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Review Article

Pyrazoline Derivatives: Potential Therapeutic Agents against Parkinson's disease

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ABSTRACT

Parkinson's disease (PD) is a neurodegenerative disorder that results in the gradual death of dopaminergic neurons in the human brain, leading to both motor impairment and a variety of non-motor symptoms. Pyrazoline is a heterocyclic compound known for its pharmacological spectrum and anti-inflammatory, antioxidant, and neuroprotective properties. Recent studies have highlighted its potential in modulating key pathways involved in PD, such as oxidative stress, mitochondrial dysfunction, and neuroinflammation, all of which are central to the progression of Parkinson's disease. These derivatives have shown promise in preclinical models by mitigating neuronal damage and preserving motor function, making them attractive candidates for further research. This review included the background on Parkinson's disease, current treatment options, common synthetic route of Pyrazoline ring, current medicines used for the treatment of PD, and recent studies done on Pyrazoline ring as anti-Parkinson's.

Keywords: Pyrazoline, Parkinson's Disease, Monoamine oxidase-B(MAO-B), Catechol-O-methyltransferase (COMT), and Deep brain stimulation (DBS).

INTRODUCTION

Background on Parkinson's disease:

Parkinson's disease (PD) is one of the most common neurodegenerative disorders, approximately 1% of people over 60 and 4% of people over 85 suffer from PD[1]. It is a progressive neurodegenerative disorder, that primarily affects the motor functions of the body[2]. It is distinguished by the loss of dopamine-producing neurons in the brain's substantianigra, which is essential for the regulation of motor functions of the body[3]. Motor dysfunctions, including tremors, stiffness, bradykinesia, postural instability, dystonia, and vocal complaints, are the main symptoms of Parkinson's disease. In addition to psychological symptoms like anxiety and sadness, PD patients also experience autonomic dysfunctions like constipation and orthostatic hypotension. (Fig.1)[4-6]. Therefore, rather than impacting the central nervous system, it is also a systemic disease, responsible for the non-motor symptoms[6]. Parkinson's disease is more common inolder age people, making it clear that aging is a major risk factor for the development of PD[7]. Environmental factors also responsible for inducing Parkinson's disease, including heavy metals, smoking, exposure to pesticides, and other pollutants.[8]

Mutations in genes such as SNCA (alpha-synuclein), LRRK2, PARK2 (Parkin), PINK1, and GBA1 are associated with familial forms of PD and influence disease progression. Mutations in the SNCA gene, which encodes alpha-synuclein, play a significant role in the pathogenesis of Parkinson's disease.[9]These mutations can lead to overproduction, misfolding, or aggregation of alpha-synuclein into toxic forms that disrupt cellular functions. Accumulated alpha-synuclein forms Lewy bodies, hallmark features of PD, which impair neuronal health by interfering with mitochondrial function, synaptic activity, and protein degradation pathways. Such disruptions contribute to the selective degeneration of dopaminergic neurons in the substantianigra, a key pathological feature of Parkinson's disease.[10]Mutations in the LRRK2 gene, particularly in the G2019S variant, are the most common genetic causes of Parkinson's disease.[11] LRRK2 encodes leucine-rich repeat kinase 2, a protein involved in cellular signaling, autophagy, and mitochondrial function. Mutations often increase LRRK2's kinase

activity, leading to abnormal protein phosphorylation, disrupted vesicle trafficking, and impaired lysosomal degradation.

These changes result in toxic protein accumulation, neuroinflammation, and dopaminergic neuron degeneration, contributing to the motor and non-motor symptoms of Parkinson's disease.[12] Mutations in the PARK2 gene, which encodes the protein parkin, are associated with autosomal recessive juvenile Parkinson's disease. Parkin is an E3 ubiquitin ligase crucial for protein degradation and mitochondrial quality control.[13]Mutations disrupt Parkin's function, leading to impaired clearance of damaged mitochondria and toxic protein accumulation. This contributes to increased oxidative stress, mitochondrial dysfunction, and eventual dopaminergic neuron death, particularly in the substantianigra. PARK2 mutations highlight the role of impaired protein and mitochondrial homeostasis in Parkinson's disease pathology.[14]

Mutations in the GBA1 gene, which encodes the enzyme glucocerebrosidase, are linked to an increased risk of developing Parkinson's disease, especially in individuals with Gaucher's disease.[15] The mutations result in the dysfunction of glucocerebrosidase, leading to the accumulation of glucocerebroside within lysosomes. This build-up impairs cellular function, increases oxidative stress, and contributes to neuroinflammation and dopaminergic neuron degeneration. Individuals with GBA1 mutations may experience Parkinson's disease symptoms earlier and more severely, highlighting the gene's role in disease pathogenesis.[16]

Mitochondrial dysfunction in Parkinson's disease (PD) is a critical factor in the degeneration of dopaminergic neurons. It involves impaired energy production due to defects in the electron transport chain leading to reduced ATP levels.[17] This dysfunction generates excessive reactive oxygen species (ROS), causing oxidative damage to cellular components. Mutations in genes like PINK1 and Parkin disrupt mitochondrial quality control, preventing the clearance of damaged mitochondria. Together, these processes amplify oxidative stress, calcium dysregulation, and neuronal vulnerability, accelerating PD progression.[18]

Approximately 20 different causative genes have been identified in familial forms of PD, PRKN gene is the most commonly identified causal gene in Japan.[19] Single Nucleotide Polymorphisms (SNPs): Genome-wide association studies (GWAS) have identified more than 200 genes that are potential drivers for the development of sporadic PD. These studies focus on SNPs that show significant frequency differences between patient and control groups, suggesting their involvement in PD pathogenesis.[20]Among the important genes identified through GWAS, SNCA (alpha-synuclein) and LRRK2 (leucine-rich repeat kinase 2) are highlighted as both causative genes for Mendelian forms of PD and contributors to sporadic PD development.[21]

Nitrogenous heterocyclic with a high electron density, pyrazoline derivatives are crucial for the broad pharmacological spectrum.[22] 3-substituted pyrazolinederivativesappear to be the most important pyrazolinesfor the novel drug discovery nowadays. Heterocyclic compounds containing nitrogen and oxygen are commonlyavailable in nature like alkaloids, nucleic acid, protein, vitamins, and pigments as bio-molecules in plants and animals.Nitrogen-containing heterocyclic class of compounds ofnumerousbiological activities as drug candidates provides an outstanding case history for modern drug discovery. Additionally, it highlights the unpredictable nature of the pharmacological range resulting from structural alterations to a pharmacophore drug molecule that contains a nitrogen-containing heterocyclic ring. In general, pyrazoline derivatives are involved invariousbiological activities and are used for a wide class of drug discovery.

Pyrazoline-containing drugs have widely usedin the treatment of Parkinson’s disease and other neurodegenerative diseasedue to their neuroprotective and antioxidant activity.[23]Studies on Pyrazolines indicate that these compounds can hinder the activity of monoamine Oxidase-B (MAO-B), an enzyme that is involved in the breakdown of dopamine in the brain.[24] By the inhibition of MAO-B, pyrazoline derivatives help to maintain dopamine levels, which is crucial for managing the motor function of the body.[25]Additionally, pyrazoline compounds have been studied for their ability to decreaseinflammation and oxidative stress in the brain, both of which are significant factors in the progression of Parkinson’s disease. [26]These properties make pyrazoline derivatives promising candidates for further research and development as potential therapeutic agents for PD[27].

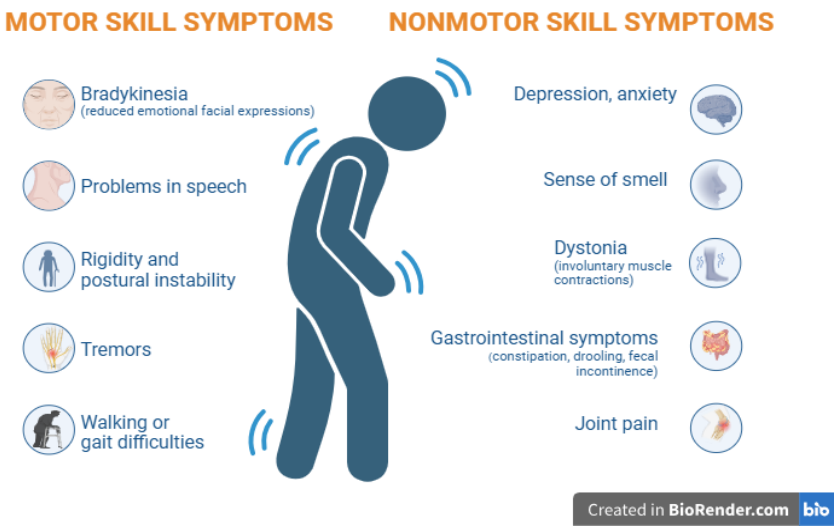


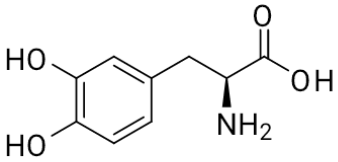
Figure1. Motor skill and non-motor skill symptoms of Parkinson's disease.[28]

Current treatment options

Pharmacological Treatments

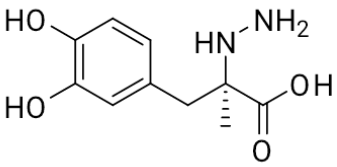
One of the best ways to treat PD treatment is dopamine replacement therapy with levodopa.[29]Dopamine agonists, MAO-B inhibitors, and COMT inhibitors class of the drug are also used in the treatment of PD.[30]Levodopa therapy is widely used for the effective treatment of motor symptoms of Parkinson's disease (PD).[31-32]

People who are suffering from PD have low concentrations of dopamine, a neurotransmitter found in the precursor form, levodopa.[33,] Unlike dopamine, levodopa can easily permeate the BBB to reach inside the brain, further metabolized and converted into the active form (dopamine) in the brain, helping to manage the depleted level of dopamine.[34]Levodopa is almost always givenwith a combination ofcarbidopa (as in the drug Sinemet).[35] Carbidopaobstructs the pathway of an enzyme that is involved inthe metabolismof levodopa before it enters the brain, thereby it helps in increasing thebioavailability of levodopa inside the brain and eliminating side effects like constipation, nausea, and vomiting.[3]



Levodopa

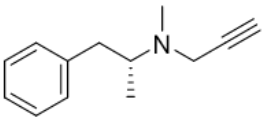
1



Carbidopa

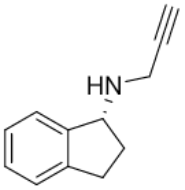
2

Inhibitors of monoamine oxidase-B (MAO-B) are a category of medicines that are frequently used in managing motor and non-motor symptoms of Parkinson's disease.[37]Mechanism of action of MAO-B is by inhibiting the activity of the monoamine Oxidase-B, which involves the metabolism of dopamine in the brain and helps to manage PD symptoms.[38]Inhibitionof MAO-B enzyme, MAO-B inhibitors help to maintain the standard concentration of dopamine in the brain, thereby helping to improve the motor symptoms of PD).[39] Selegiline (Eldepryl, Zelapar), Rasagiline (Azilect), and Safinamide (Xadago) are the most common MAO-B inhibitor given in the PD treatment[40].



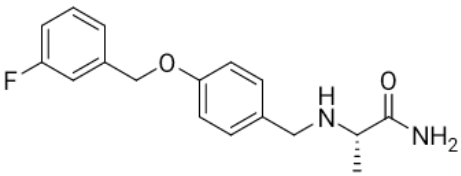
(Selegiline)
(2R)-N-methyl-1-phenyl-N-prop-2-ynylpropan-2-amine

3



(Rasagiline)
(1R)-N-prop-2-ynyl-2,3-dihydro-1H-inden-1-amine

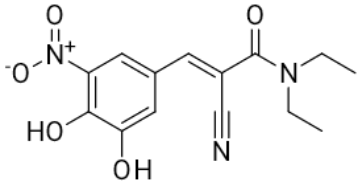
4



(Safinamide)
(2S)-2-[[4-[(3-fluorophenyl)methoxy]phenyl]methyl amino]propanamide

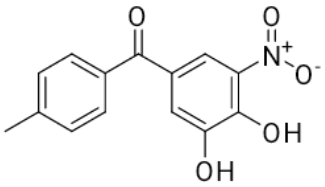
5

Catechol-O-methyltransferase (COMT) inhibitors are given with levodopa to manage the motor and non-motor symptoms of Parkinson's disease (PD).[41] They work by inhibiting the enzyme COMT, which is involved in breaking down levodopa in the body, thereby extending the duration of stability of levodopa and increasing its effect.[42]Tolcapone (Tasmar®), Opicapone (Ongentys®), Entacapone (Comtan®), and Carbidopa-Levodopa-Entacapone (Stalevo®) are medicines which are frequently given inParkinson disease.[43]



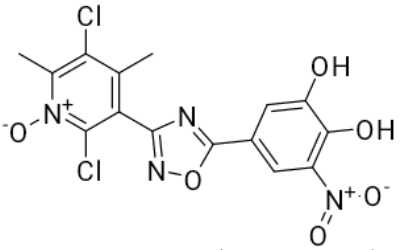
Entacapone (Comtan®)

7



Tolcapone (Tasmar®)

8



Opicapone (Ongentys®)

9

Surgical Treatments

The deep brain stimulation (DBS) procedure is used for patients with Parkinson's disease (PD) who exhibit inadequate response to pharmacological treatment with severe symptoms.[44]In Deep brain stimulation (DBS) with the help ofsurgical procedure, implantation of an intracranial electrode device inside the subthalamic nucleus or globuspallidusinterna[45]. DBS caneffectively manage the symptoms of PDinthose patients who have severe symptoms of PDand can't be treated with the help of levodopa. It is the most effectivetreatment optionfor patients who suffer from severe symptoms like motor fluctuations, dyskinesias, and tremors.[46]Patients who suffer from symptoms of dementia, untreated depression, and severe postural instability can't be treated by Deep brain stimulation. Stroke; infection; cognition changes; changing or worsening psychological symptoms; difficulty in speech, gait, problem in vision; and new-onset paresthesias are the severe side effects associated with deep brain stimulation treatment[47].

Non-Pharmacological Treatments

To control symptoms of PD and enhance the quality of life, patients need to include occupational therapy, speech therapy, and physical therapy in their routine.[48]Exercise has been demonstrated to enhance motor abilities and functionality, thus a person who suffers from PD should be physically active as much as possible. Parkinson's disease patients canbenefit from community-based programs like speech therapy tailored to their condition and boxing sessions, which can help in the progression of PD.Adequateamount of hydration in the body is necessary to escape the symptoms of nausea, vomiting, and constipation.[49]

Challenges of Current Treatment Options for Parkinson's Disease

Symptom Management vs. Disease Modification: Symptom management in Parkinson's disease focuses on alleviating motor and non-motor symptoms, primarily through medications like Levodopa and dopamine agonists, which temporarily restore

dopamine levels.[50] while these treatments improve quality of life, they do not halt or slow the disease's progression, leading to diminishing effectiveness over time and side effects such as dyskinesia. In contrast, disease modification aims to address the root causes of Parkinson's by slowing or stopping neurodegeneration. However, no currently available treatments achieve true disease modification, leaving a significant gap in therapeutic strategies and highlighting the need for innovative approaches that go beyond managing symptoms to altering the course of the disease.[51]

Adverse Effects: Adverse effects in Parkinson's disease treatments are a significant challenge, particularly with long-term use of medications like Levodopa. While these drugs effectively manage symptoms initially, they often lead to complications such as motor fluctuations and dyskinesia.[52] Dopamine agonists can cause side effects like hallucinations, impulse control disorders, and sleep disturbances. Non-motor symptoms, such as anxiety or cognitive decline, may also worsen as a result of medication. These adverse effects not only reduce the effectiveness of treatment over time but also complicate the management of the disease, emphasizing the urgent need for therapies with fewer side effects and more sustainable benefits.[53]

Short Duration of Effect: The short duration of effect is a major limitation of current Parkinson's disease treatments, particularly with medications like Levodopa. While it is highly effective in reducing motor symptoms, its benefits are often short-lived, requiring frequent dosing throughout the day.[54] over time, patients may experience "wearing-off" phenomena, where the medication's effects diminish before the next dose, leading to periods of impaired movement. This fluctuating control of symptoms disrupts daily life and makes consistent management of the disease challenging. Addressing this issue requires the development of longer-acting treatments or innovative delivery methods to ensure sustained symptom relief.[55]

Blood-Brain Barrier: The blood-brain barrier (BBB) poses a significant challenge in treating Parkinson's disease because it restricts many therapeutic compounds from reaching the brain. The BBB is a protective layer that prevents harmful substances in the bloodstream from entering the brain, but it also blocks potentially beneficial drugs. For example, dopamine itself cannot cross the BBB, which is why treatments like Levodopa a precursor to dopamine are used to treat Parkinson's disease.[56] However, even with Levodopa, only a fraction reaches the brain, leading to reduced efficiency and potential side effects from peripheral metabolism. Overcoming the BBB is crucial for developing advanced therapies, such as targeted drug delivery systems or biologics, that can directly address the neurodegeneration underlying Parkinson's disease.[57]

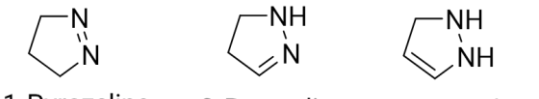
Non-motor symptoms: Non-motor symptoms in Parkinson's disease, such as depression, anxiety, sleep disturbances, cognitive decline, and autonomic dysfunction, present significant challenges in the treatment. These symptoms often have a profound impact on quality of life and can even precede motor symptoms, yet current therapies primarily focus on motor symptom management.[58] Non-motor symptoms are complex, stemming from widespread neurodegeneration beyond the dopaminergic system, making them harder to treat with conventional medications like Levodopa. This gap in effective management highlights the need for holistic approaches and therapies that address the full spectrum of Parkinson's disease, not just its motor symptoms management.[59]

Individual variability: Individual variability in Parkinson's disease significantly complicates treatment, as patients experience diverse symptoms, progression rates, and responses to therapy. Factors such as age, genetics, comorbidities, and the severity of neurodegeneration influence how individuals respond to treatments like Levodopa or dopamine agonists. Some may benefit greatly from these medications, while others experience limited relief or intolerable side effects. Additionally, non-motor symptoms and the impact of the disease on daily life vary widely, requiring highly personalized treatment plans. This variability underscores the challenge of developing universally effective therapies and highlights the need for precision medicine approaches in managing Parkinson's disease.[60]

Chemical Structure and Properties of Pyrazoline

Pyrazoline belongs to the class of heterocyclic compounds having five-member rings that

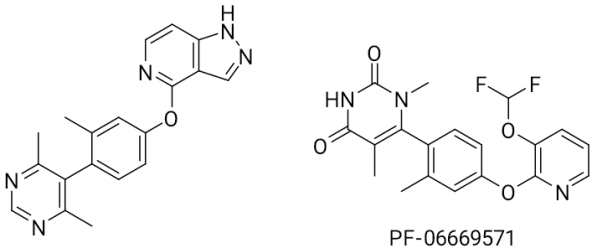
contain two nitrogen atoms.[61] They were found in the three isomeric forms listed below: 1-pyrazoline**10**, 2-pyrazoline**11**, and 3-pyrazoline**12**.[62]Two or three substitutions were made in 2-pyrazolines to investigate their pharmacological potential during drug discovery. Furthermore, other heterocyclic rings, such as imidazole, thiazole, and oxazole, are isosteres of pyrazoline.[63]



10 11 12

The stability of Pyrazoline derivatives enthused the chemist to alter the pyrazoline's structure in several ways to discover a wide range of medicinal compounds with various pharmacological properties.[64]Pyrazoline moiety has been widely investigated by medicinal chemists in the field of drug discovery to treat a variety of diseases. Pyrazolinederivatives have been used for the treatment of numerous diseases including anticancer, anti-Alzheimer's, antitubercular, anticonvulsant, anti-inflammatory, antidepressant, antimicrobial, anti-HIV, anti-malarial, monoamine oxidase (MAO) inhibitory, anti-cholinesterase, cannabinoid antagonist, anti-EGFR, anti-parkinsonian.[65-66]

Pyrazoline-Based Compounds in Clinical Trials for Parkinson's disease Therapy:



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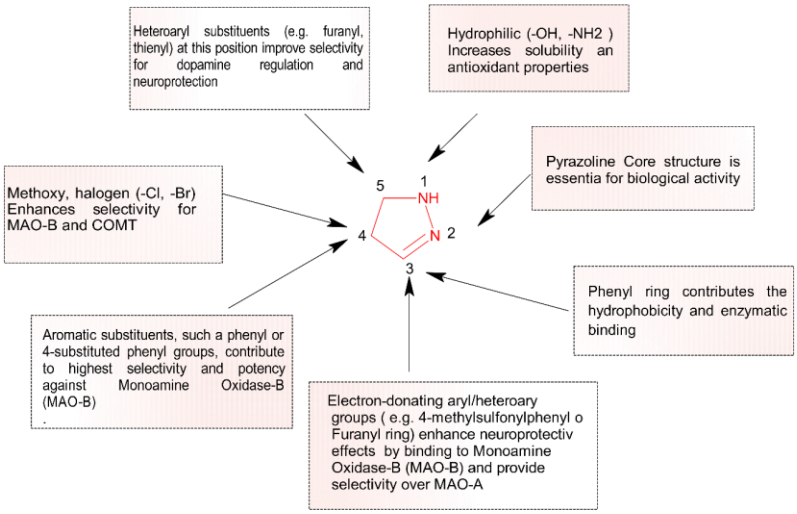
Razpipadon

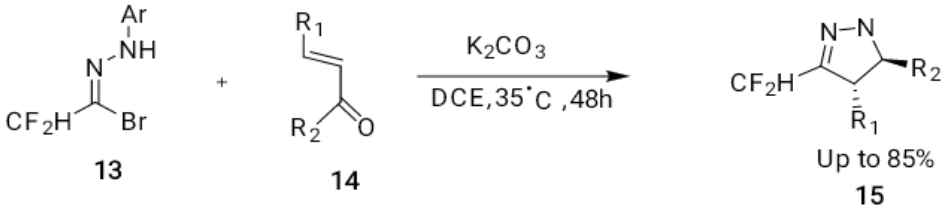
SAR of pyrazoline as anti-Parkinson drugs



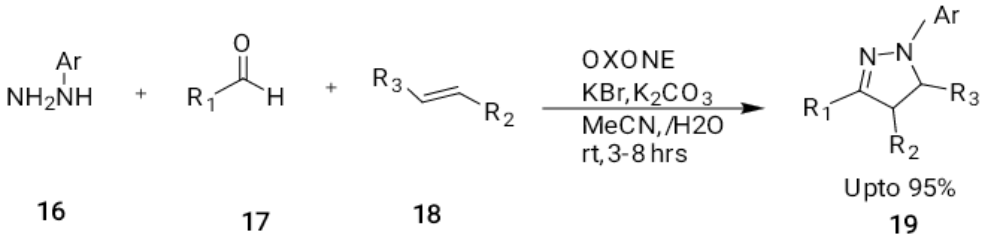
Synthesis methods:

Pyrazolines are familiar and have significant biological activity, five-membered heterocyclic compounds having nitrogen as heteroatom in the ring, have been synthesized using a variety of techniques.[67-68]From the perspective of organic chemistry, chalcones, and substituted hydrazine derivatives are cyclized in a basic alcoholic medium to yield N-substituted Pyrazolinederivatives.[69]

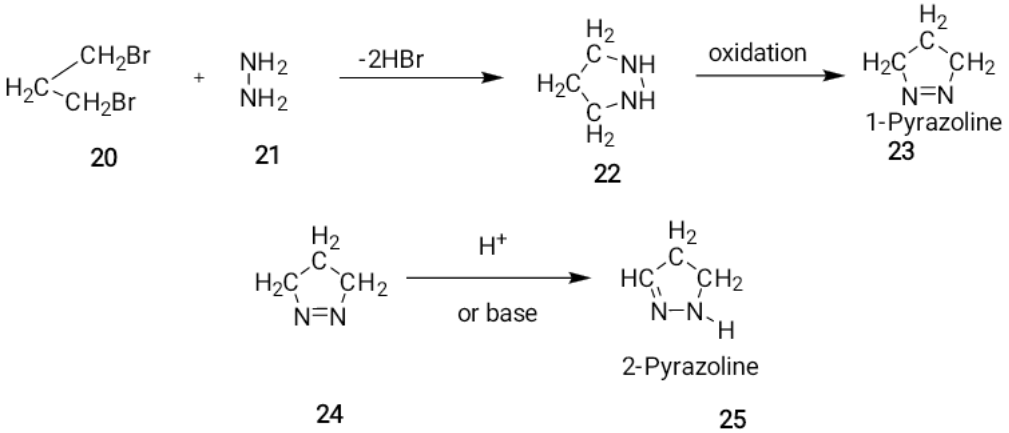
a. By combining diazomethane with olefin double bonds that have been activated by electron-withdrawing groups, pyrazolines can be synthesized. The McGreer research group has successfully synthesized several intriguing 1-pyrazolines using this technique.



R[1]=H, aryl, alkyl
R2=aryl, alkylOMe, OEt, NH2, amine



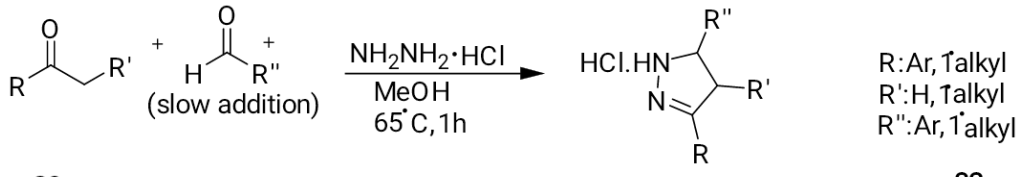
b. It has been reported that 1, 3-dibromopropane and hydrazine can be used to synthesize pyrazolidine, providing a pathway similar to that of azoethane synthesis. Because 1-pyrazolines easily tautomerize to 2-pyrazolines in both acid and base, the oxidation and work-up should proceed quickly and as close to neutrality as feasible.



c. Alkyl dihalides, primary amines, and hydrazine are converted into nitrogen-containing heterocyclic in a one-pot green synthesis using a straightforward cyclo-condensation process in an alkaline aqueous media under microwave irradiation.

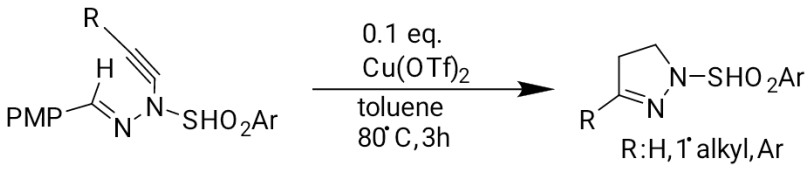
1M NaOH, 120 C,20m

d. Pyrazoline intermediates were easily produced in mild conditions by one-pot green and effective condensations of ketones, aldehydes, and hydrazine monohydrochloride. As an alternative, pyrazolines can be heated in DMSO with oxygen to produce 3,5-disubstituted or 3,4,5-trisubstituted pyrazoles using an oxidation procedure.



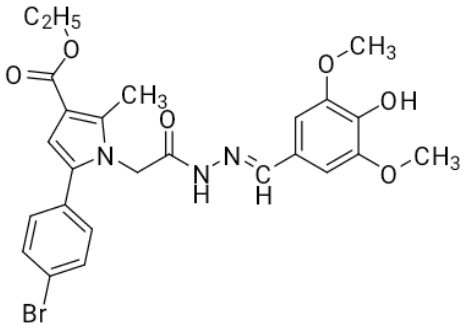
29 30 31 32

e. Through the establishment of intramolecular carbon and nitrogen bonds, an effective copper(II)-catalyzed cyclization of easily available N-propargyl hydrazones gives high yields of N-acyl and N-tosyl-substituted pyrazolines. The Cu(II) catalyst typically acts as a Lewis acid to cyclize an iminium-ion intermediate, which, when hydrolyzed, produces the required pyrazolines.



33 34

Maya Georgieva. et al. (2024) After conducting neuroprotective and antioxidant activities on subcellular fractions in several injury models, Maya Georgieva et al discovered that derivatives 35 and 36 were the most effective. For possible hMAOA/hMAOB inhibitory effects, a 1 µM concentration of each molecule from the series was also investigated. All assessed structures exhibited no hMAOA activity, according to the data, and hMAOB effects were seen; compounds 35 and 36 displayed actions resembling those of selegiline. The most promising compounds for additional research as possible selective MAOB inhibitors were identified as 35 and 36, which had the best hMAOB selectivity index >204.[70]



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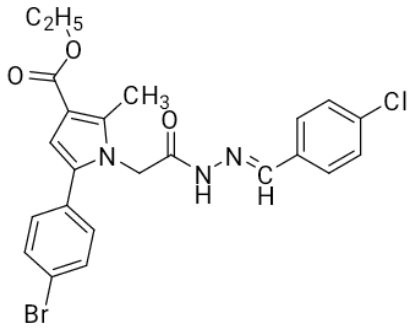
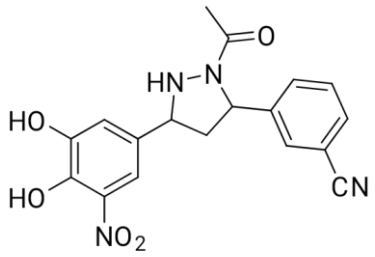


36

Rialette. et al. (2020) New chalcone and pyrazoline compounds were synthesized by Rialetteet al and tested as inhibitors of rat COMT and human MAO. With an IC_{50} value of 0.048 µM, compound 37 was shown most effective COMT inhibitor activity. Compared to the reference COMT inhibitor entacapone, which has an IC_{50} value of 0.23 µM. The findings showed that the chalcones (IC_{50} = 0.14–0.29 µM) are less effective COMT inhibitors than the pyrazoline derivatives (IC_{50} = 0.048–0.21 µM). The pyrazoline and chalcone derivatives have IC_{50}values greater than 41.4 µM, making them poor MAO inhibitors.[71]



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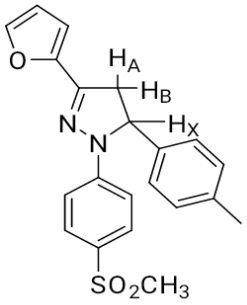
AhmetÖzdemiret.al. (2018) The series of 1-(phenyl/4-substituted phenyl)-3-(2-furanyl/thienyl)-5-aryl-2-pyrazoline derivatives were synthesized by AhmetÖzdemiret. al. usingchalcones. 6-hydroxydopamine (6-OHDA)-induced neurotoxicity model of Parkinson's disease in the rat and pheochromocytoma (PC-12) Adh cell line is used to examine for in-vitroneuroprotective properties for all synthesized compounds. When compared to the 6-OHDA-positive control group, 4-Methyl sulfonylphenyl substituted compounds 38 (20%) and 39 (23%) were shown to be the most promising neuroprotective agents due to their inductive functions in cell survival (43% and 42%, respectively).[72]



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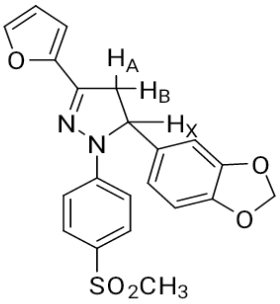

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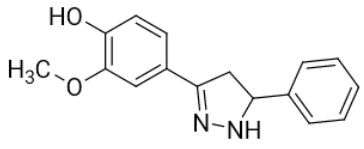
Vishnuet. al. (2016) synthesized a variety of novel 2-methoxy-4-(5-phenyl-4,5- dihydro-1H-pyrazol-3-yl) phenol analogs and performed their ability to inhibit human MAO. Except for compound 40, which selectively inhibits hMAO-B, and compound 41, which is a nonselectiveMAO inhibitor, all synthesized derivatives were shown selective and reversible inhibition ofhMAO-A. Compound 42 was determined to be the most effective hMAO-A inhibitor, with a selectivity index of (SI = 1.02 × 10−5) and a Ki = 0.06 ± 0.003 μM.[73]



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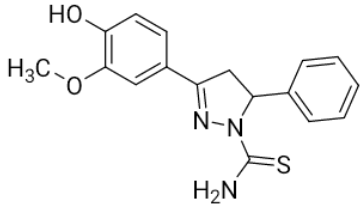

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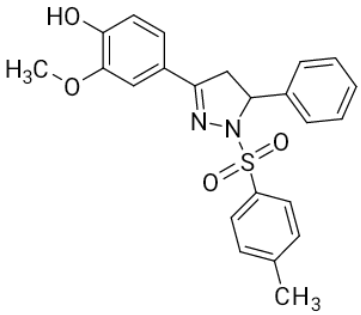
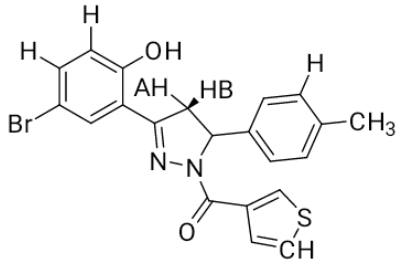


41

Begüm et. al. (2014) synthesized a new series of 2-pyrazoline and hydrazone derivatives and performed human monoamine oxidase (hMAO) inhibitor activity. The reversible action of the hMAO inhibition is demonstrated by all synthesized compounds. All of the compounds markedly and selectively inhibited hMAO-A, and compound 43, showed selective MAO-B

inhibitory activity. Compounds 43 and 44 showed the strongest inhibitory action against the hMAO-A based on the experimental Ki values, whereas compound 44 with a bromine atom at R4 of the pyrazoline's A ring seemed to be the most selective MAO-A inhibitor.[74]



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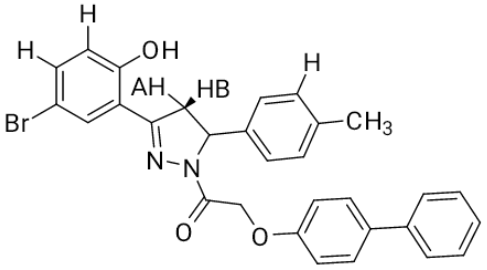

44

CONCLUSION

In conclusion, Pyrazoline derivatives have emerged as promising drug candidates for combating Parkinson's disease. These compounds show broad pharmacological properties, including antioxidant, anti-inflammatory, and neuroprotective activities, all of which are essentialin managing of PD. By targeting monoamine oxidase-B (MAO-B) and catechol-O-methyltransferase (COMT) enzymes. Pyrazoline derivatives show potentialagainst PD. Moreover, advancements in structure-activity relationship (SAR) studies have optimized the pharmacokinetic profiles of these compounds, enhancing their bioavailability and efficacy. Experimental models have provided encouraging data, demonstrating their ability to manage the motor and non-motor symptoms of Parkinson's disease. Although these literature findings are promising, translating them into clinical practice requires rigorous testing, including large-scale clinical trials to confirm their safety and therapeutic potential. Continued exploration and development of these compounds could mark a significant leap forward in the search for effective treatments against Parkinson's disease.

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Conflict of Interests

The authors declare that there is no conflict of interest.

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