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# Heterocyclic Compounds' Therapeutic Potential in Alzheimer's and Parkinson's Disease by Targeting at Mitochondrial Homeostasis and Signalling

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**ABSTRACT:**

The therapeutic potential of heterocyclic compounds in neurodegenerative illnesses such as Alzheimer's and Parkinson's has garnered a lot of attention. These molecules target signaling pathways and mitochondrial homeostasis. Although the exact processes that cause Parkinson's disease and promotion are still unknown, there is a lot of evidence that a faulty cell reinforcement system, mitochondrial dysfunction, intracellular Ca2+ dyshomeostasis, and an excess of (ROS and RNS) all play important roles in the pathophysiology of these neurological disorders. Technological progress in the future has led to a dramatic increase in the prevalence of neurological diseases associated with aging. However, except from severely limited palliative care, there is no effective defensive treatment or treatment available. Consequently, there is an immediate need to enhance disease-modifying treatments and preventative measures to address Promotion/PD. A neuroprotective pathway for treating neurodegenerative illnesses may be shown by differentiating evidence or the development of drugs suitable for reestablishing Ca2+ homeostasis and signaling, since dysregulated Ca2+ metabolism promotes oxidative damage and neuropathology in these conditions. Decreased Ca2+ take-up through voltage-operated Ca2+ channels (VOCCs) is one of several methods to regulate mitochondrial Ca2+ homeostasis and signaling. Several heterocyclic compounds have modulatory effects on Ca2+ homeostasis and dealing, and this article surveys those effects. It also discusses how these compounds can direct impaired mitochondrial capability and related free-revolutionary production in the beginning and development of Parkinson's disease (PD). In addition to summarizing the clinical preliminary results, this thorough audit details the heterocycles' substance synthesis.

Keywords: Heterocyclic Compounds, Therapeutic Potential, Alzheimer's, Parkinson's Disease, Targeting, Mitochondrial Homeostasis, Signalling

## 1. Introduction

Progressive neuronal loss and mental degeneration characterize the incapacitating neurodegenerative illnesses known as Alzheimer's disease (AD) and Parkinson's disease (PD), which pose a substantial global health problem. The crucial demand for novel therapeutic techniques is underscored by the fact that, after decades of research, compelling cures for many diseases remain elusive. Recent research has brought attention to the fact that mitochondrial dysfunction and disrupted signaling pathways play a role in the development of (AD) and (PD). As essential organelles for cellular energy production and balance, mitochondria have recently emerged as potential therapeutic intervention targets.

The medicinal possibilities of heterocyclic compounds are noteworthy. These diverse natural chemicals possess at least one ring structure that is not carbon-based. Because of their structural variety, they can bind to particular atomic sites linked to mitochondrial function and neurodegenerative signaling cascades. Mitochondrial dynamics, (ROS) production, and mitochondrial layer potential regulation are all fundamental components in brain health and disease development.

Because of their ability to modulate neuronal damage and restore mitochondrial homeostasis, heterocyclic compounds hold therapeutic promise in (AD) and (PD). These chemicals have antioxidant properties that help reduce oxidative stress, a symptom of neurodegenerative disorders, by scavenging reactive oxygen species (ROS). They may also regulate mitochondrial dynamics and biogenesis, which would improve mitochondrial repair and increase cell resistance to severe insults.

Also, processes that are unexpectedly linked to the development of AD and PD—such as neuroinflammation, apoptosis, and synaptic dysfunction—can be modulated by heterocyclic chemicals. There is hope that these chemicals can alleviate symptoms and even halt or reduce the progression of disease by targeting these pathways.

We study the most recent developments in our knowledge of the therapeutic processes of heterocyclic compounds in Alzheimer's disease and Parkinson's disease, with a particular emphasis on how these compounds interact with signaling pathways and mitochondrial homeostasis. Our goal in elucidating these molecular processes is to shed light on the development of new pharmaceutical interventions that may pave the way for effective therapies for these terrible neurodegenerative illnesses.

**As intimate associates in Alzheimer's disease, mitochondrial deficiencies and oxidative stress**

Dementia and trouble executing mental tasks are symptoms of (AD), a neurological illness. Impaired mitochondrial capacity is a key factor in the onset of (AD). The default mode organization, which is associated with amyloid and tau formation and breakdown in Alzheimer's disease, experiences decreased activity as a consequence of glucose difficulties. Axonal transport is a cellular activity that controls the movement of neurotransmitters, proteins, lipids, and organelles; it interacts closely with mitochondrial dynamics.

Samples of the AD brain showed anomalies in the shape of microtubules and a decrease in the number of healthy mitochondria. The fusion-fission machinery firmly directs the dynamics of the mitochondria, which act as a quality control system. Proteins, lipids, organelles, and neurotransmitters are all dynamically handled via axonal transport, a cellular process. Postmortem brain tissues from AD patients showed an upregulation of Drp1 and Fis1 and a decrease of Opa1, Mfn1, and Mf2 mRNA and protein levels. The neurons of AβPP mice were shown to have an excessive amount of mitochondrial damage. Mice engineered with the amyloid precursor protein (Application) transgene had abnormal mitochondrial distribution and mitochondrial axonal dealing defects.

A β collection can also evaluate one's ability to create mitochondria. Mitochondria produced from postmortem tissues of late-onset Alzheimer's disease have shown improved Aβ dysfunction. Mediating the Aβ1-40 and Aβ1-42 mitochondrial assimilation are the receptor components of the translocase of the external layer (TOM), which doesn't contain the Δψm. The Aβ quality is utilized to create many animal models of Alzheimer's disease (AD), which show side effects of systemic mitochondrial failure including decreased COX versatility, impaired mitochondrial respiration, increased glycolysis, and enhanced oxidative pressure.
Prolonged mitochondrial dysfunction is an important component in Alzheimer's disease brains that leads to free radicals aging excessively fast and can prompt Aβ and tau pathology. The accumulation of Aβ or tau inside mitochondria advances oxidative damage as well as hinders the activity of crucial mitochondrial proteins. The interaction between the mitochondrion and Aβ1-40 and Aβ1-42 causes mitochondrial oxidative damage, decreased COX action, and increased H2O2 level, which are side effects of early Aβ plaque advancement. Aβ diminishes the rate of mitochondrial respiration and Δψ age activated by various complex I and IV substrates.
The ATP synthase and other important mitochondrial catalysts were demonstrated to be significantly oxidized and nitrated in the hippocampus of AD individuals, according to redox proteomic investigations. ROS-actuated functional changes in the F1Fo-ATP synthase could be one way by which OXPHOS is lacking in Alzheimer's disease. There is protein nitration in AD as well. Brain samples taken after death from Alzheimer's disease patients showed a dramatic rise in the number of 3-NTpositive neurons.

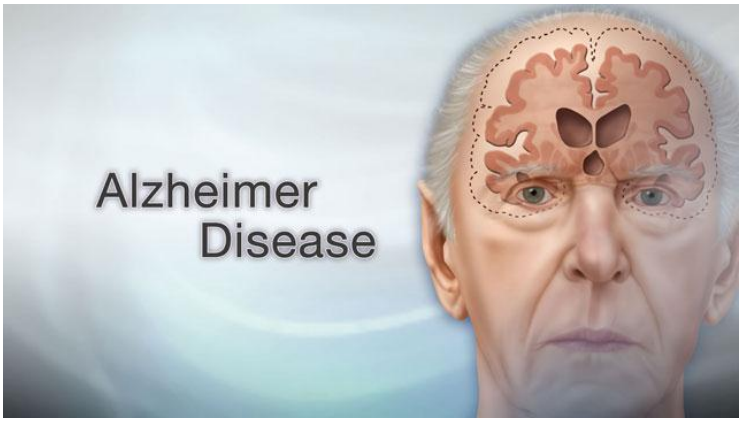


Figure 1: Alzheimer disease

**Impaired Mitochondrial Function And Associated Oxidative Damage In Parkinson's Disease**

The neurodegenerative disorder known as (PD) manifests itself over time as dopamine (DA) neurons in the substantia nigra (SN) and the striatum lose their axonal projections. Neuronal cytoplasmic aggregates known as (LB), which are mainly made up of α-syn and ubiquitin, signal the existence of the disease. Family-predominant PD is caused by mutations or multiplications of quality points in SNCA and LRRK2.
Morphologically abnormal mitochondria are another kind of mitochondrial abnormality in Parkinson's disease. Approximately 80% of the mitochondria in SN DA neurons from PD patients had an abnormal shape, enlarged appearance, and disrupted cristae patterns. Unlike Alzheimer's disease (AD), PD patients' plasma thiamine levels do not change. However, cerebrospinal fluid (CSF) samples from PD patients showed a markedly reduced free thiamine level.
Systemic deficiencies in complex I assembly and reduced mobility might lead to an insufficient oxidative limit, which in turn contributes to the degeneration of DA neurons. When this

happens, it can cause an increase in mitochondrial deficits and an excess of reactive oxygen species (ROS) and reactive nitrogen species (RNS). There was less complicated I movement in the SN tissue of human postmortem tissues. Patients with late-onset PD show reduced synergist activity of mind-boggling I in their brain and peripheral tissues, including skeletal muscle, platelets, and lymphocytes.

There was a significant decrease in OPA1 antibodies in SN tissue from patients with sporadic PD, which raises the possibility that mitochondrial dysfunction and neurodegeneration in PD are both caused by errors in mitochondrial dynamics. Changes in dealing along axons may be a silent but long-lasting factor disrupting mitochondrial homeostasis in PD, since mitochondria are transported bidirectionally by microtubules and actin filaments.

Through its regulation of dynamics, transport, and flexibility, α-Syn exerts substantial influence over mitochondrial respectability. Mutations A53T and A30P in α-syn caused mitochondrial rupture through a route that does not include DRP1 and resulted in an increase in OPA1 cleavage. Axonal transport deficits, characterized by changes in kinesin and dynein markers, can be caused by synthetic α-syn fibrils. Changes in mitochondrial movement were caused by overexpression of α-syn, particularly in A53T transformation, which implies that mitochondrial distribution along axons is not uniform. Axonal transport allows α-Syn to get to deeper regions of the brain and build up in dystrophic axons, where it is distributed and made on both the right and left sides of the cell.

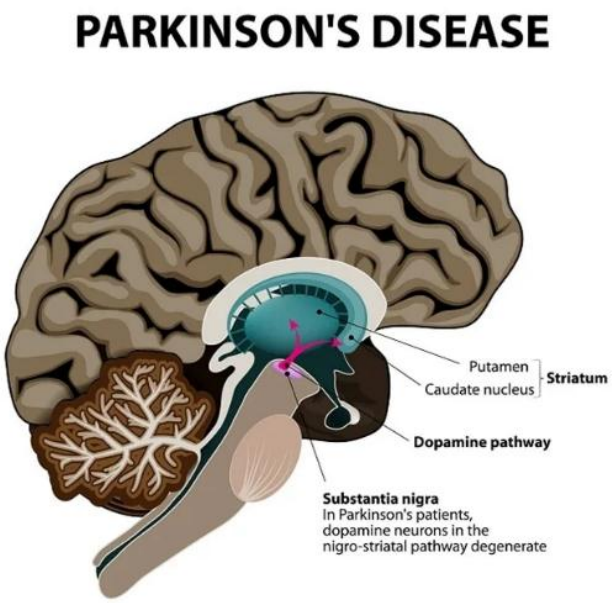



Figure 2: Parkinson’s disease

**Heterocyclic compounds modulate calcium signaling and homeostasis in Alzheimer's and Parkinson's diseases**

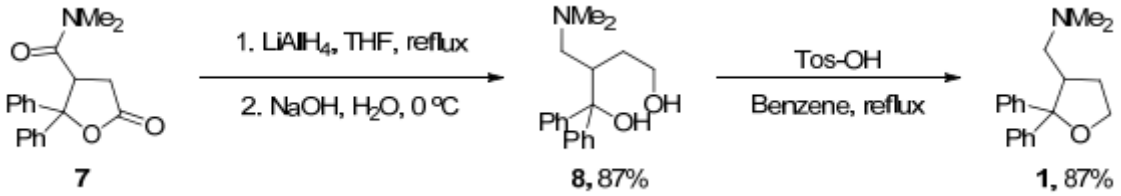
Deregulation of Ca2+ homeostasis and signaling is an important factor in the progression of AD and PD. By activating L-type VOCCs and NMDA or AMPA receptors, or by creating Ca2+-penetrable holes in the plasma membrane, Aβ peptides contribute to an excess of intracellular Ca2+ accumulation. Ca2+ levels in the cytosol and mitochondria are enhanced when IP3 and RyRs are activated or when there are genetic mutations in PS, which increase Ca2+ spill in the extracellular space. The mitochondrial Ca2+ take-up 1 protein (MICU1) is upregulated in postmortem human PD brains, fibroblasts, and mice when the gene encoding LRRK2 has mutations. These findings point to mitochondrial Ca2+ dyshomeostasis as a critical component in the etiology of AD and PD. The ability of these heterocyclic compounds to

modulate Ca2+ signaling makes them promising pharmacological agents for the treatment of neurodegenerative diseases (Figure 1).

**ANAVEX2-73**

ANAVEX2-73 is a nonselective ligand for the sigma-1 receptor (S1R) and the muscarinic acetylcholine receptor (mAChR); it controls the exchange of calcium ions between the ER and mitochondria through its interactions with IP3 receptors. Particle channel guidance is attained, apoptosis is decreased, and the nuclear erythroid 2-related factor 2 (NRF2)/cancer preventive agent response component (ARE) pathway is activated. According to a phase IIa clinical trial, ANAVEX2-73 has the makings of a genetic biomarker for disease and treatment response. Results showed that ANAVEX2-73 improved understanding and ability in early-stage Alzheimer's disease (AD) patients in a randomized, placebo-controlled, phase IIb/3 clinical trial. Moreover, it restored mice's learning abilities following intracerebroventricular injection of the neurotoxic Aβ25-35 peptide. The uprightness and capability of mitochondria were also sustained by ANAVEX2-73, which increased the action of confusing IV and oxygen consumption in all situations. Additionally, it decreased lipid peroxidation, the ratio of Bax to Bcl-2, and the production of CYT C. In a Ca2+-subordinate manner, ANAVEX2-73 also reestablished mitochondrial respiration and shielded complex IV action levels from Aβ poisonousness. In order to break down damaged organelles and accumulated proteins, it facilitated autophagosome formation and autophagic transition. A phase II extension trial in Parkinson's disease (PDD) patients lasted 48 weeks and found clinical benefits. Researchers are currently studying its bioavailability, safety, efficacy, and two-fold visually impaired phase III preliminary in patients with Alzheimer's disease, Parkinson's disease with dementia, and Rett syndrome.

Foscolos explained the remarkable synthesis of ANAVEX2-73 (1-(2,2-diphenyltetrahydro-3-furanyl)- N, Ndimethylmethanamine hydrochloride) 1. To create ANAVEX2-73, the main step is to open lactone 7 to deliver 1,4-diol 8. Then, at that point, utilizing corrosive catalyzed cyclodehydration, the item is transformed into ANAVEX2-73 1, as displayed in Plan 1.




Scheme 1: Exclusive overall manufacturing of ANAVEX2-73 1.

**Caffeine**

The most often consumed psychoactive component is caffeine, a purine alkaloid included in the majority of plant foods. Espresso amplifies its inherent mobility thanks to its rich bioactive components, which include antioxidants, niacin, potassium, and magnesium. Although there are no changes in the steady-state clustering of certain Ca2+-restricting proteins or extrusion processes, coffee alters Ca2+ signaling and promotes its release. Caffeine improves learning and memory by increasing cerebral blood flow, cerebrospinal fluid production, and Na+/K+ ATPase levels.

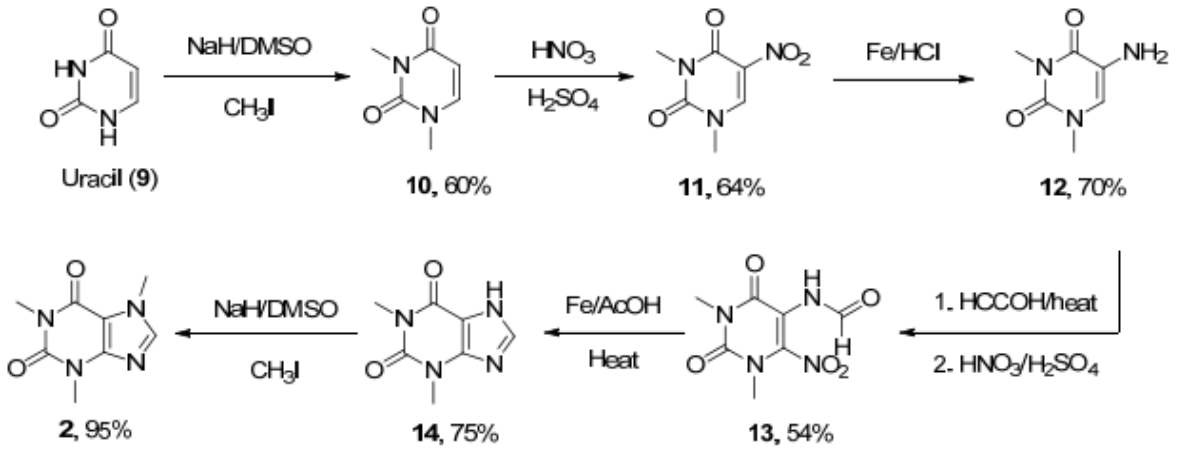
There are no obvious adverse effects on the central nervous system associated with daily caffeine consumption, although it has been associated with a decreased risk of developing (PD) and (AD). Research has shown that consuming espresso regularly (at least 2 cups per day) can significantly slow down cognitive deterioration. Moderate espresso consumption in middle age was associated with a decreased risk of dementia and AD in later life, according to the CAIDE

longitudinal epidemiological study. However, tea consumption was not correlated with this finding.

For the first time, researchers in the Honolulu Heart Program found that coffee may help people with Parkinson's disease. After controlling for factors including age and pack-years smoked, the prevalence of PD in espresso users dropped fivefold. An extensive meta-analysis found a nonlinear correlation between espresso consumption and the prevalence of Parkinson's disease (PD). At three cups daily, the maximum protective effect was attained. Still, using tea and caffeine at lower dosages was directly associated with a decreased risk of PD, especially in men compared to women and in Europeans and Asians compared to Americans.

To mitigate the neurotoxicity caused by rotenone, caffeine was administered in a portion subordinate manner. Overall gathering performance was increased by caffeine infusion via the peritoneal course, and oxidative damage and neuroinflammation were diminished in rats given rotenone. Additionally, the mental chemical activity of acetylcholinesterase (AChE) and Na+/K+ ATPase was normalized. The degrees of CYT P450, glutathione-S-transferases, and vesicular monoamine transporter 2 (VMAT-2) were balanced in mice given 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine with caffeine.

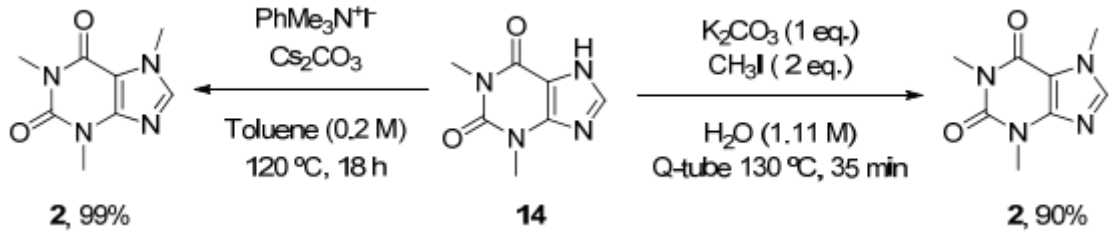
Caffeine has a demonstrated track record of long-term safety, in spite of its complex pharmacological and molecular characteristics. It is a promising therapeutic area for the treatment of neurodegenerative diseases because of its minimal expense and high accessibility. Caffeine (1,3,7-trimethyl-3,7-dihydro-1H-purine-2,6-dione) 2 production, according to Narayan et al. [94], includes seven chemical stages. The reaction of uracil 9 with a strong base, for example, sodium hydride in dimethyl sulfoxide (DMSO), results in 1,3-dimethyluracil 10. After that, 5-amino-1,3-dimethyluracil 12 is shaped by nitrating and diminishing this chemical with hydrochloric acid and iron. Nitro subordinate 13 originally obtained theophylline 14 utilizing two typical strategies, which included a synergist reduction step and an intramolecular heterocyclization response with iron and acidic corrosive. The age of caffeine 2 was caused by the last methylation at position 7. 10% was the overall response yield, or the item delivered by a complex response (Scheme 2).




Scheme 2: Caffeine 2 production from uracil 9

Methodologies for the N-methylation of theophylline 14 have been accounted for better than before. An early technique overcome the solvent constraint by completing reactions under extreme tension using the Q-tube technology. Consequently, there was a discernible rise in both temperature and pressure, which in turn reduced the response time. High yields of the target compounds could be achieved by using water as a green solvent. As methylating agents, Schnürch's group refined quaternary ammonium salts in an additional investigation. The

authors advocated for a different standard when it came to the monoselective methylation and ethylation of amides, indoles, and related chemicals (Scheme 3).




Scheme 3: Exciting new methods for N-methylating theophylline 14

**Diltiazem**

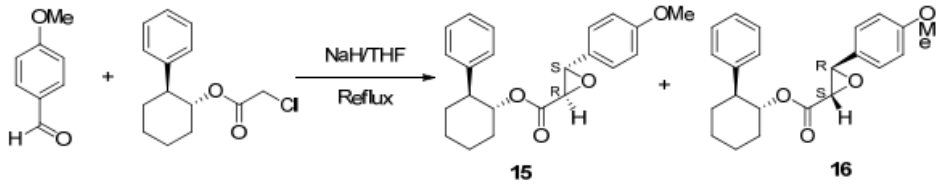
Vasodilator, antihypertensive, and antiarrhythmic actions are exhibited by diltiazem, a non-dihydropyridine calcium channel blocker. It zeroes in on VOCCs in particular because of their critical role as mediators of Ca2+ convergence into neurons when the layer is depolarized. Research has demonstrated the way that diltiazem can alleviate cognitive deficiencies like learning and cognitive decline in individuals with Alzheimer's disease. The consequences of the trials showed that the administration of diltiazem forestalled the surge of Ca2+ ions that Aβ mediated to forestall and downstream damage to neurons by restraining the development of Aβ25-35-set off AChE through the regulation of L-type VOCCs. Treatment with diltiazem supported survival rate and decreased intracellular Ca2+ fixation by hindering L-type Ca2+ channels in vitro.

An increased risk of acquiring Alzheimer's disease (AD), which causes neurofibrillary degeneration in neurons, has been associated with cross-openness to aluminum in drinking water, in one structure or another. Be that as it may, oxidative damage, AChE upregulation, and memory and learning shortfalls were all ameliorated in mice after therapy with diltiazem. No clinical exploratory investigation has connected diltiazem to an increased risk of creating (PD).

Cav1.2 and Cav1.3 are L-type VOCCs that regulate the spontaneous death of DA ergic neurons in the SN region of the brain. The progression of Parkinson's disease increases the probability of deterioration of these L-type VOCCs. The prolonged opening of L-type VOCCs caused via autonomous speed making leads to mitochondrial oxidative pressure, which thus causes delayed cytoplasmic Ca2+ handling and resulting overload in SN DA neurons.

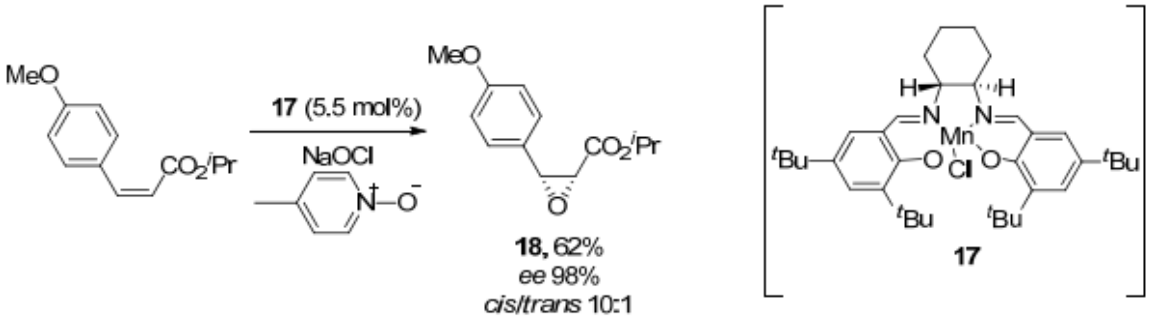
Although diltiazem has lowered nitrite and MDA levels and increased the movement of many cancer prevention agent enzymes when administered intraperitoneally, there is a dearth of data on the drug's potential effects on cell reinforcement in Alzheimer's disease or Parkinson's disease. Diltiazem, when given orally to AD mice model, decreased TBARS and nitrite levels, increased SOD levels, and decreased glutathione enzymatic activity.

In the initial asymmetric synthesis of diltiazem, a diastereoface-separating nucleophilic addition was used to establish the two adjacent stereogenic focuses, an essential move toward the cycle. Direct crystallization was utilized by Schwartz to separate the diastereomeric glycidic esters (15 and 16) because of their distinct variances in dissolvability. One notable item that was obtained is glycidic ester 15, which is the normal isomer for making diltiazem 3. 54% production (Scheme 4).



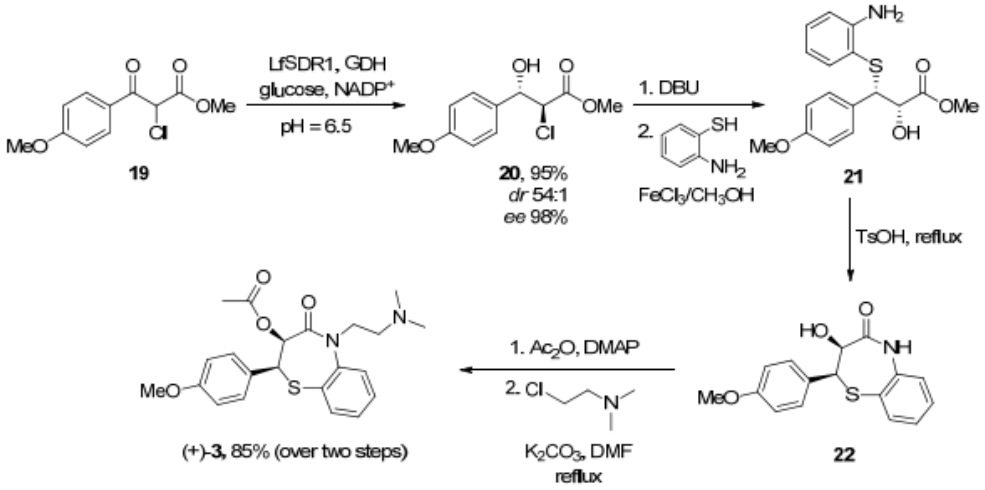

Scheme 4: Schwartz's method for producing diltiazem 3.

Jacobsen et al. planned the synthesis of 3 in 1994 using a manganese-catalyzed asymmetric epoxidation of cinnamate esters, which featured an enantiomerically pure critical intermediate step 18. (Scheme 5).




Scheme 5: Crucial 18-enantiomer intermediate for diltiazem 3 synthesis

There are other synthetic pathways to produce diltiazem 3 from a chiral epoxide intermediate. One can obtain the enantiomerically pure epoxide by direct acquisition, by adding metal complexes, or by presenting a chiral aid in the response. Using yeast-catalyzed processes or lipase to induce chirality in the material is a helpful technique. Chen detailed the most time-consuming procedure utilized to make diltiazem 3. Enantiomerically pure hydroxy ester 20 was produced from racemic keto ester 19 through dynamic reductive active resolution catalyzed by ketoreductase. The middle 21, which was easily amidated by intramolecular acid, was also created using two common procedures: ring closure and ring opening. To obtain diltiazem 3, benzothiazepinone 22 was anticipated to require two more processes. Diltiazem 3 is obtained through eight steps of chemoenzymatic synthesis, with a response yield of approximately 45% (Scheme 6)




Scheme 6: Diltiazem production by chemoenzymatic means 3.

**Latrepirdine**

Latrepirdine is a carboline that inhibits the activity of the H1 histamine receptor (H1R), increasing the amount of acetylcholine in the brain and improving mental performance. It has the ability to modify DA, serotonin, glutamate, and NMDA receptors, among other neurotransmitter receptors. Twenty-one clinical trials including latrepirdine have demonstrated noteworthy improvements in perception, ability, and social outcomes in patients with mild to moderate (AD).

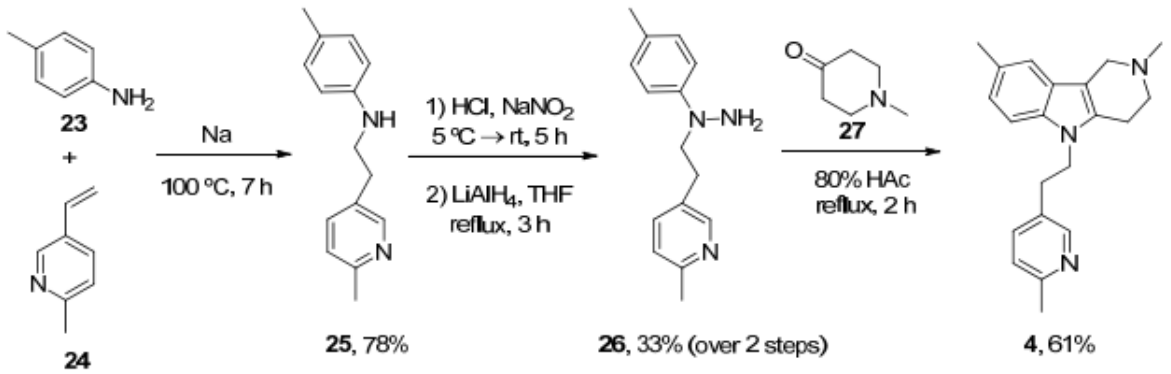
Latrepirdine reduced neuropsychiatric symptoms and improved mental capacity in people with mild to moderate AD in a pilot clinical trial. Following 60 mg/day of latrepirdine for 26 and 52 weeks in patients with mild to moderate AD, a phase II randomized, twofold visually impaired, sham treatment controlled clinical investigation shown a significant increase in awareness, competence, and social outcome without adverse effects. In a meta-analysis, researchers found that latrepirdine improved the neuropsychiatric stock scale, a tool for assessing psychopathology in dementia patients, but it had no effect on general cognizance.

The L-type VOCCs current was limited, protecting neurons from Aβ-induced toxicity, when exposed to latrepirdine. Intraperitoneal latrepirdine reverted learning loss and cognitive decline in addition to the constant fractional weakening of brain cholinergic activities, which causes dementia. Memory impedance produced by scopolamine was amplified in both adult and young rats treated with latrepirdine. Macaque rhesus.

In 5xFAD mice, latrepirdine improved mental function, but it was ineffective in reducing Aβ-related pathologies. Studies using FDG-PET revealed that mature mice exposed to latrepirdine used more brain glucose. The compound's targeting of the mPTP opening can also protect mitochondrial capacity.

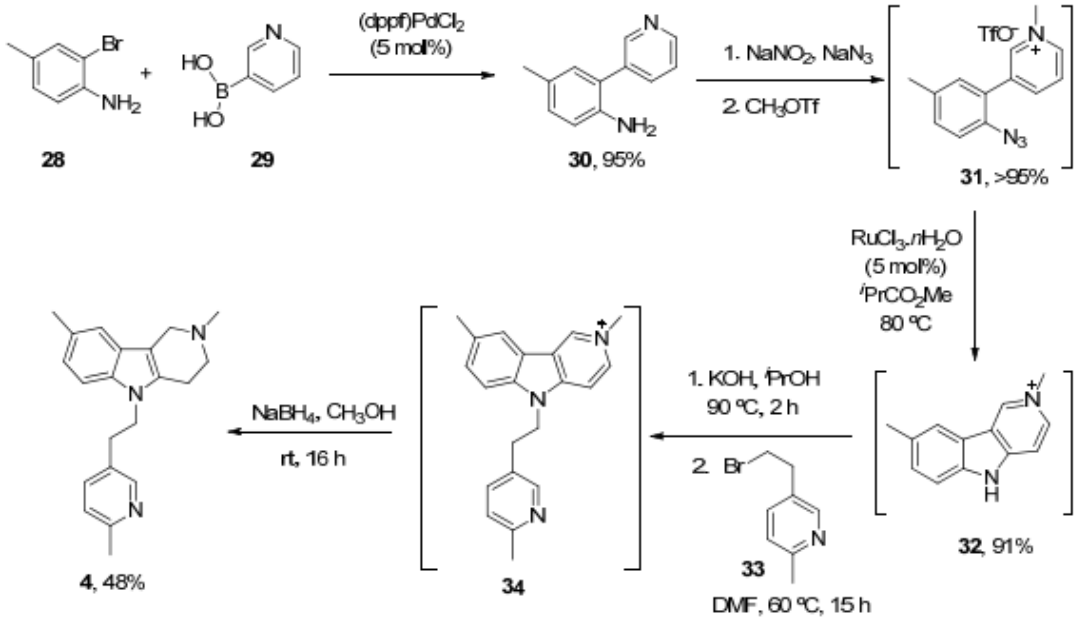
In Tg mice overexpressing γ-syn treated with latrepirdine, the drug reduced methamphetamine-actuated poisonousness and improved lifespan and engine performance in exploratory Parkinson's disease (PD). In conclusion, latrepirdine treatment for AD patients resulted in the restoration of mental measures, learning, and psychiatric symptoms. This was mostly due to latrepirdine's ability to boost cholinergic focus by blocking either the histamine receptor or the AChE receptor. By promoting autophagy and increasing mitochondrial capacity and intracellular inclusion leeway, latrepirdine may also stimulate neuroprotective movements.

2-(6-methyl-3-pyridinyl) ethyl-2,3,4,5-tetrahydro-2,8-dimethyl-5- latipirdineThe initial product of the Fischer indole reaction was -1Hpyrido[4,3-b] indole) 4. However, a later synthesis reported by Zheng et al. obtained the target item 4 out of 4 response phases, with a general response yield of roughly 16 percent, utilizing p-toluidine 23 and 2-methyl5-vinylpyridine 24 as commercial starting materials. 1-methylpiperidin-4-one 27 and 2-methyl-5-(2-(1-(p-tolyl)hydrazinyl)ethyl)pyridine 26 were cyclized at reflux temperature and 80% HAc. (Scheme 7)




Scheme 7: Zheng's method for producing latrepirdine 4

An effective ruthenium(III) catalysis was also used to deliver latrepirdine 4. The important element was the stereoselective organization of γ-carboline 32 from ortho-substituted aryl azide 31, which was catalyzed by RuCl3·nH2O. The total synthesis, which consisted of six steps, yielded about 47%. (Scheme 8).




Scheme 8: The synthesis of latrepirdine 4 is catalyzed by ruthenium(III).

**Nifedipine**

A dihydropyridine Ca2+ channel blocker of the first generation, nifedipine is used to treat hypertension and manage angina pectoris. It is essential for neuronal processes brought on by membrane depolarization and for Ca2+-mediated reactions brought on by a variety of stimuli and signaling pathways. Nifedipine may be a useful therapeutic drug for the treatment of neurodegenerative illnesses, such as (PD) and (AD), according to mounting data.

Nifedipine inhibits the increase in intracellular Ca2+ levels and transcriptional activity of CREB generated by APOE ε4, indicating a potential involvement of L-type VOCCs in neuronal responses to APOE ε4. Aβ-mediated increases in cytosolic Ca2+ concentration and synaptic disease are inhibited by nifedipine exposure, suggesting that Ca2+ influx through L-type VOCCs plays a role in Aβ toxicity.

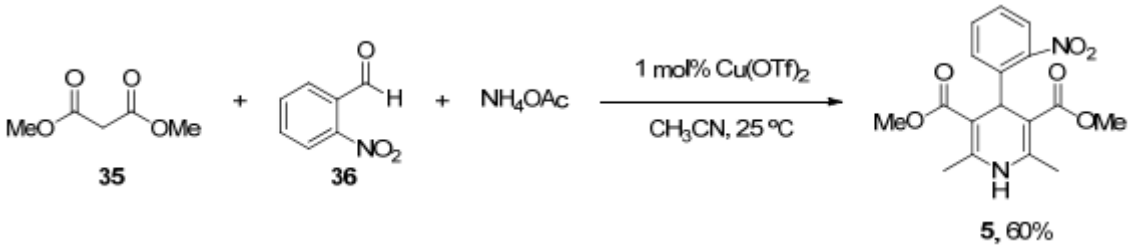
When nifedipine was administered, the amount of released Aβ1-42 and important gamma secretase complex constituents (including PS1) was greatly reduced. Nifedipine treatment alleviated neuron functional deficits, repaired post-hypoxic associated damage, and increased the survival rate of CNS neurons grown from PS1-deficient animals. Additionally, nifedipine prevented the rise in the concentration of [Ca2+]cyt at rest in the cortical neurons of 3xTg-AD or APPsw animals.

The results of the one available clinical investigation may have been compromised by inadequate statistical power, as there was no evidence of an association between nifedipine and the prevalence of Parkinson's disease. It has been suggested that a key component of the PD-related disruption of the basal ganglia circuitry is the subthalamic nucleus (STN). Nifedipine treatment eliminated burst firing and reduced burst frequency irreversibly.

Subcutaneous injection of nifedipine decreased apomorphine-prompted rotation and partially reestablished striatal DA levels in rats with 6-OHDA lesion. Niferopine forestalled nobiletin-prompted DA release in mice that had MPTP infused into them. The (SOP) and the high-edge

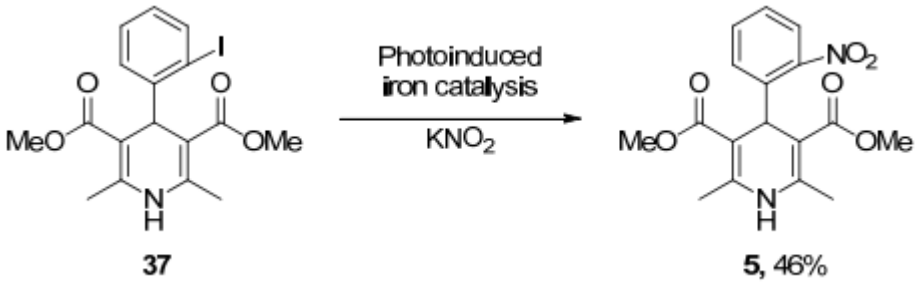
Ca2+ spike (HTS) are two of several Ca2+ conductance sources that affect the generation of action potentials in SN DA neurons. Niferopine is an antagonist of L-type VOCCs and is engaged with factors like Aβ and tau pathology, DA neurodegeneration, synaptic function, oxidative pressure, and apoptotic cell death.

Singh announced the initial synthesis of nifedipine 5 (3,5-dimethyl 2,6-dimethyl-4-(2-nitrophenyl)- 1,4-dihydropyridine-3,5-dicarboxylate) through an acid-catalyzed reaction including an enamine and two perhydro-heterocycles. New manufactured techniques were created, including strong phase synthesis and one-pot dissolvable free synthesis. One of the most common manufactured courses to pyridines is the Hantzsch reaction. The synthesis of 1,4-dihydropyridines requires an aldehyde, a nitrogen donor, and two units of β-keto ester. Sudalai and colleagues used ammonium acetate as the nitrogen donor, 2-nitro-benzaldehyde as the aldehyde, and dimethylmalonate as the β-keto ester (Scheme 9)



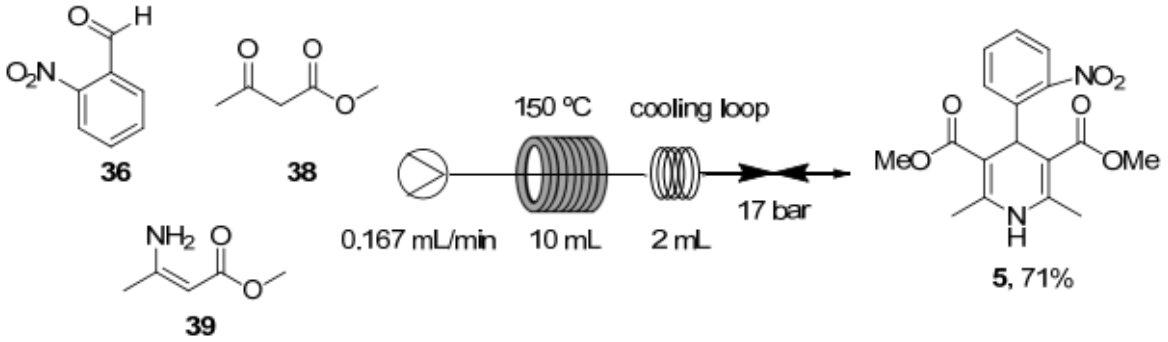

Scheme 9: The Hantzsch reaction was utilized to create nifedipine 5.

One relatively new approach to synthesising nifedipine 5 was the use of photoinduced iron-catalyzed ipso-nitration, a technique known as single-electron transfer. Aryl iodine 37 efficiently converted the iodine to nitro substituent via photocatalysis, resulting in 5 with a high yield (Scheme 10)



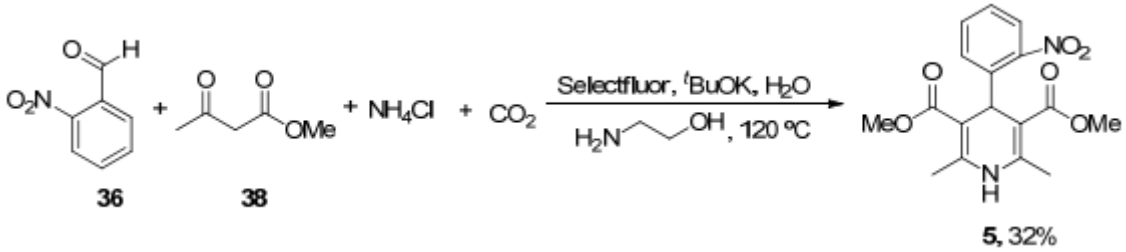

Scheme 10: Nifedipine 5 synthesised by photoinduced ipso-nitration with iron catalyst

The first stream multicomponent construction of nifedipine 5 was previously described. A 10 mL stainless-steel curl reactor was heated to 150 ◦C and a flow rate of 0.167 mL·min−1 was used to add methanol solutions of compounds 36, 38, and 39 in order to obtain nifedipine 5 with a yield of 71%. (Scheme 11)




Scheme 11: Nifedipine 5's first flow multicomponent synthesis.

Environmental concerns were considered throughout the development of nifedipine 5. Dihydropyridine derivatives were synthesized by exposing ketones with an ammonium cation to CO2 during a bare metal multicomponent cycloaddition event. A 32% yield of nifedipine 5 was achieved by reacting methyl acetoacetate 38 with o-nitro benzaldehyde 36 in an aqueous solution containing ammonium chloride (NH4Cl) and carbon dioxide (CO2) (Scheme 12).




Scheme 12: Making nifedipine 5 with an environmentally friendly method

**Nimodipine**

A Ca2+ channel blocker called nicodipine is used to prevent brain damage from low blood flow. It opposes Cav1.2-1.3 L-type VOCCs and exhibits a stronger preference for the Cav1.2 channel. Unlike nifedipine, which often exhibits peripheral effects, nimodipine has a particular constraining preference for dihydropyridine receptors. It has been suggested that it could have therapeutic value for patients with Parkinson's disease (PD) or Alzheimer's disease (AD) in clinical trials.

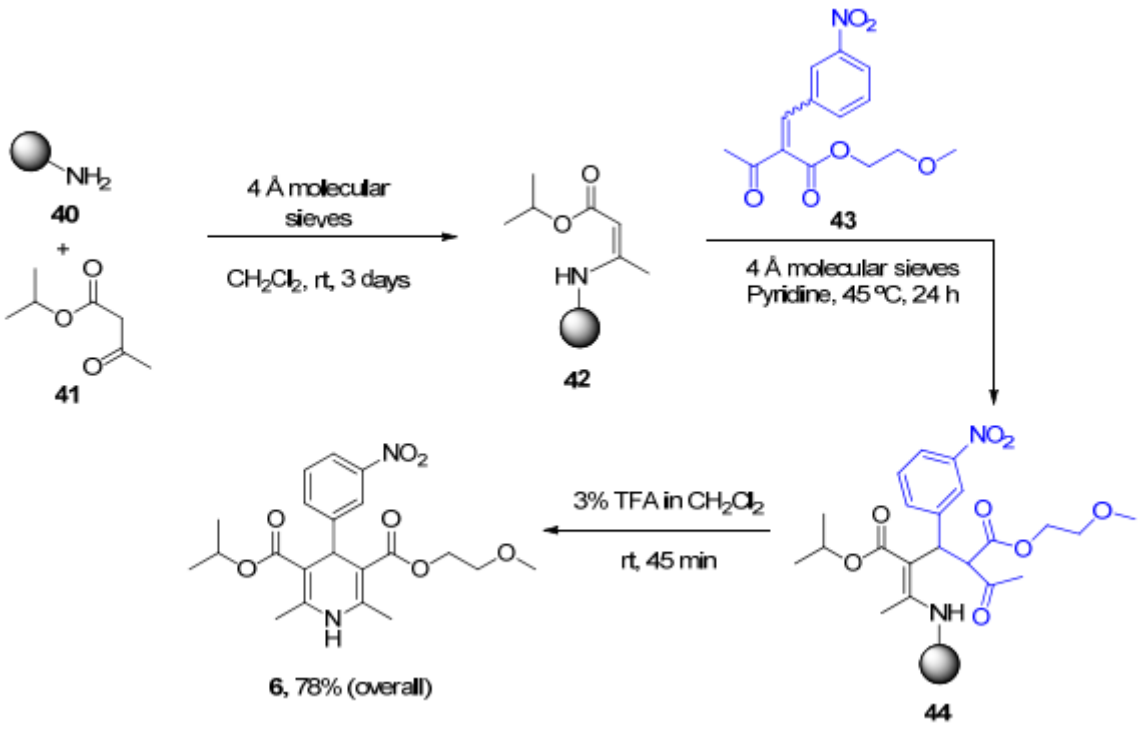
People with Alzheimer's disease or another kind of essential degenerative dementia have shown improvement in their mental, emotional, and behavioral symptoms after taking nimodipine. Based on a comprehensive analysis of fourteen randomized clinical trials, nimodipine treatment enhanced cognitive capacity and the (SCAG) scale in Alzheimer's disease (AD) dementia and mixed AD/CV disease. By altering the synaptosome's Ca2+-restricting proteins, long-term nimodipine treatment reversed memory and learning impairments associated with aging.

By regulating BDNF and acetylcholine, imidapine exacerbated the mental deterioration caused by scopolamine. In fully grown rhesus monkeys, it also exacerbated memory dissatisfaction. Nimodipine exposure reduced Ca2+ flood and related Aβ1-42 accumulation, obstructed Aβ25–35-mediated deleterious effects, and limited Aβ clustering via upregulating glutathione S-transferase activity, leading to reduced oxidative damage.

Nimodipine has not yet been the subject of any clinical trials involving Parkinson's disease patients. Nevertheless, through improving social outcomes, boosting synaptic transmission and neuron survival, boosting mitochondrial capabilities, and reducing oxidative stress and irritation, it has demonstrated beneficial benefits on AD and PD. Although nimodipine is

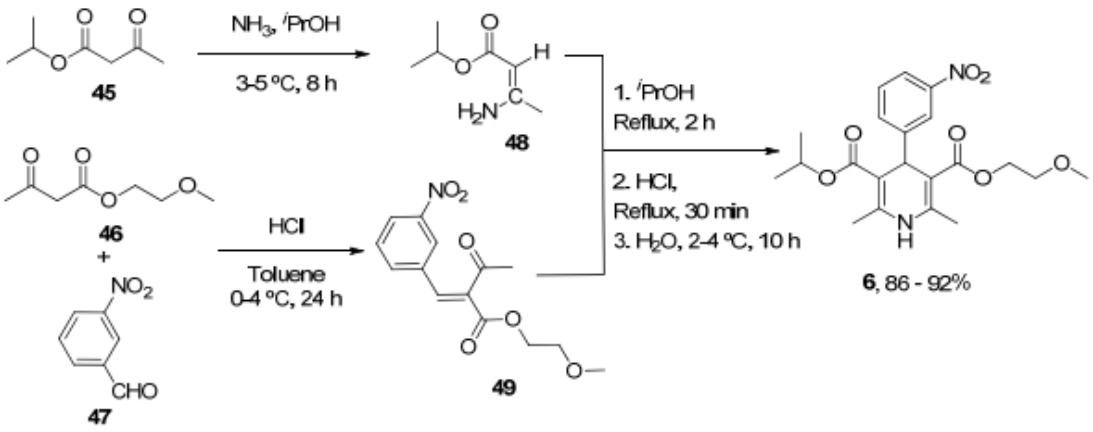
generally well tolerated, elevated dosages may cause headache, nausea, reduced blood pressure, myalgia, and stomach problems. Additionally, isolated CNS symptoms like tachycardia, sleeplessness, and increased engine activity have been explained.

Nimodipine (3-(2-Methoxyethyl) 5-propan-2-yl 2,6-dimethyl-4-(3-nitrophenyl)) was incorporated via a strong phase synthesis, as portrayed by Gordeev et al.- 3,5-dicarboxylate, 1,4-dihydropyridine, and other bioactive dihydropyridines. The immobilized N-fastened enamine component 42 was combined with the suitable 2-benzylidene α-keto ester 43 to create enamine 44. The free enamino ester was obtained by treating this intermediate with trifluoroacetic acid; item 6 is then generated by a spontaneous cyclization in solution (Scheme 13).




Scheme 13: Production of nimodipine 6 in solid phase.

The high demand for nimodipine in Russia's market has led Pharm. Sintez Co. to advocate for a different way to manufacture the drug in pilot numbers. Two compounds, 1-methylethyl-3-amino-crotonate (48) and 2-methoxyethyl-2-(3-nitrobenzyl-idene) acetoacetate (49), are produced throughout the procedure. The cyclocondensation of the two compounds with hydrochloric acid as a solvent (iPrOH) managed the expense of the end product 6 in terms of purity and high return (Scheme 14).




Scheme 14: Pharm. Sintez. Co. (Moscow, Russian Federation) is producing nimodipine 5 in trial batches.

## 2. Conclusion

In summary, because of their specific balance of mitochondrial homeostasis and signaling pathways, heterocyclic compounds offer a viable avenue for therapeutic mediation in Parkinson's and Alzheimer's illnesses. Throughout the previous few years, several potential medications for treating PD or AD have failed miserably. The optimal illness stage and therapy time frame for clinical trials will likely require more investigation. Neuropathological and biochemical assessments have pointed to mitochondrial dysfunction as the likely source of the rise in free radicals and Ca2+-induced poisonousness, two key features of the neurodegenerative process characterized by AD and PD. Based on a review of both experimental and clinical evidence, scientists have concluded that neurodegenerative diseases like Alzheimer's and Parkinson's may be able to be slowed or stopped in their tracks by enhancing therapeutic interventions targeted at mitochondrial Ca2+ signaling. Several strategies for restoring normal signaling and Ca2+ homeostasis in mitochondria have been detailed. Ca2+ take-up blocking via L-type VOCCs is one conceivable strategy; this reduces glutamate-interceded excitotoxicity and inhibits Ca2+ transients at postsynaptic or presynaptic sites. Selective antagonists of Cav1.2-1.3 L-type VOCCs also have advantageous properties because delayed opening of L-type channels produces greater Ca2+ release and flood and its aggregation in DA neurons.

## 3. References

1. Amadoro, G.; Corsetti, V.; Atlante, A.; Florenzano, F.; Capsoni, S.; Bussani, R.; Mercanti, D.; Calissano, P. Interaction between NH (2)-tau fragment and Abeta in Alzheimer's disease mitochondria contributes to the synaptic deterioration. Neurobiol Aging 2012, 33, 833 e831-825, doi: 10.1016/j.neurobiolaging.2011.08.001. https://www.sciencedirect.com/science/article/pii/S0197458011003022
2. Bobba, A.; Amadoro, G.; Valenti, D.; Corsetti, V.; Lassandro, R.; Atlante, A. Mitochondrial respiratory chain Complexes I and IV are impaired by beta-amyloid via direct interaction and through Complex I-dependent ROS production, respectively. Mitochondrion 2013, 13, 298–311. https://www.sciencedirect.com/science/article/pii/S1567724913000615
3. Butterfield, D.A.; Mattson, M.P. Apolipoprotein E and oxidative stress in brain with relevance to Alzheimer's disease. Neurobiol Dis 2020, 138, 104795, doi:

10.1016/j.nbd.2020.104795.
https://www.sciencedirect.com/science/article/pii/S096999612030070X

4. Doulias, P.T.; Tenopoulou, M.; Greene, J.L.; Raju, K.; Ischiropoulos, H. Nitric oxide regulates mitochondrial fatty acid metabolism through reversible protein S-nitrosylation. Sci Signal 2013, 6, rs1, doi:10.1126/scisignal.2003252. https://pubmed.ncbi.nlm.nih.gov/20837516/
5. Kim, D.I.; Lee, K.H.; Gabr, A.A.; Choi, G.E.; Kim, J.S.; Ko, S.H.; Han, H.J. Abeta-Induced Drp1 phosphorylation through Akt activation promotes excessive mitochondrial fission leading to neuronal apoptosis. Biochim. Biophys. Acta 2016, 1863, 2820–2834. https://www.sciencedirect.com/science/article/pii/S0167488916302233
6. Li, X.C.; Hu, Y.; Wang, Z.H.; Luo, Y.; Zhang, Y.; Liu, X.P.; Feng, Q.; Wang, Q.; Ye, K.; Liu, G.P.; et al. Human wild-type fulllength tau accumulation disrupts mitochondrial dynamics and the functions via increasing mitofusins. Sci. Rep. 2016, 6, 24756.https://www.nature.com/articles/srep24756
7. Niedzielska, E.; Smaga, I.; Gawlik, M.; Moniczewski, A.; Stankowicz, P.; Pera, J.; Filip, M. Oxidative Stress in Neurodegenerative Diseases. Mol Neurobiol 2016, 53, 4094-4125, doi:10.1007/s12035-015-9337-5. https://link.springer.com/article/10.1007/S12035-015-9337-5
8. Putcha, D.; Eckbo, R.; Katsumi, Y.; Dickerson, B.C.; Touroutoglou, A.; Collins, J.A. Tau and the fractionated default mode network in atypical Alzheimer's disease. Brain Commun 2022, 4, fcac055, doi:10.1093/braincomms/fcac055. https://academic.oup.com/braincomms/article-abstract/4/2/fcac055/6545190
9. Rao, V.K.; Carlson, E.A.; Yan, S.S. Mitochondrial permeability transition pore is a potential drug target for neurodegeneration. Biochim Biophys Acta 2014, 1842, 1267-1272, doi: 10.1016/j.bbadis.2013.09.003. https://www.sciencedirect.com/science/article/pii/S0925443913002810
10. Song, I.K.; Lee, J.J.; Cho, J.H.; Jeong, J.; Shin, D.H.; Lee, K.J. Degradation of Redox-Sensitive Proteins including Peroxiredoxins and DJ-1 is Promoted by Oxidation-induced Conformational Changes and Ubiquitination. Sci Rep 2016, 6, 34432, doi:10.1038/srep34432. https://www.nature.com/articles/srep34432
11. Tapias, V.; Jainuddin, S.; Ahuja, M.; Stack, C.; Elipenahli, C.; Vignisse, J.; Gerges, M.; Starkova, N.; Xu, H.; Starkov, A.A.; et al. Benfotiamine treatment activates the Nrf2/ARE pathway and is neuroprotective in a transgenic mouse model of tauopathy. Hum. Mol. Genet. 2018, 27, 2874–2892. https://academic.oup.com/hmg/article-abstract/27/16/2874/5025679
12. Verma, M.; Callio, J.; Otero, P.A.; Sekler, I.; Wills, Z.P.; Chu, C.T. Mitochondrial Calcium Dysregulation Contributes to Dendrite Degeneration Mediated by PD/LBD-Associated LRRK2 Mutants. J Neurosci 2017, 37, 11151-11165, doi:10.1523/JNEUROSCI.3791-16.2017.
https://www.jneurosci.org/content/37/46/11151.abstract
13. Vossel, K.A.; Xu, J.C.; Fomenko, V.; Miyamoto, T.; Suberbielle, E.; Knox, J.A.; Ho, K.; Kim, D.H.; Yu, G.Q.; Mucke, L. Tau reduction prevents Abeta-induced axonal transport deficits by blocking activation of GSK3beta. J. Cell Biol. 2015, 209, 419–433. https://rupress.org/jcb/article-abstract/209/3/419/38182
14. Xiao, H.; Jedrychowski, M.P.; Schweppe, D.K.; Huttlin, E.L.; Yu, Q.; Heppner, D.E.; Li, J.; Long, J.; Mills, E.L.; Szpyt, J.; et al. A Quantitative Tissue-Specific Landscape of Protein Redox Regulation during Aging. Cell 2020, 180, 968-983 e924, doi: 10.1016/j.cell.2020.02.012. https://www.cell.com/cell/fulltext/S0092-8674(20)30156-2?dgcid=raven_jbs_aip_email

15. [15] Yoboue, E.D.; Sitia, R.; Simmen, T. Redox crosstalk at endoplasmic reticulum (ER) membrane contact sites (MCS) uses toxic waste to deliver messages. Cell Death Dis 2018, 9, 331, doi:10.1038/s41419-017-0033-4. https://www.nature.com/articles/s41419-017-0033-4