



## NOVEL DRUG THERAPY IN PARKINSON'S DISEASE

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### ABSTRACT

Parkinson's ailment is the maximum not unusual place Neuro-degenerative disorder. Several new medicinal drugs are discovered, maximum of which might be versions of formerly current merchandise, such new dosage varieties of already-authorized merchandise, or cost-saving usual formulations were proposed. These new merchandise make contributions to the general public health, protection of the people, extra get right of entry to medication, greater client choice, and a aggressive market that complements affordability and first-rate and care. However, those new approvals that we seek advice from as novel capsules are most of the greater honestly modern merchandise that regularly assist earlier scientific care to some other level. This article consists of observe of current capsules and novel capsules withinside the Parkinson's ailment remedy and additionally describes their medicinal chemistry i.e knowledge its structure, synthesis, structural pastime relationships, mechanism of action, healing uses, negative consequences etc. These capsules are capable in diverse regions to satiate, cause them to appropriate for its healing use and for drug formulations and discoveries

**Keywords:** Neuro-degenerative disorder, new approvals, medicinal chemistry, novel capsules, synthesis, structural pastime relationship, medication.

### 1. INTRODUCTION

A lack of dopamine-producing cells withinside the mind that outcomes in a complicated array of signs and symptoms is referred to as as Parkinson's ailment (PD) however it's far in most cases related with modern lack of motor control. Major reason of incapacity some of the elder is Parkinson's ailment. After Alzheimer's.

Common diagnostic standards usually require the initiation of antiparkinson's medicinal drug earlier than the prognosis may be confirmed. This ambiguity may be perplexing for number one care physicians, ailment, presently the second one maximum not unusual place neurological degenerative ailment affecting global is Parkinson's ailment. Young-onset Parkinson's ailment is a circumstance in which an person beneath neath forty years of age may also increase PD. It is hard to diagnose PD.



Fig: 1

Fig. 1: Parkinson's ailment. Especially whilst the ailment provides with out the feature tremor. Some- instances PD circumstance wherein no tremors arise can be unsuitable for a Parkinson ailment is frequently viable in number one care.[1]

**Objective:**

This article offers a dialogue concerning latest improvement of drug medicinal drugs to deal with Parkinson's ailment. The predominant goal is to go looking the latest novel tablets used and to make out the Parkinson ailment circumstance whose predominant functions are:

- Slowed movement
- Balance
- Gait & stability problems.

Drugs utilized in PARKISON DISEASE THERAPY, and to supply a element facts specifying the medication and NOVEL DRUGS accredited so far, for the remedy of this Neuro- degenerative ailment and describe approximately the chemistry.

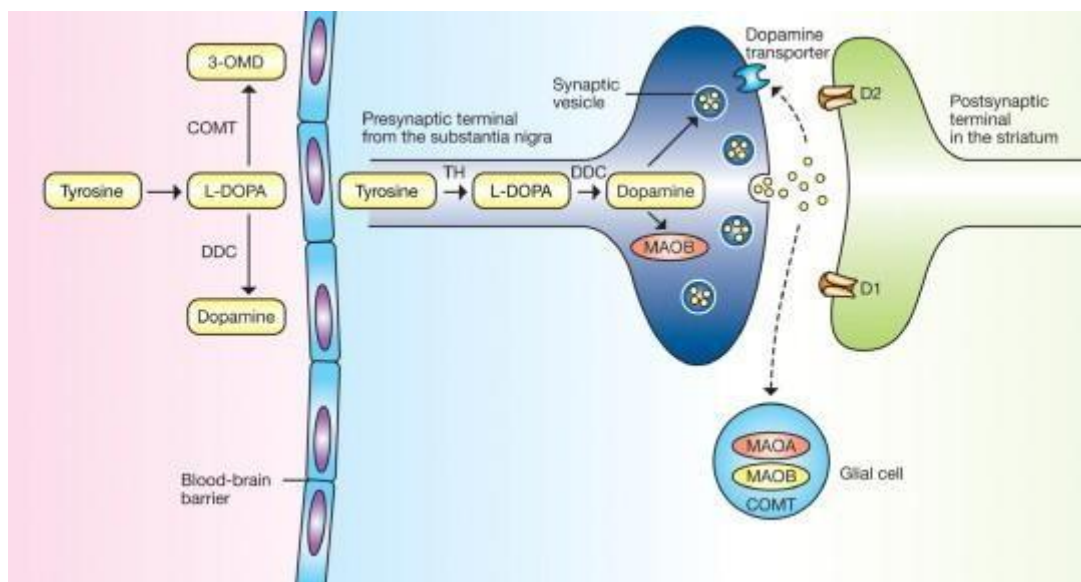


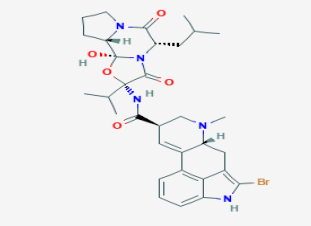
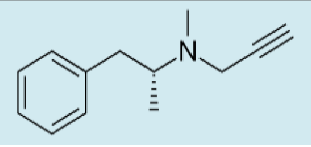
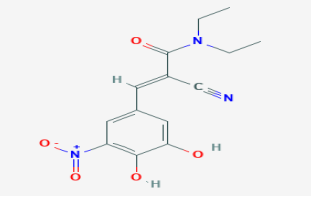
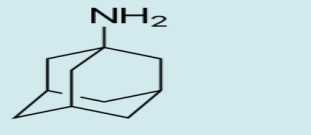
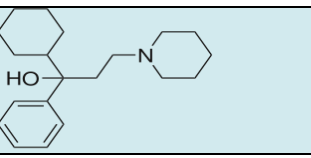
Fig-3: Mechanism of Action of Dopamine

#### General Mechanism of Action Parkinson's :

Disease is a progressive neurodegenerative disorder with motor defects due to the imbalance between the dopaminergic (inhibitory-D2, excitatory-D1 receptors). These are amplified by K<sup>+</sup> channels, respectively. Parkinson's disease is characterized by dopamine deficiency. Levodopa is considered to act through D1 and D2 receptors present in the straitum and it regulates the activity of the two pathways having opposite effects on the thalamic input to the motor cortex.

#### Classification of Anti Parkinson's Drugs:

Drugs affecting Brain Dopaminergic system			
Class	Example	IUPAC	Structure
Dopamine precursor	Levodopa	(2S)-2-amino-3-(3,4-dihydroxyphenyl)propanoic acid	
Peripheral decarboxylase inhibitors	Carbidopa Benserazide	(2S)-3-(3,4-dihydroxyphenyl)-2-hydrazino-2-methylpropanoic acid	

<b>Dopaminergic agonists</b>	<b>Bromocriptine</b> Ropinrole Pramipexole	(6aR,9R)-5-bromo-N- [(1S,2S,4R,7S)-2-hydroxy-7-(2-methylpropyl)-5,8-dioxo-4-propan-2-yl-3-oxa-6,9-diazatricyclo[7.3.0.02,6]dodec an-4- yl]-7-methyl-6,6a,8,9- tetrahydro- 4H-indolo[4,3- fg]quinoline-9- carboxamide	
<b>MAO-B inhibitors</b>	<b>Selegeline</b> Rasageline	(R)-N-methyl-N-(1-phenylpropan-2-yl)prop-3-yn-1- amine	
<b>COMT inhibitors</b>	<b>Entacapone</b> Tolcapone	(E)-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)-diethylprop-2-enamide	N,N- 
<b>Glutamate (NMDA)receptor agonist(Dopamine facilitator)</b>	<b>Amantadine</b>	Adamantan-1-amine	
<b>Drugs Affecting Brain Cholinergic System</b>			
<b>Central anticholinergics</b>	<b>Trihexylphenidyl</b> Procyclidin Biperiden	(RS)-1-Cyclohexyl-1-phenylpiperidyl)propan-1-ol	3-(1- 
<b>Antihistaminics</b>			
	<b>Orphenadrine</b> Promethazine	N,N-dimethyl-2-[(2- methylphenyl)- phenylmethoxy]ethanamine	
<b>Miscellaneous Drugs</b>			
<b>Antidepressants</b>	Amitryptilline Trazadol	3-(10,11-dihydro-5H-dibenzo[a,d]cycloheptene- 5-ylidene)-N,N-dimethylpropan-1-amine	
<b>Vitamin-E</b>	Tocopherol	2,7,8-trimethyl-2-(4,8,12- trimethyltridecyl)-3,4- dihydrochromen-6-ol	
<b>Glutamate release inhibitor</b>	Lamotrigine	6-(2,3-dichlorophenyl)- 1,2,4-triazine-3,5-diamine	
<b>Glutamate release antagonist</b>	Remacimide	2-amino-N- (1,2diphenylpropan-2- yl)acetamide	
<b>Glia-derived neurotrophic factor</b>	GDNF		

A novel drug or novel molecular entity (NME) is a drug complex molecule previously not approved by the FDA / EMA. This is different from the drug previously approved, which is different but approved in the new state. It also distinguishes from generics. Generic drug is the same NME generic

(usually) patent-free formulation, but manufactured by an alternative company. To minimize these clinical complications, a new compound has been developed. New drugs and bioproducts for the treatment of PD need to address dopaminergic neuroprotection, reduce early neurodegeneration and improve dopaminergic neurotransmission. [Four]

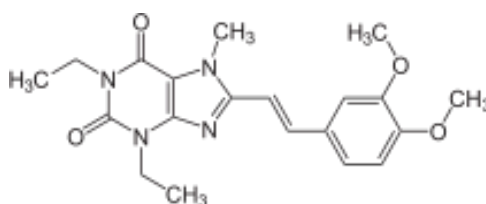
Many of the new drugs have been introduced for the treatment of in Parkinson's disease, some of which are briefly described here.

1. Istradefylline
2. Nilotinib
3. 3.Safinamide
4. Isradipine
5. Ionosine
6. Stalevo
7. Idazoxan
8. Mirtazapine
9. Apomorphine Infusions
10. Rotigotine Skin patches
11. Pimavanserin

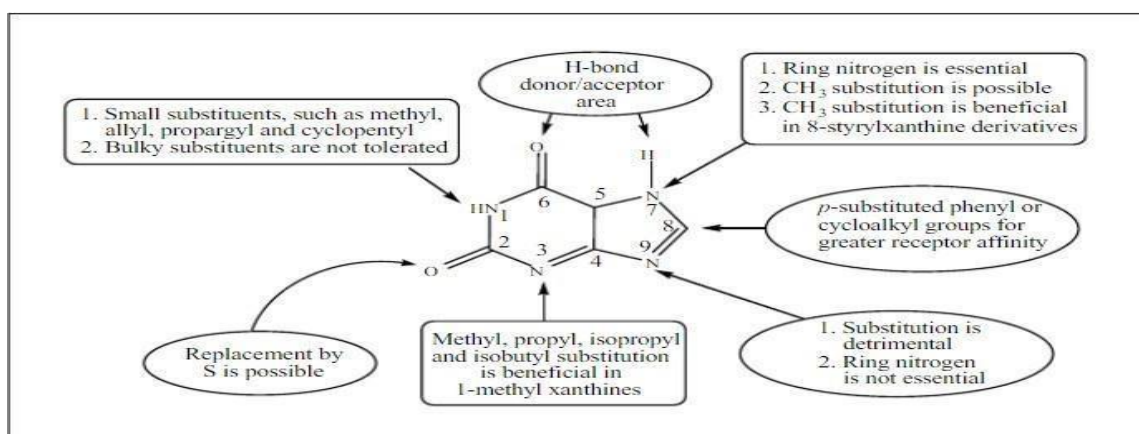
### Istradefylline :

**Istradefylline or KW6002** was developed by Japanese Kyowa Hakko Kirin for the treatment of Parkinson's disease as an adjunct to standard of care. Unlike preferred dopaminergic treatment plans for Parkinson's. Istradefylline objectives adenosine A2A receptors within the basal ganglia. This vicinity of the mind is fantastically concerned in motor control. Istradefylline is indicated as an accessory remedy to [levodopa] and [carbidopa] for Parkinson's disease. This drug changed into first permitted in Japan on 25 March 2013. Istradefylline changed into granted FDA approval on 27 August 2019[5] Istradefylline, bought below the logo call Nouriazan.

### Structure



### Structural Activity Relationship Synthesis



## Route 1

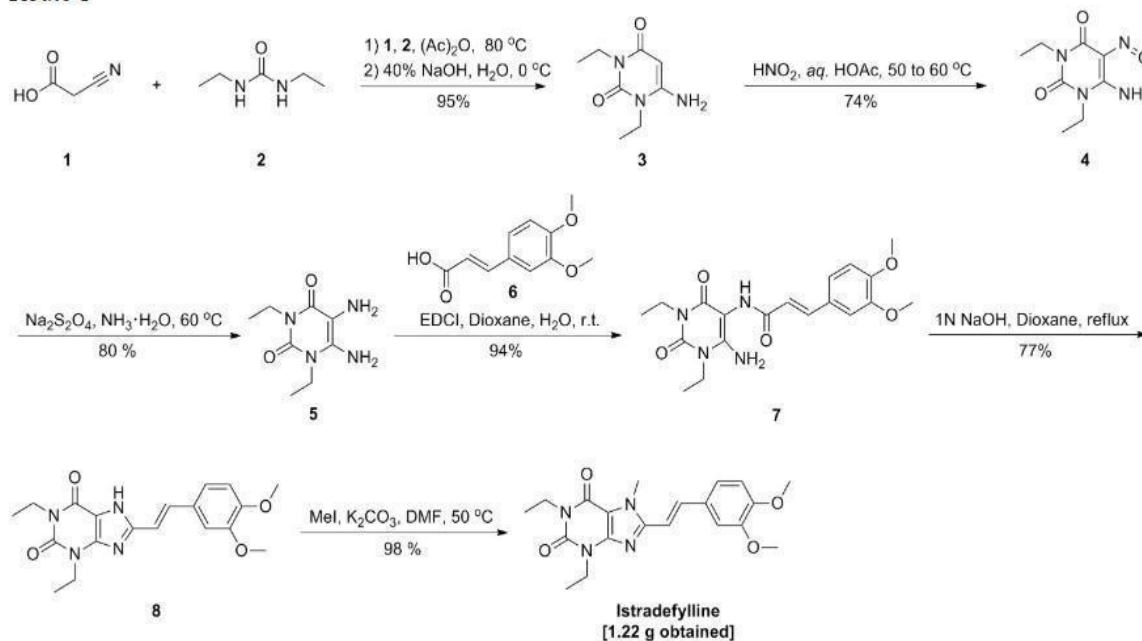


Fig. 5: SAR of Istradefylline.

Antagonist used similarly to carbidopa and levodopa for the remedy of “off” episodes. The unique mechanism of motion of the drug is unknown however it's far presumed to lessen the over pastime of the striatal pathway, restoring the stability of basal ganglia.

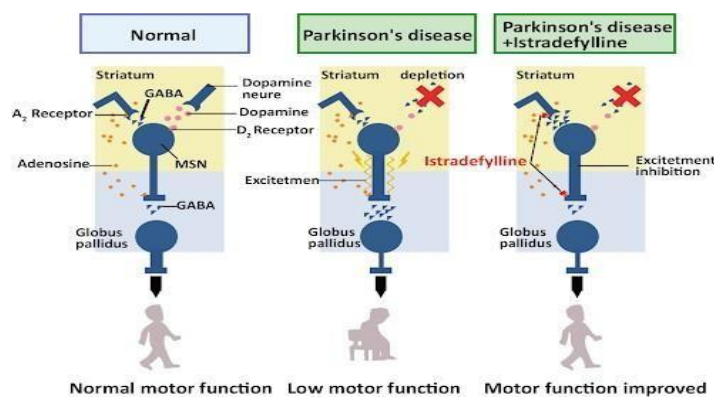


Fig-4: Motor function in PD.

Therapeutic uses Istradefylline is utilized by human beings with Parkinson`s sickness taking carbidopa/levodopa to lessen the quantity of "off" time (durations of gradual motion or stiffness).

## Adverse effects

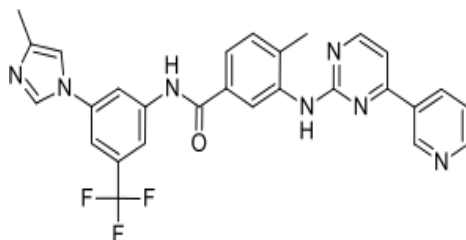
- Involuntary muscle movements,
- dizziness,
- constipation,
- nausea,
- hallucinations, and
- Insomnia

## Nilotinib:

Nilotinib via way of means of Novartis is a ability new remedy for Parkinson`s sickness (PD).

A medical trial investigating the repurposed most cancers drug Nilotinib in human beings with Parkinson's sickness unearths that it within reason secure and properly tolerated. Researchers additionally document locating an growth in dopamine, the chemical misplaced becau se of neuronal destruction, and a lower in neurotoxic proteins withinside the mind amongst examine participants. Finally, they are saying Nilotinib, a tyrosine kinase inhibitor, doubtlessly halts motor and non-motor decline.

### Structure:



**IUPAC name:** 4-methyl-N-[3-(4-methyl-1H-imidazol-1-yl)-5-(trifluoromethyl)phenyl]-3-[[4-(3-pyridin-3-ylpyrimidin-2-yl)amino]benzamide.

**Molecular formula:** C<sub>28</sub>H<sub>22</sub>F<sub>3</sub>N<sub>7</sub>O

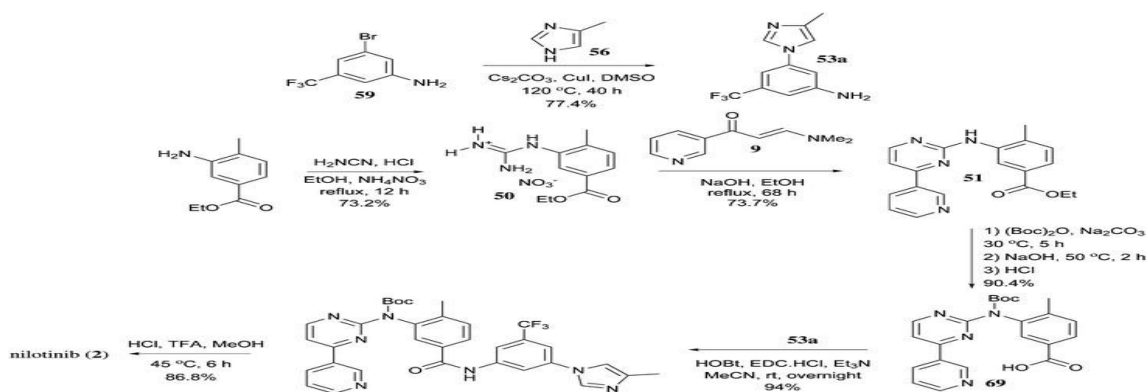
**Molecular weight:** 529.52 g/mol

### Mechanism of Action:

Nilotinib blocks the non-receptor Abelson (Abl) tyrosine kinase, however its precise mechanism of movement in Parkinson`s disorder remains beneath neath investigation. The desire is this technique should sluggish down or prevent Parkinson`s progression. The consequences of the first protection observe have to be to be had soon.

### Synthesis:

The 5-bromo-3-(tri fluoro methyl) phenyl amine became reacted with four-methyl-1H- imidazole withinside the presence of cesium carbonate and cuprous iodide to gain 3-trifluoromethyl-5-(four-methyl-1H-imidazol- 1- yl) phenyl amine(four). Ethyl 3-amino-four- methyl benzoate became reacted with cyanamide to gain the guanidine, which cyclized with 3-dimethylamino 1-(3- pyridinyl) -2- propylene-1-one to offer ethyl4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl] amino] benzoate(eight). Compound eight became subjected to Boc protection, hydrolysis, amidation and then condensation with compound four to offer 4methyl-N-[3-(4-methyl-1H-imidazol-1- yl)-5-( trifluoromethyl)phenyl]-3-[N-tert butoxycarbonyl-4-(3-pyridinyl)-2-pyrimidinyl] amino] benzamide(10). After deprotection, nilotinib became obtained.



**Fig-6: Synthesis of Nilotinib.**

### Therapeutic uses:

Parkinson`s sickness and experimental Parkinsonism.[69] Idazoxan, as an accessory Nilotinib is used withinside the remedy of Parkinson sickness. Nilotinib is used to deal with a positive kind of blood most cancers (continual myelogenous leukemia-CML). It works via way of means of slowing or preventing the increase of cancer cells.

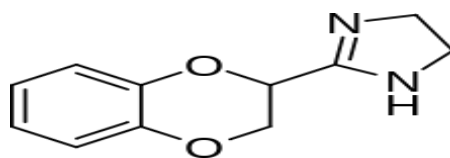
### Adverse effects

- Itching,
- Headache,
- Nausea,
- Fatigue,
- Tiredness,
- Joint or muscle aches or pain,
- Back Pain,
- Diarrhoea,
- Constipation.

### IDAZOXAN:

It has been proposed that Idazoxan in aggregate with L-dopa can also additionally offer a unique technique to the remedy of Parkinson's sickness with a view to now no longer most effective lessen the dyskinesic aspect effects, however enlarge the anti-parkinsonian movements of L- dopa. The  $\alpha_2$ -adrenoceptor antagonist idazoxan can also additionally enhance motor signs in to dopamine replacement, can also additionally show beneficial withinside the remedy of parkinsonian sufferers in any respect ranges of sickness progression.

### Structure:



IUPAC Name: ( $\pm$ )-2-(2,3-dihydro-1,4- benzodioxin-2- yl)-4,5-dihydro-1H- imidazole.

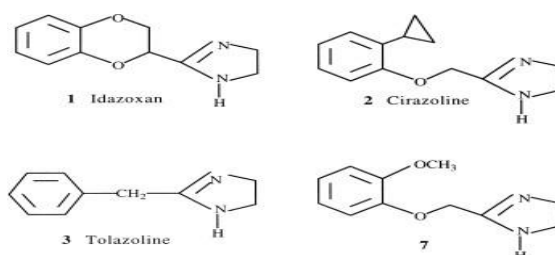
Molecular formula: C<sub>11</sub>H<sub>12</sub>N<sub>2</sub>O<sub>2</sub> Molecular weight: 204.225g.

### Mechanism of action:

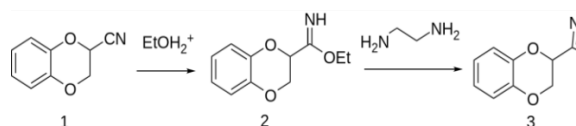
Idazoxan complements the antiparkinsonian moves of levodopa and decreases dyskinesia in MPTP dealt with primates. It has been proven time and again that stimulation of the noradrenergic device will beautify reminiscence retrieval idazoxan, will increase firing of noradrenergic neurons of the locus coeruleus twofold at a dose that has no detectable impact on overt conduct which includes locomotor pastime.

### Structure Relation Activity:

Although on the  $\alpha_1$ -adrenoreceptor all of the compounds displayed a widespread agonist pastime, on the  $\alpha_2$ -adrenoreceptor they confirmed both agonist or antagonist pastime relying on the character of the phenyl substituent. The qualitative structure–pastime courting led us to the realization that the oxygen atom withinside the side-chain is vital for  $\alpha_1$ -agonist pastime, at the same time as the cyclopropyl ring is not, and can be changed through numerous corporations. Of the corporations studied, isopropoxy seems to be the best. Instead, the identical substitution (i.e., isopropoxy for the cyclopropyl ring) at  $\alpha_2$ -adrenoreceptors reasons a reversal of pastime. On the different hand, the cyclopropyl ring appears to be important for  $\alpha_1$ -selectivity.



### Synthesis:



**Therapeutic uses:**

- It has antidepressant impact however has now no longer been reached the market
- Antipsychotic
- In pathogenesis of schizophrenia.

**Adverse reactions:**

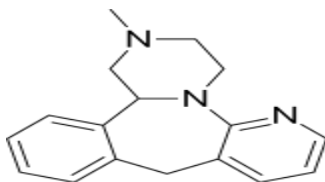
Dyskinesia is a common and disabling facet impact in sufferers with Parkinson's, Idazoxan without a doubt extends LDOPA's anti parkinsonian benefits.[17]

**Isradipine:**

Isradipine Fails to Slow Early Parkinson Disease Progression in Phase three Study.[19] Isradipine is a medicine presently used to deal with excessive blood strain and is going via way of means of the emblem call of DynaCirc®. It is classed as a calcium channel blocker. Isradipine stuck the eye of researchers for Parkinson's disease (PD) whilst facts from huge medical research confirmed that human beings taking isradipine had a decrease threat of growing PD. It is concept that during dopamine neurons withinside the brain, neurons which die in Parkinson's disease, the access of calcium in those neurons over time ends in damage. Isradipine blocks the interest of unique channels withinside the neuron that permit the calcium to enter, as a result stopping the dying of the neurons (nerve cells) that produce dopamine and might sluggish the development of PD. It isn't but recognized if Isradipine has useful results on PD. Data from the trial will offer greater statistics on its effectiveness in human beings with PD. In addition, low blood strain is a not unusual place symptom of PD, so this medicine can also additionally get worse the condition.

**MIRTAZAPINE:**

Pramipexole (Mirapex®) is a drug this is powerful at assuaging motion deficits related to Parkinson's disorder. However, pramipexole can set off compulsive behaviours and behavioral addictions, such as trouble gambling, in a few patients. Mirtazapine, an strange antidepressant reduces the consequences of drug dependancy in pre-scientific fashions and in humans. This examine targets to decide if mirtazapine can lessen pramipexole-brought on gambling-like conduct in a version of PD, even as leaving the motor blessings intact.[20] Psychotic signs regularly arise as a worry in Parkinson's disorder patients, and a fixed of standards for Parkinson's disorder with psychosis (PDPsy) has been established. Mirtazapine progressed the patient's refractory psychotic signs, specially her visible hallucinations, with out worsening her motor signs.

**Structure:**

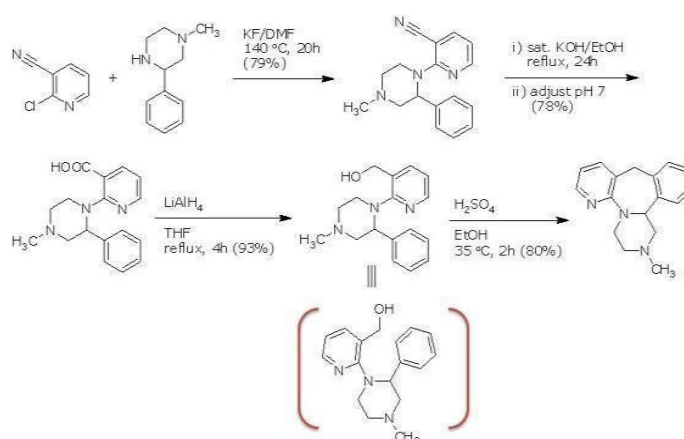
**IUPAC name:** (±)-2-Methyl- 1,2,3,4,10,14b hexahydropyrazino [2,1- a]pyrido[2,3-c],[2]benzazepine

**Molecular formula:** C<sub>17</sub>H<sub>19</sub>N<sub>3</sub> **Molecular weight:** 263.35 g/mol.

**Mechanism of action:**

- Blockade of pre-synaptic alpha 2 receptors, which reasons the growth withinside the launch of nor- epinephrine from the nor- adrenergic nerve endings and of serotonin from serotonergic nerve endings.
- Blockade of 5HT-2A Presynaptic receptors.
- Blockade of H1 receptors. (It isn't recognized which of this movements greater essential for the antidepressant effect.)



**Mirtazapine****Synthesis****Fig. 7: Synthesis of Mirtazapine Therapeutic uses.****Synthesis:**

- Psychosis associated Parkinson therapy
- Antidepressant

**Adverse reactions:**

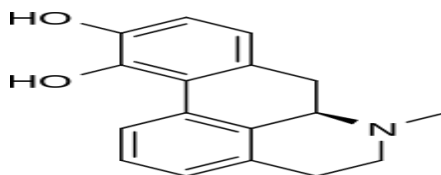
- Sedation and drowsiness.
- Constipation, urge for food stimulation, Weight gain.

**Contraindications:**

- REMERON (mirtazapine) Tablets are contraindicated in sufferers with a acknowledged allergic reaction to mirtazapine.
- Starting REMERON in a affected person who's being dealt with with MAOIs consisting of linezolid or intravenous methylene blue is likewise contraindicated due to an improved hazard of serotonin syndrome.

**Apomorphine INFUSION:**

**Apokyn (apomorphine)** is utilized by injection to deal with loss of frame motion manipulate in sufferers with superior Parkinson's ailment among doses of levodopa treatment. It has the equal impact as dopamine, a certainly going on chemical messenger observed withinside the brain.



IUPAC Name: (6aR)-6-methyl-5,6,6a,7-tetrahydro-4Hdibenzo[de,g]quinoline- 10,11-diol

Molecular formula: C<sub>17</sub>H<sub>17</sub>NO<sub>2</sub> Molecular weight: 267.332g/mol.

**Mechanism of action:**

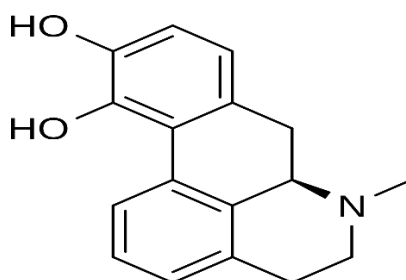
Apomorphine's R-enantiomer is an agonist of each D1 and D2 dopamine receptors, with better pastime at D2. Apomorphine improves motor feature with the aid of using activating dopamine receptors withinside the nigrostriatal pathway, the limbic system, the hypothalamus, and the pituitary gland. It additionally will increase blood go with the drift to the supplementary motor region and to the dorsolateral prefrontal cortex (stimulation of which has been located to lessen the tardive dyskinesia effects of L-DOPA). Parkinson's has additionally been located to have extra iron on the web sites of neurodegeneration; each the R- and S-enantiomers of apomorphine are potent iron chelators and radical scavengers. Apomorphine additionally reduces

the breakdown of dopamine within the brain (even though it inhibits its synthesis as well). [19][20] It is an effective up-regulator of several neural growth factors, [21] specifically NGF and BDNF, epigenetic down-regulation of which has been related to addictive behavior in rats.

Apomorphine causes vomiting with the aid of acting on dopamine receptors within the chemoreceptor trigger zone of the medulla; this turns on the nearby vomiting center.

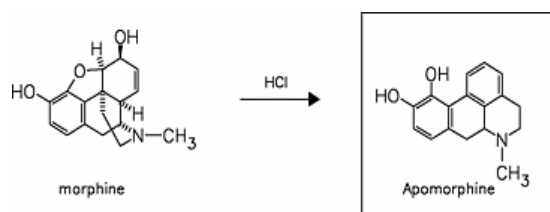
### Structure Activity relationship

- The side chain of dopamine (DA) is flexible (rotation around  $\beta$ -carbon phenyl bond).
- Compounds with catechol ring & amino-ethyl moiety of DA are held in inflexible conformation. Ex: Apomorphine.
- It has shape similarities in trans- $\alpha$ -rotamer conformation.



### STRUCTURE

#### Synthesis:



#### Therapeutic uses:

Apokyn can be used as much as 5 instances an afternoon as a small injection beneath the skin, the use of a tool just like the only used for insulin injection in human beings with diabetes. Apokyn begins off evolved operating as early as 10 mins after the injection, with maximum human beings feeling comfort from the "off" episode inside 20 mins. It typically lasts for as much as ninety mins, so it's critical sufferers now no longer forestall taking their different Parkinson's medications.

#### Adverse reactions:

Apokyn have to now no longer be occupied with drugs for nausea, vomiting, or irritable bowel syndrome, as critical facet results might also additionally occur, including seriously low blood stress and lack of consciousness.

#### Contraindications:

- The main and absolute contraindication to the use of apomorphine is the concurrent use of adrenergic receptor antagonists; combined, they reason an excessive drop in blood stress and fainting.
- IV management of apomorphine is extraordinarily discouraged, as it could crystallize within the veins and create a blood clot (thrombus) and block a pulmonary artery (pulmonary embolism).

## 2. DISCUSSION

Parkinson's disorder changed into observed in historic era. It changed into defined in historic writing. There isn't any precise remedy for PD however exceptional medicines are to be had that are used to deal with PD. The remedy consists of plant primarily based totally remedy, medicinal capsules inclusive of dopamine which replaces with dopamine substitute therapy, surgical remedy inclusive of deep mind stimulation (DBS). These signs are examined with the aid of using medicinal drug with levodopa. According to researchers there's desire for improvement for technique which now no longer handiest treatment plans PD however additionally assist to manage improvement of PD. The remedy is turning into greater state-of-the-art as there are new techniques are evolved as NOVEL DRUGS FOR PARKINSON which lead a course to deal with this neurodegenerative disorder, many capsules were observed and this play an crucial function in stopping the disorder. This novel capsules along side their medicinal chemistry

primarily based totally on its structure, synthesis, SAR'S, mechanism of action, healing uses, Adverse outcomes and contraindications etc. are mentioned above withinside the concept that's useful in drug layout and modulation.

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### 3. SUMMARY

Parkinson`s sickness is the maximum not unusual place Neuro-degenerative ailment. Several new medicines are observed, maximum of which can be versions of formerly present products, such new dosage kinds of already approved products, or cost-saving time- honored formulations the NOVEL DRUGS for its remedy were proposed. This thesis describes concerning the PARKINSON DISEASE and its hi story, genetics, the generally used tablets for its remedy and their medicinal chemistry and additionally it describes approximately the newly observed tablets for the remedy of this ailment alongside with their medicinal chemistry. This technique turned into mentioned to make out a quick concept concerning the medicine used these days maximum generally to deal with the sickness and the primary aim turned into to have a look at concerning tablets to get a clean concept approximately its chemistry which used for its method and in numerous different aspects.

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### 4. CONCLUSION

In conclusion, the technique has been implemented to apprehend the aetiology of PD and to discover its genetic reasons in addition to remedy strategies. Based at the strong and green technique implemented on this study, which turned into executed with out dimensionality reduction, greater biologically treasured consequences were obtained.

In this study, a few pills were proposed as novel remedies for PD. Parkinson`s ailment is maximum not unusual place form of motion ailment visible in medical practice. Early prognosis may be made with excessive index of suspicion. Most of the sufferers reply to dopa agonists or L- dopa preparations.

Parkinson`s ailment is an incurable ailment that has proved tough to manipulate and deal with with current therapies.

Disease change is the remaining aim for drug improvement however has, so far, remained elusive.

Several NOVEL DRUGS has been evolved and are determined beneficial for the remedy and prevention of Parkinson`s ailment as mentioned above i.e Istradefylline, Nilotinib, Safinamide, Stalevo, Ideosaxon, Ionosine, Mirtazapine, and it additionally offers a quick rationalization concerning their medicinal chemistry.

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