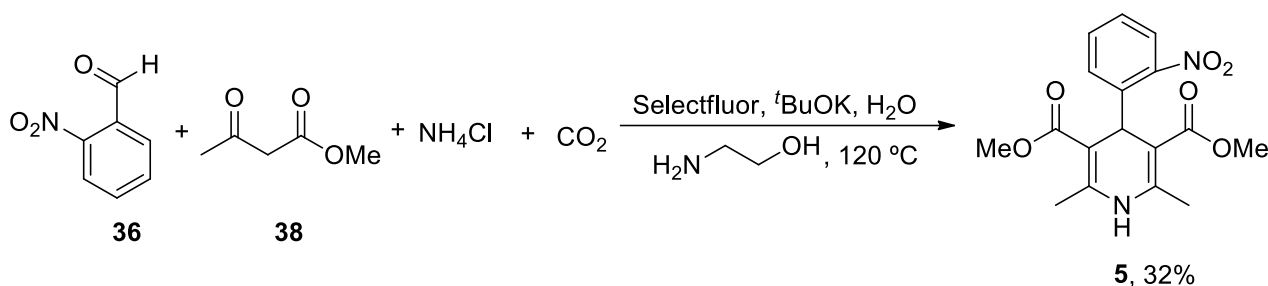
Scheme 10. Synthesis of nifedipine **5** through a photoinduced iron-catalysed *ipso*-nitration via single-electron transfer.

The first flow multicomponent synthesis of nifedipine **5** was reported elsewhere.^[394] Methanol solutions of compounds **36**, **38** and **39** were loaded to a heated 10 mL stainless steel coil reactor (150°C) at 0.167 mL min^{-1} to obtain nifedipine **5** in 71% yield (**Scheme 11**).



Scheme 11. First flow multicomponent synthesis of nifedipine **5**.

More recently, Xiang *et al.* described a green methodology for the synthesis of nifedipine **1**.^[395] A metal-free multicomponent cycloaddition of ketones with an ammonium cation under a CO_2 atmosphere is used to obtain the desired dihydropyridine derivatives. Thus, using methyl acetoacetate **38** and *o*-nitrobenzaldehyde **36**, in the presence of ammonium chloride (NH_4Cl) and CO_2 in aqueous solution, **5** was obtained in 32% yield (**Scheme 12**).



Scheme 12. Green methodology for the synthesis of nifedipine 5 reported by Xiang et al. 2021.

6. Nimodipine

Nimodipine (Nimotop) is a Ca^{2+} channel blocker utilized to prevent brain damage as a consequence of reduced blood flow. The molecule antagonizes the Cav1.2-1.3 L-type VOCCs, showing a greater affinity for the Cav1.2 channel.^[396] As a highly lipophilic compound, nimodipine can easily cross the BBB and reaches elevated concentrations in the CSF. The drug has specific binding affinity for dihydropyridine receptors, in contrast to nifedipine that shows predominantly peripheral effects. Nimodipine has been proposed to be of potential therapeutic utility in clinical trials of subjects with AD or PD. The beneficial effects attributable to nimodipine are related to clinical symptoms, cognitive function, and overall physical activity. The drug was shown to be more effective in primary degenerative dementia rather than in multi-infarct dementia.^[397] A multicenter, double-blind, placebo controlled, randomized clinical trial of nimodipine (30 mg/kg tris in die) for 3 months demonstrated its efficacy to prevent behavioral, cognitive or affective impairments in patients with primary degenerative dementia of the Alzheimer's type.^[398,399] An identical dose of nimodipine resulted in a marked improvement of the global functional state in individuals with mental deterioration of degenerative or vascular origin.^[400] A review article of several double-blind, placebo-controlled clinical trials using nimodipine demonstrated its beneficial properties in elderly subjects suffering from a cognitive impairment syndrome.^[401] The first randomized, double-blind, controlled trial focusing on subcortical vascular dementia was carried out in 2005 and concluded that nimodipine might exert a protective effect against cardiovascular comorbidities.^[402]

Clinical observations have been confirmed by experimental research. Nimodipine possess the potential to reverse learning and memory defects in both young and aged hypertensive rats.^[403,404] Bilateral injection of $\text{A}\beta_{1-42}$ in the entorhinal cortex of rats led to delayed acquisition in a spatial reference memory task and decreased excitatory transmission. Long-term treatment with nimodipine prevented aged-related attenuation of learning and memory through modulation of synaptosome Ca^{2+} -binding proteins.^[405] Administration of nimodipine improved reversal spatial learning impairment and synaptic current defects associated with $\text{A}\beta$ pathology.^[406,407] Age-related increase of the L-type Ca^{2+} channel protein $\alpha 1\text{D}$ in the CA1 region of the hippocampus correlated with higher working memory defect, but nimodipine-treated rats for several months exhibited lower $\alpha 1\text{D}$ immunoreactivity and improved spatial working memory.^[408] Nimodipine ameliorated scopolamine-induced cognitive decline via its regulatory effect on the brain-derived neurotrophic factor (BDNF) and acetylcholine, which were elevated in both the cortex and hippocampus.^[409] Nimodipine also ameliorated memory failure in aged rhesus monkeys.^[410] Sustained depolarization-mediated increase of cytosolic levels of Ca^{2+} (but not released from the ER) produce substantial amounts of intraneuronal $\text{A}\beta_{1-42}$ and cell death in primary rat cortical neuron cultures. Exposure to nimodipine reduced Ca^{2+} influx and associated $\text{A}\beta_{1-42}$ accumulation.^[411] Nimodipine restored the neurophysiological responses of ghrelin on the $\Delta\Psi\text{m}$ in young but not older neurons from Tg2576 female mice incubated with the oligomeric $\text{A}\beta_{1-42}$ fragment, indicating that $\text{A}\beta$ -mediated intracellular Ca^{2+} dysregulation is only reversible during the early stages of $\text{A}\beta$ pathology.^[412] MTT assay and morphometric cell counting showed that treatment with nimodipine protected both rat corti-

cal and hippocampal neurons from A β_{25-35} -induced cell death.^[413] In primary rat hippocampal neuron cultures, A β_{25-35} fragment triggered reversible enhancement in intracellular Ca²⁺ content and bursts of action potentials, which were exacerbated after extracellular Mg²⁺ removal. Treatment with the L-type blocker nimodipine inhibited A β_{25-35} -mediated toxic effects in both cortical and hippocampal neuronal cultures.^[414,415] A different study using the same cultures confirmed that addition of nimodipine limited A β_{25-35} -related Ca²⁺ uptake and apoptotic effect.^[416,417] Patch-clamp recording studies demonstrated that nimodipine inhibits A β_{25-35} peptide excessive Ca²⁺ current density. Nevertheless, exposure to nimodipine did not mitigate inhibit oxidative damage associated to A β_{25-35} . These results suggest that A β significantly enhances Ca²⁺ trafficking via nimodipine-sensitive L-type VSCCs, which leads to free radical-induced neuronal loss.

Okadaic acid promoted phosphorylation of tau by increasing Ca²⁺ influx through L-type VOCCs, since nimodipine attenuates phospho-tau levels in SH-SY5Y neuroblastoma cells.^[418] H4/APPsw cells or primary neuronal cultures derived from the cerebellum of Tg2576 AD mice incubated with nimodipine displayed an augmented A β_{42} secretion. In addition, a comparable effect was described in Tg2576 mice injected with nimodipine, which showed a marked increase in A β_{42} plasma concentration. Thus, the drug may modulate the release of A β_{42} through an elusive mechanism rather than its capacity to inhibit Ca²⁺-influx pathways.^[419] Driving tau expression in M4/6 neurons led to increased sensitivity of Ca²⁺ transients to nimodipine. This effect was ablated in M4/6 neurons co-expressing tau and Ca- α 1D-RNAi.^[420] Moreover, the authors demonstrated that knockdown of the *Drosophila* L-type Ca²⁺ channel Ca- α 1D reverses tau-induced olfactory memory abnormalities by restoring Ca²⁺ handling. Elevated Ca²⁺ concentration aggravated A β -mediated behavioral impairment and defective chemotaxis, resulting in a shortened lifespan in *C. elegans* overexpressing A β_{1-42} .^[421] Exposure to nimodipine extended lifespan and rescued motor lesions, synaptic deficiencies, and DAergic degeneration in worms. Furthermore, nimodipine limited A β aggregation via through upregulation of glutathione S-transferase activity, resulting in an attenuation of oxidative damage. LPS-treated rats exhibited important memory deficits, enhanced synaptosomal Ca²⁺ uptake, and microglial (but not astrocytic) stimulation with subsequent cytokine storm but administration of nimodipine reversed LPS-induced toxicity.^[422] A dose-dependent depletion of A β -stimulated IL-1 β content and release was detected following nimodipine exposure in both the N13 microglia cell line and cultures of primary mouse microglia together with reduced cell loss.^[423] In addition, the molecule mitigated A β -induced intracellular accumulation of IL-1 β in mice receiving a stereotaxic hippocampal injection of oligomeric A β_{1-42} peptide.

A more recent study reported that nimodipine combined with piracetam results in a significant improvement of cognitive abilities and quality of life scores in patients with vascular dementia after an ischemic stroke.^[424] Sadleir *et al.* showed that oral administration of nimodipine to 5XFAD mice did not have a beneficial effect on amyloid pathology, since the molecule did not prevent neuritic dystrophy or reduce cortical or hippocampal A β content.^[425] However, the treatment did not exacerbate the AD phenotype, suggesting a safety and tolerability profile. It has been described that iron uptake, which competes with Ca²⁺ for entry into neurons through the L-type VOCCs, can be inhibited with nimodipine in a dose-dependent fashion in potassium chloride stimulated neuronal cells.^[426] The data suggest that, under cellular iron overload conditions, iron uptake occurs through L-type VOCCs. Subcutaneous delivery of nimodipine reversed behavioral abnormalities, preserved the number of DAergic neurons in the locus coeruleus, and attenuated microglial activation in LPS-infused rats.^[427] Exposure to nimodipine blocked DA neuron pacemaker activity, which can be restored by virtual Cav1.3 channels.^[428] In contrast, virtual NMDAR were not capable of restoring regular pacing in nimodipine-silenced DA neurons. In vitro and in vivo studies demonstrates that incubation with nimodipine abolishes autonomous pacemaking in DA neurons and the underlying $\Delta\Psi_m$ oscillations.^[178]

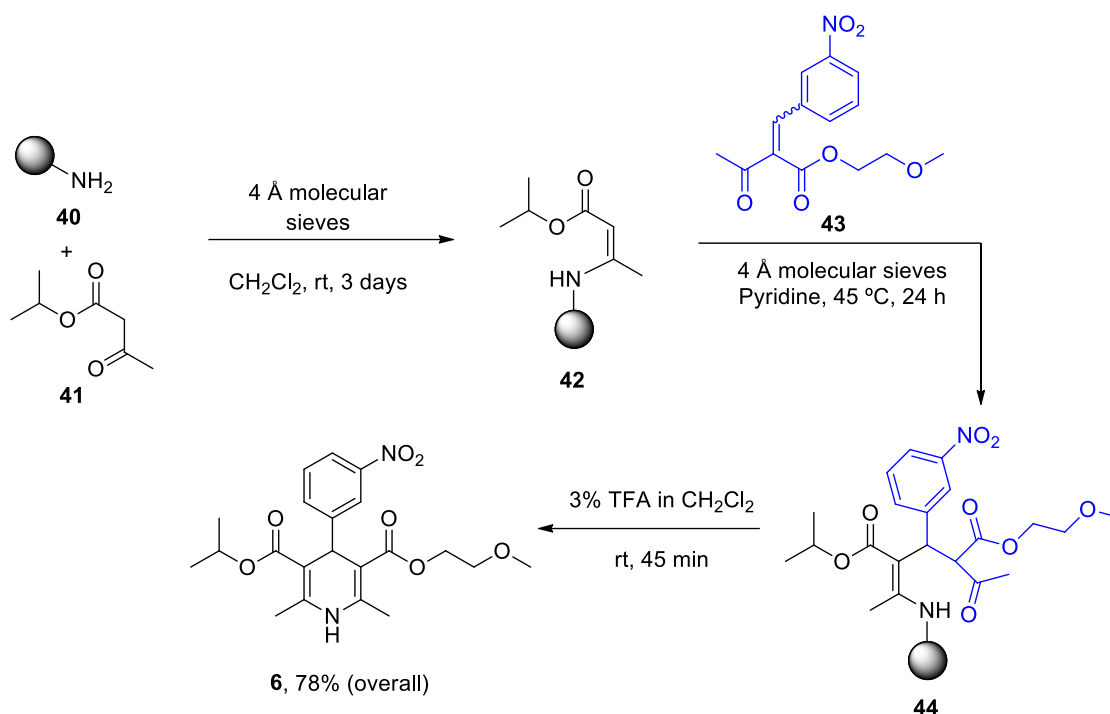
Primary culture of cerebellar granule neurons incubated with MPP⁺ led to prominent cell death but nimodipine limited the effect of the neurotoxin.^[429] MPP⁺ elevated cytosolic

Ca^{2+} content and induced cell death parallel to mitochondrial depolarization and fragmentation in vitro.^[430] However, exposure to nimodipine diminished Ca^{2+} levels, improved cell survival rate, and restored mitochondrial morphology. Nimodipine also ameliorated MPTP-induced behavioral phenotype and limited striatal DA depletion, SN neuronal loss, and oxidative insult without regulating MAO-B activity. The data indicated that nimodipine has the ability to improve mitochondrial function and integrity and involves L-type VOCCs in MPTP-mediated nigrostriatal DA neurodegeneration. In a different study, the same authors reported defective function in proteins involved in the modulation of intracellular Ca^{2+} homeostasis, including calbindin and calpain. This abnormal function was rescued by nimodipine treatment.^[431] A different report showed that nimodipine had no effect on behavioral impairment and striatal DA depletion but preserved DA neurons from death in marmosets injected with MPTP.^[256] Similar findings were observed in MPTP-treated mice, in which treatment with nimodipine protected DA neurons in the SN but no changes were found in the striatum.^[255]

Nimodipine simultaneously upregulated DA release whilst suppress AChE release in both rat cerebral cortex and striatum.^[432] Nimodipine prevented dendritic spine loss and behavioral abnormalities but not associated rotational asymmetry in DA-grafted rats.^[433] Moreover, exposure to nimodipine did not impact DA graft survival but promoted graft reinnervation of striatum. Continuous-release pellets of nimodipine prevented locomotor disturbances, in unilateral 6-OHDA mesencephalic lesions.^[434] Intrastratial injection of 6-OHDA in rats caused a significant loss of retrogradely fluorogold and DAergic labelled neurons in the SN at 1-month post-injection. Nimodipine treatment failed to improve behavioral phenotype or nigrostriatal DA degeneration.^[435] Exposure to nimodipine increased survival of SN (but not VTA) DA neurons in axotomy-induced rat model.^[364] Although the precise mechanism remains elusive, the ability of the drug to counteract the inflammatory processes may be crucial for mitigating axotomy-induced neurodegeneration. Knockdown of Homer1, a postsynaptic density scaffold protein that regulates synaptic plasticity and Ca^{2+} signaling, preserved DA neurons from MPP⁺ toxicity.^[436] This protective effect was linked to attenuated Ca^{2+} -mediated ROS generation, which in turn, was dependent on the modulatory activities on ER Ca^{2+} trafficking and release through plasma membrane Ca^{2+} channels. Nimodipine significantly decreased the amount of NO• and LPS-activated microglia, which releases pro-inflammatory mediators such as interleukin-1 β (IL-1 β), prostaglandin E2 (PGE2), and tumor necrosis factor- α (TNF- α).^[437] In addition, in the absence of microglia, pretreatment with nimodipine did not exert a neuroprotective effect against MPP⁺-mediated DA toxicity. Nimodipine also downregulated DA uptake in neuron-glia cultures from mice lacking functional NADPH oxidase (an enzyme involved in the production of O₂^{•-}) incubated with LPS. Taken together, these findings indicate that nimodipine protects DAergic neurons by mitigating the inflammatory response and by inhibiting NADPH oxidase-ROS signaling pathway.

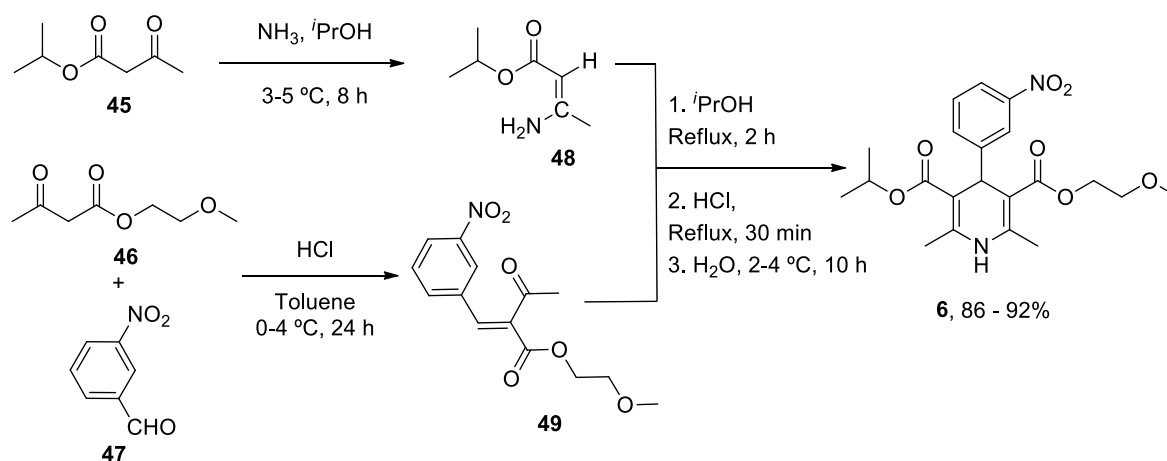
In summary, the L-type Ca^{2+} channel blocker antagonist nimodipine protects from A β and presenilin pathology and from LRRK2- and α -syn-induced toxicity. The molecule ameliorates behavioral outcome, increases synaptic transmission and neuron survival, improves mitochondrial function, and attenuates oxidative stress and inflammation. Nimodipine is, in general, well tolerated although sensations of warmth and skin reddening can occur. High concentrations of the drug can result in reduced blood pressure, headache, nausea, muscle weakness, and gastrointestinal complaints.^[397-399] Isolated CNS symptoms, such as insomnia, tachycardia, and increased motor activity have been reported. Nimodipine exhibits a low incidence of severe side-effects.

A solid-phase synthesis was reported by Gordeev in 1996 for the preparation of nimodipine (3-(2-Methoxyethyl) 5-propan-2-yl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate) **6** and other bioactive dihydropyridines.^[438] Condensation of the immobilized *N*-tethered enamino component **42** with the corresponding 2-benzylidene α -keto ester **43** provided the conjugated enamine **44**. This intermediate was treated with trifluoroacetic acid to obtain the free enamino ester which spontaneously cyclizes in solution to afford the desired product **6** (Scheme 13).



Scheme 13. Solid-phase synthesis of nimodipine 6 reported by Gordeev.

More recently, due to a considerable demand of nimodipine in the Russian market, Pharm. Sintez Co. has developed a new technology to produce the drug in pilot batches.^[439] The approach includes the production of 1-methylethyl-3-amino-crotonate 48 and 2-methoxyethyl-2-(3-nitrobenzylidene)acetoacetate 49. Cyclocondensation of both compounds, 48 and 49, employing *i*PrOH as the solvent and in the presence of hydrochloric acid, afforded the final product 6 in high yield and purity (**Scheme 14**).



Scheme 14. Production of nimodipine 5 in pilot batches by Pharm. Sintez. Co.

Abbreviations

Ac: acetate; DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene; DMAP: 4-dimethylaminopyridine; DMF: dimethylformamide; DMSO = dimethyl sulfoxide; Dppf = 1,1'-bis(diphenylphosphino)ferrocene; GDH: glutamate dehydrogenase; NADP⁺: nicotinamide-adenine dinucleotide phosphate; Tf: trifluoromethanesulfonate; TFA: trifluoroacetic acid; THF: tetrahydrofuran; Tos = Ts: toluenesulfonyl.

Conclusions and Future Directions

Multiple candidate drugs for treating AD or PD have failed over the last years. Further research is still needed to determine the therapeutic time window and the stage of the disease that should be used in clinical trials. Neuropathological and biochemical assessments support the notion that mitochondrial dysfunction causes an increase of free radicals and Ca^{2+} -induced toxicity, which are important factors in the neurodegenerative process described in AD and PD. Based on the combination of preclinical and clinical data, there is a general consensus that development of therapeutic interventions targeting mitochondrial Ca^{2+} signaling may slow or stop the progression of neurodegenerative diseases, including AD and PD. A set of strategies to normalize mitochondrial Ca^{2+} homeostasis and signaling has been described. One potential approach involves Ca^{2+} uptake blockade through the L-type VOCCs, which inhibits Ca^{2+} transient at either presynaptic or postsynaptic sites and attenuates glutamate-mediated excitotoxicity. Selective antagonists of Cav1.2-1.3 L-type VOCCs also exhibit beneficial properties since prolonged opening of L-type channels results in augmented Ca^{2+} release and influx and its accumulation in DA neurons. Chemical synthesis, also revised here, may lead to the development of novel derivatives with increased efficiency and/or availability. The capability of heterocyclic agents of modulating mitochondrial Ca^{2+} content and signaling and the ability to preserve mitochondrial biogenesis and function provides a plausible biological basis for their neuroprotective effect. In summary, decreasing the susceptibility of neurons to injury should not only reduce the incidence of AD or PD but also slow the progression, broadening the therapeutic window for patients with early-stage disease.

Author Contributions: VT, LN, and CV participated in the conceptualization of the article, wrote the initial manuscript, prepared the figures and tables, and contributed to revisions. AB, PGA, and LFP discussed the chemical synthesis, prepared the chemical equations and structural formulas, and revised the manuscript. All authors read and approved the final version of the manuscript.

Funding support: This work was supported by the Excellence Program #CCVC8485 from Junta de Castilla y León, Spain, and by grant #RTI2018-099298-B-100 from Ministry of Science and Innovation, Spain, to CV and LN, and grant #VA294P18 from Junta de Castilla y León, Spain, to LN. VT is supported by the Maria Zambrano's Excellence Program (#CL-EI-2021 IBGM) from the Ministry of Science and Innovation and the University of Valladolid, Spain, as well as by the Internationalization program of Junta de Castilla y León, Spain.

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