**REVIEW**

# Recent updates on structural insights of MAO-B inhibitors: a review on target-based approach

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## Abstract

Parkinson's disease is a neurodegenerative disorder characterized by slow movement, tremors, and stiffness caused due to loss of dopaminergic neurons caused in the brain's substantia nigra. The concentration of dopamine is decreased in the brain. Parkinson's disease may be happened because of various genetic and environmental factors. Parkinson's disease is related to the irregular expression of the monoamine oxidase (MAO) enzyme, precisely type B, which causes the oxidative deamination of biogenic amines such as dopamine. MAO-B inhibitors, available currently in the market, carry various adverse effects such as dizziness, nausea, vomiting, lightheadedness, fainting, etc. So, there is an urgent need to develop new MAO-B inhibitors with minimum side effects. In this review, we have included recently studied compounds (2018 onwards). Agrawal et al. reported MAO-B inhibitors with $IC_{50}$ 0.0051 µM and showed good binding affinity. Enriquez et al. reported a compound with $IC_{50}$ 144 nM and bind with some critical amino acid residue Tyr60, Ile198, and Ile199. This article also describes the structure–activity relationship of the compounds and clinical trial studies of related derivatives. These compounds may be used as lead compounds to develop potent compounds as MAO-B inhibitors.

## Abbreviations

| | |
|---|---|
| MAO | Monoamine oxidase |
| PD | Parkinson's disease |
| DA | Dopamine |
| FDA | The food and Drug Administration |
| TH | Tyrosine hydroxylase |
| AADC | Aromatic amino acid decarboxylase |
| DOPAC | 3,4-Dihydroxy phenylacetic acid |
| HMV | Homovanillic acid |
| DDC | Dopa decarboxylase |
| DAT | Dopamine transporter |
| COMT | Catechol-O-methyl transferase |
| FAD | Flavin adenine dinucleotide |
| MAOIs | MAO inhibitors |
| SAR | Structure–activity relationship |
| BHT | Butylated hydroxytoluene |
| EWG | Electron-withdrawing group |
| EDG | Electron donating group |
| BBB | Blood Brain Barrier |
| CNS | Central nervous system |

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## Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disease clinically known as a movement disorder. It is a leading cause of motor problems and mental disabilities [1, 2]. Loss of dopaminergic neurons in substantia nigra which results in reduction in the concentration of dopamine (which is an inhibitory neurotransmitter) in the brain [3–5] is characteristic in PD. Due to inadequate dopamine concentration (Fig. 1), there is less inhibition of striatal neurons(control the balance of body movements), which is responsible for the difficulty in controlling movements in PD patients [6].

Age is a significant risk factor in Parkinson's disease development, majorly older people are affected, but people below the age of 21 years(juvenile cases) are also affected [7, 8]. There are two types of symptoms of PD, motor symptoms such as tremors, stiffness, and slow movements, and a problem with balance and non-motor symptoms such as depression, insomnia, and cognitive dysfunction [9, 10]. Parkinsonism caused by Parkinson's disease is called primary
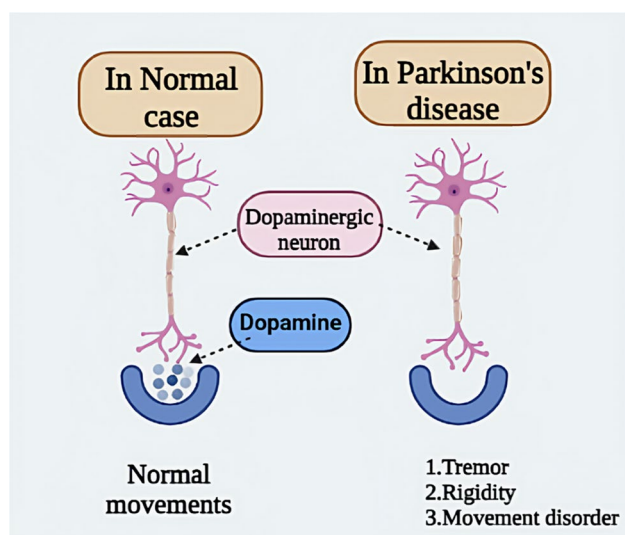
**Fig. 1** Normal neurons v/s neurons in Parkinson's disease

parkinsonism, and the parkinsonism caused by other neurodegenerative diseases is called secondary parkinsonism [11, 12]. Parkinson's disease is a multifactorial condition that contains genetic and various environmental factors which give rise to the genesis of the disease [1]. This disease has diverse nature as its symptomology differs from one individual to another; this disease may be influenced by demographical factors, environmental factors, and exposure to some neurotoxins which target the substantia nigra neurons [13]. Risk factors that may cause PD are exposure to some pesticides or cleaning chemicals, old age, family history, and inhalation of heavy metals [14–16]. The most important mechanisms involved in the development of Parkinson's disease include misfolded aggregates of proteins, oxidative stress, mitochondrial damage, failure of protein clearance pathway, neuroinflammation, and genetic mutation [17, 18]. According to the survey, the prevalence of Parkinson's disease in elderly patients ranges from 20 to 70% [19]. A report by global trends 2019 suggested that the age-standardized incidence rate of Parkinson's disease was 13.43/100,000 [20]. For society, Parkinson's disease conveys a mounting socioeconomic burden [9]. Cases of Parkinson's disease are higher in men than women, which may be due to estrogen, which may act as a neuroprotective agent. The risk of disease development is lower in females, but they have higher mortality and progression of the disease [21, 22]. Out of various reasons, the leading cause of PD is recognized as the irregular expression of mitochondrial monoamine oxidases (MAO) enzyme, which may be related to the unnecessary metabolism of monoamine neurotransmitters, responsible for various neurodegenerative disorders [23–26].

The therapy which is currently in use focuses on treating PD by improving motor problems by increasing the dopamine concentration in the brain or by stimulating the dopamine (DA) receptors [27, 28]. Approved drugs that are used to treat Parkinson's disease (Fig. 2). Dopamine precursor Levodopa, Carbidopa/Benserazide [29, 30], which are peripheral decarboxylase inhibitors. Agonists of dopamine receptors such as pramipexole/Apomorphine [31]. MAO-B inhibitors [32] such as Selegiline/Rasagiline/Safinamide. COMT inhibitors [33] as Tolcapone/Opicapone/Entacapone comprises the approved drugs which are in use to treat Parkinson's disease.rasagiline and Selegiline are irreversible MAO-B inhibitors, whereas Safinamide is a reversible MAO-B inhibitor recently approved by the food and Drug Administration (FDA) as an anti-parkinsonian agent [34, 35]. However, these drugs have limitations, such as safinamide causing retinopathy and several clinical problems in patients with liver impairment [36]. So, there is an urgent need to design and develop novel reversible MAO-B inhibitors to circumvent these problems. Other than MAO-B other targets which can be used to treat PD are α-Syn, Glutamate receptors, Molecular chaperones and autophagic pathways, and GPR109A [37]. PD belongs to synucleinopathy which develops with time. Degeneration of dopaminergic neurons and accumulation of *alpha-syn* protein intracellularly as Lewy bodies is the major reason for pathology of PD progression [38]. *Glutamate receptors* modulate neural transmission in basal ganglia and this ability of glutamate receptors is used as possible targets for the treatment of PD. The primary motor symptoms of PD are alleviated due to modulated activity of the receptors in the dopamine replacement therapy. The reduced progression of PD is delaying the neurodegenerative process due to the antagonism of these receptors [39]. Molecular chaperones regulate cellular proteostasis by balancing the folding and misfolding processes. Misfolded proteins are corrected by the chaperone system and contribute to proteostasis. In the PD brain, autophagic mechanisms are markedly dysregulated. The autophagic mechanisms that influence the illness phenotype include genes associated to PD [40, 41]. *GPR109A* is a G protein-coupled receptor which is also knowns as hydroxycarboxylic acid receptor 2. The GPR109A is found in macrophages and has a role in inflammation. In PD, GPR109A mediates inflammatory action in PD and can be targeted for treatment [42]. Various medications are used to treat PD, but MAO-B inhibitors play a significant role in treating PD. MAO-B inhibitors reduce the degradation of dopamine by penetrating the blood–brain barrier and inhibit central MAO activity [43]. MAO-B inhibitors showed very good safety and efficacy in early and advanced stages of PD. It is reported in some clinical studies that when the patient use the MAO-B inhibitors for a longer duration there is a decrease in the consumption of levodopa [44, 45].

**Fig. 2** Approved drugs to treat Parkinson's disease
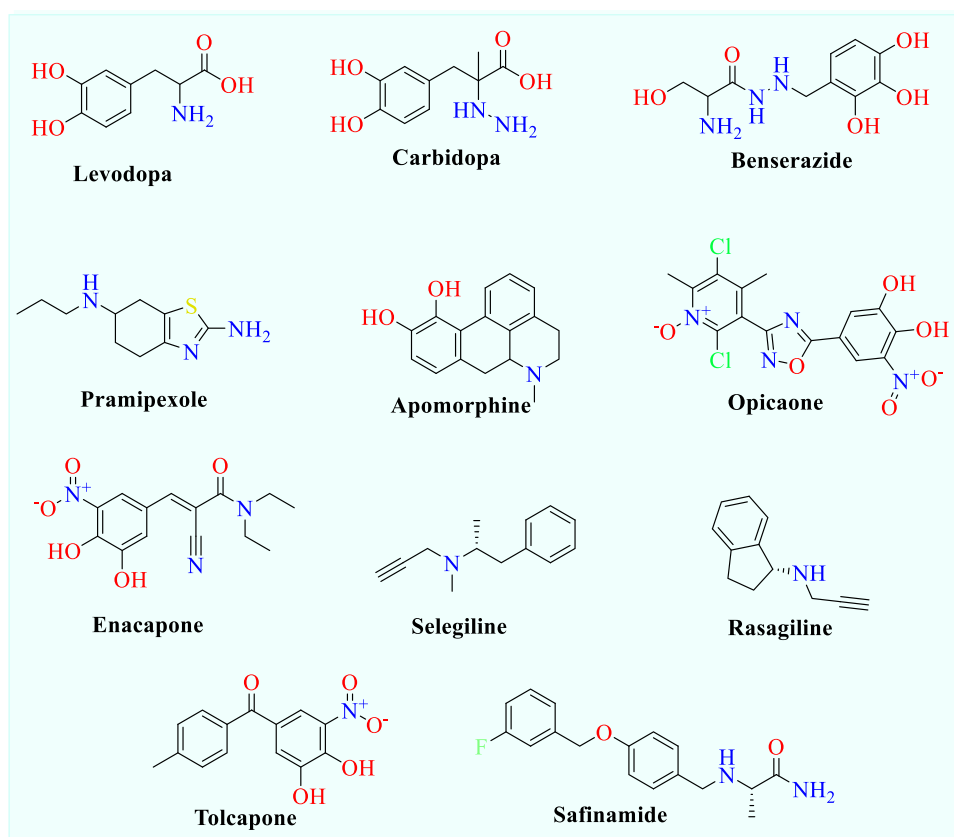


## Mechanism of anti-parkinsonian drugs

Tyrosine, which is transferred from the blood–brain barrier, is converted to levodopa with the help of Tyrosine hydroxylase (TH) (Fig. 3). Levodopa is then converted to Dopamine by aromatic amino acid decarboxylase (AADC) [46–48]. Dopamine formed is stored in vesicles until they are released into the synaptic cleft and binds and activates dopamine receptors in the striatum's neurons [49, 50]. The free dopamine is metabolized by the MAO-B enzyme into 3,4-dihydroxy phenylacetic acid (DOPAC) and further converted to Homovanillic acid (HMV) by COMT [51, 52]. Levodopa used in the treatment of PD, is a Dopamine precursor. Levodopa can cross the blood–brain barrier and be converted to Dopamine by the Dopa decarboxylase (DDC) enzyme in the presynaptic neuron of substantia nigra [53, 54]. The Dopamine formed is stored in vesicles until they are released into the synaptic cleft and binds and activates dopamine receptors on the neurons of the striatum, which control the motor activities of the body, smoothening movements and reducing muscle tone [55, 56]. After binding to the receptors and its activation, the DA quickly unbound from the receptor reuptake by the Dopamine transporter (DAT) [57, 58].

Levodopa in the periphery is susceptible to the metabolism by Catechol-O-methyl transferase (COMT), which can be inhibited by drugs such as Tolcapone or Entacapone and Dopa decarboxylase (DDC), which are inhibited by drugs such as Carbidopa or Benserazide [59, 60].

To prevent the metabolism of Dopamine in the brain, drugs such as MAO-B (Monoamine oxidase type B) inhibitors (Selegiline, Rasagiline, Safinamide) and COMT inhibitors (Tolcapone or Entacapone) are used [61, 62]. In addition, dopamine receptor agonists (Bromocriptine, Pramipexole, Ropinirole) activate the Dopamine receptors, which further control the mobility of the body [63, 64].

## Problems in currently available mao inhibitors

The major metabolic enzymes for regulating biogenic amine levels in the brain and other tissues are monoamine oxidases (MAOs). They are present in the outer membrane of mitochondria [65].

There are two isoforms of this enzyme, MAO-A and MAO-B which are around 70% the same in amino acid sequence and have a similar structure of the active site [66]. All human tissues contain MAOs, but MAO-A predominates in the gastrointestinal system, placenta, and heart, whereas MAO-B predominates in platelets and glial cells in the brain [67]. MAOs are linked covalently to flavin adenine dinucleotide (FAD) [68]. The substrates for MAO-A are adrenaline and serotonin, whereas for MAO-B, the substrates are benzylamine and phenylethylamine

**Fig. 3** Mechanism of action of Drugs which are used in Parkinson's disease. *COMT* catechol-O-methyl transferase, *DA* dopamine, *DDC* dopa-decarboxylase, *DOPAC* 3,4-dihydroxyphenylacetic acid, *HVA* homovanillic acid, *L-DOPA* levodopa, *MAO-B* monoamine oxidase B, *3-MT* 3-methoxytyramine, *3-O-MD* 3-O-methyldopa, *DAT* dopamine transporter
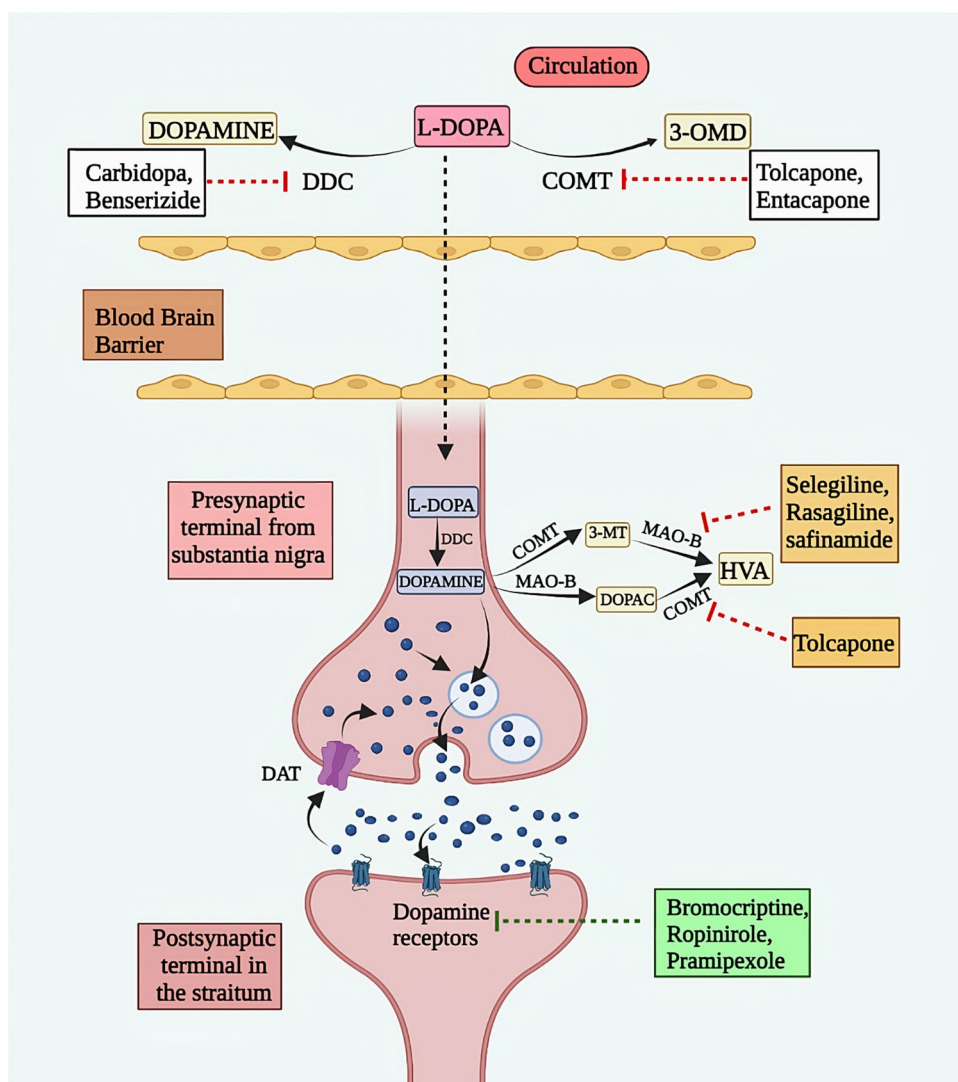
[69, 70]. Inhibitors of the MAO-A enzyme have therapeutic value against depression and anxiety, and MAO-B inhibitors are used in the treatment of Parkinson's disease and Alzheimer's disease [71, 72]. Earlier non-selective MAOs inhibitors were used, which were irreversible, but because of their toxicity, their use was reduced because Tyramine enters the systemic circulation when MAO-A is irreversibly blocked, which causes the release of norepinephrine from peripheral adrenergic neurons resulting in a hypertensive crisis, sometimes known as the "cheese reaction" [73]. It is a highly effective and helpful strategy to create novel MAO inhibitors (MAOIs) for treating various neurological and psychiatric illnesses [74]. So reversible inhibitors of MAO-A, such as moclobemide and clorgyline are used in the treatment of depression [75, 76], but these drugs have some adverse effects, such as headache, insomnia, and liver damage [77]. MAO inhibitors used in the treatment of depressive disorder, may promote the impairment of cognition and result in the progression of dementia

[78]. Drugs that are in use in the treatment of Parkinson's disease areSelegiline, Rasagiline, and safinamide, which are the selective inhibitors of MAO-B [79]. Selegiline and Rasagiline's lack of an apparent neuroprotective effect in clinical trials restricts their therapeutic applicability [80]. The main side effects of Selegiline, when used to treat Parkinson's disease, are hypotension, vertigo, and akinesia [81, 82]. It was also suggested that MAO inhibitors might have anticancer properties. Multiple cancer cells have been shown to overexpress MAO, and inhibiting the enzyme had an antiproliferative effect [83]. Rasagiline is an irreversible inhibitor of MAO-B, and it binds covalently with the active site resulting in side effects, but safinamide is a reversible inhibitor with lesser side effects [84, 85]. But safinamide cause retinopathy and several clinical problems in patients with liver impairment [36]. Due to all these limitations of the currently present MAO inhibitors, there is a demand to develop novel MAO-B inhibitors that could be used to treat Parkinson's disease.

## Recent advancements

In a study, Yeon et al. synthesized a novel series of 4-(Benzyloxy)phenyl and Biphenyl-4-yl derivatives for monoamine oxidase B (MAO-B) inhibition. In the synthesized series, compound **1** showed potential activity with an $IC_{50}$ value of 0.009 µM against MAO-B. Additionally, structure–activity relationship (SAR) studies showed that compounds that carried no carbon between biaryl-linked units showed lower inhibitory activity. At the same time, amine and trifluoromethyl substitutions at the para position were responsible for the more significant activity of compounds rather than ortho or meta substituents. Furthermore, according to substrate-dependent kinetics, compound 1 was a competitive MAO-B inhibitor. In vivo study of compound **1** for Parkinson's disease by MPTP assay showed improved motor impairment activity further correlated with MAO-B inhibitory activity in the brain. The most potent compound **1** (4-((4-(Trifluoromethyl)benzyl) oxy)phenyl)methanaminium chloride, showed better activity against PD, and it was found in the shielding of Dopaminergic neurons. Several behavioral abnormalities have been observed with the MPTP-induced mouse model used in the treatment of PD. (Fig. 4) showed the various substituents and linkers for generating potential compounds as MAO-B inhibitors [86].

Mellado et al. reported a new series of seven prenylated chalcone derivatives against MAOs. Out of those seven derivatives, compound **3** (E)-3-(4-(Dimethylamino) phenyl)-1-(4-hydroxy-3-(3-methylbut-2-en-1-yl)phenyl) prop-2-en-1-one showed the most potent MAO-B inhibitory activity with an $IC_{50}$ value of 8.19 µM. Furthermore, structure–activity relationship (SAR) studies revealed that Phenyl and methoxy group substitution inactivates the compound due to steric impedance at the active site of the enzyme, ortho substitution is less active than para substitution, and introduction of dimethylamino group increased the MAOs inhibitory potency (Fig. 5). The Kinetics study indicated that compound **3** competitively inhibited the enzyme MAO-B. It was found that compounds **2** (E)-1-(4-Hydroxy-3-(3-methylbut-2-en-1-yl)phenyl)-3-(4-methoxyphenyl)prop-2-en-1-one and **3** showed potential MAOs inhibitory activity with better antioxidant activity as compared to standard compound BHT (Butylated hydroxytoluene). The molecular docking studies showed that the activities of MAO-B inhibitors are related to hydrogen bonds and hydrophobic bonds with Tyr398 and Tyr435 amino acid residues, respectively. So, these compounds can be suitable candidates for lead discovery for PD [87].

Agrawal et al. designed and synthesized a series of isoxazole carbohydrazides derivatives against MAOs enzyme. In vitro studies showed that compounds did not show significant activity against MAO-A, but some compounds showed MAO-B inhibitory activity at $IC_{50}$ equal to 50 µM. Compound **4** (Z)-5-Phenyl-N'-(1-(m-tolyl)ethylidene)isoxazole-3-carbohydrazide, which carried a methyl group at the para position of the phenyl ring, appeared as the most potent MAO-B inhibitor with an $IC_{50}$ value of 0.0051 µM, followed by compound **5** (Z)-N'-(1-(3,4-Dimethoxyphenyl)

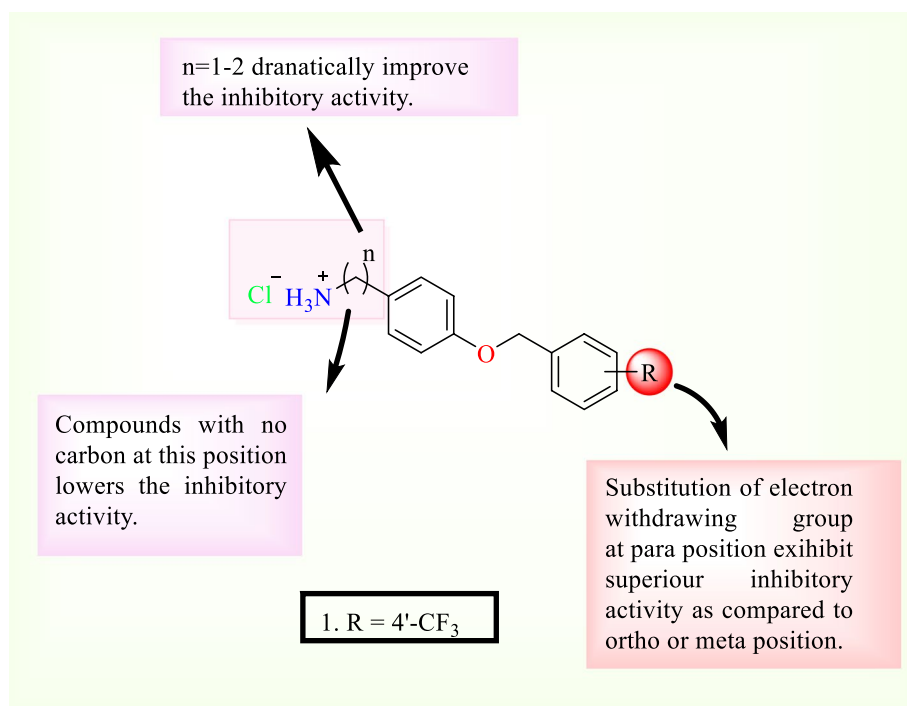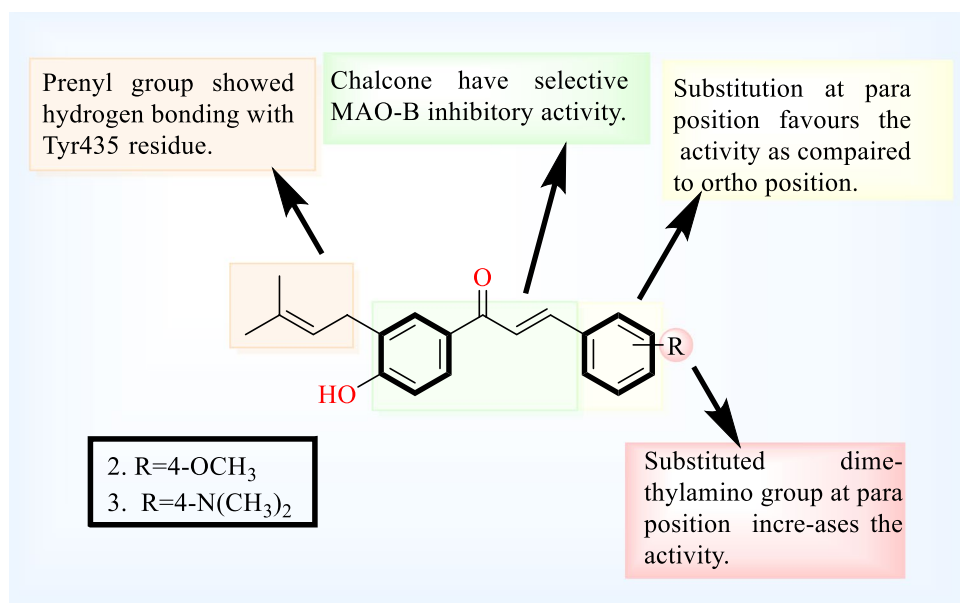**Fig. 4** 4-(benzyloxy)phenyl derivatives as MAO-B inhibitors

**Fig. 5** Prenylated chalcone derivatives as MAO-B inhibitors



Prenyl group showed hydrogen bonding with Tyr435 residue.

Chalcone have selective MAO-B inhibitory activity.

Substitution at para position favours the activity as compaired to ortho position.

Substituted dimethylamino group at para position incre-ases the activity.
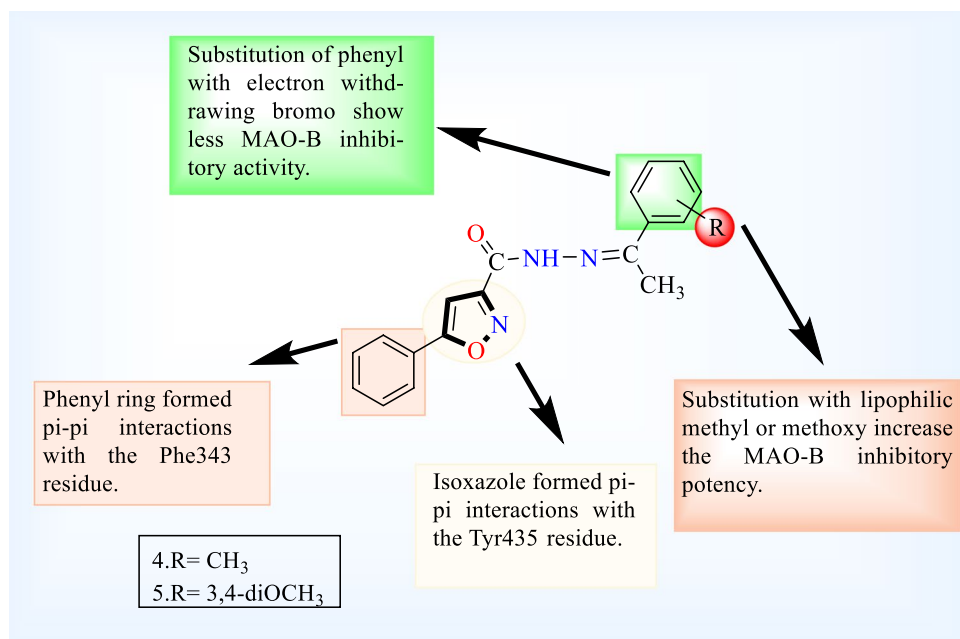
2. R=4-OCH$_3$
3. R=4-N(CH$_3$)$_2$

ethylidene)-5-phenylisoxazole-3-carbohydrazide with methoxy substituent at the meta and para positions of phenyl ring showed an IC$_{50}$ value of 0.0059 µM. The SAR showed that the substitution of the phenyl ring with the electron-withdrawing group (EWG) decreased the activity, and substituting the electron-donating group (EDG) improves the activity (Fig. 6). The enzyme kinetic studies revealed that compounds **4** and **5** were reversible and competitive inhibitors. The docking studies further unlocked the potent inhibitors' binding site interactions, and compounds fit well in the active site of MAO-B near the FAD cofactor. The synthesized compounds were subjected to in silico ADME

evaluation. All the compounds displayed favorable ADME profiles and were predicted to have good oral bioavailability. Thus, the active compounds **4** and **5** obtained in this series can be promising leads for developing isoxazole-based potent MAO-B inhibitors for treating PD [88].

In a recent study, Parambi et al. reported the synthesis of 26 oxygenated chalcone derivatives as the inhibitors of MAOs enzyme. All derivatives were potent against MAO-B, out of which compound **6** (E)-1-(Benzo[d][1,3]dioxol-5-yl)-3-(4-fluorophenyl)prop-2-en-1-one**,** was the most potent compound with an IC$_{50}$ value of 0.0021 µM. On the other hand, most of the derivatives potently inhibited MAO-A,

**Fig. 6** Isoxazole carbohydrazide derivatives as MAO-B inhibitors



Substitution of phenyl with electron withdrawing bromo show less MAO-B inhibitory activity.

Phenyl ring formed pi-pi interactions with the Phe343 residue.

Isoxazole formed pi-pi interactions with the Tyr435 residue.

Substitution with lipophilic methyl or methoxy increase the MAO-B inhibitory potency.

4.R= CH$_3$
5.R= 3,4-diOCH$_3$

and Compound **7** (E)-1-(Benzo[d][1,3]dioxol-5-yl)-3-(4-ethylphenyl)prop-2-en-1-one**,** was the most potent MAO-A inhibitor showed an $IC_{50}$ value of 0.029 μM. Additionally, dialysis experiments showed that compounds **6** and **7** were reversible inhibitions of the MAOs enzyme. The SAR studies disclosed that replacement of halogen atoms such as fluorine from para to any other position results in a decrease in the MAO-B inhibition, ethyl group at para position results in non-selective MAO-A inhibition and increasing the number of 'n' (number of alkyl groups between two oxygen atoms) results in an increase of inhibition potency (Fig. 7). The Kinetic studies showed that **6** and **7** competitively inhibited both the MAO isoforms, MAO-A and MAO-B ($K_i$ values of 0.016 and 0.00050 μM respectively). Cytotoxicity studies

revealed that potent compounds were non-toxic at 200 μg/ml with a tiny percentage of cell death [89].

Enriquez et al. reported twelve novel 3-thiophenylcoumarins as effective inhibitors of MAOs enzyme. Compound **8** 3-(4-Bromothiophen-2-yl)-7-hydroxy-2H-chromen-2-one was found to be the most potent compound with an $IC_{50}$ value of 144 nM. Additionally, structure–activity relationship studies (Fig. 8) showed that the presence of a hydroxy group at 8-position of coumarin enhances the MAO-A inhibitory activity, coumarin scaffold is essential for activity, selectivity for MAO-B increased when a single hydroxy group is present at 7-position of the coumarin ring. The Kinetics studies showed that compounds were reversible inhibitors. The derivatives showed neuroprotective agents
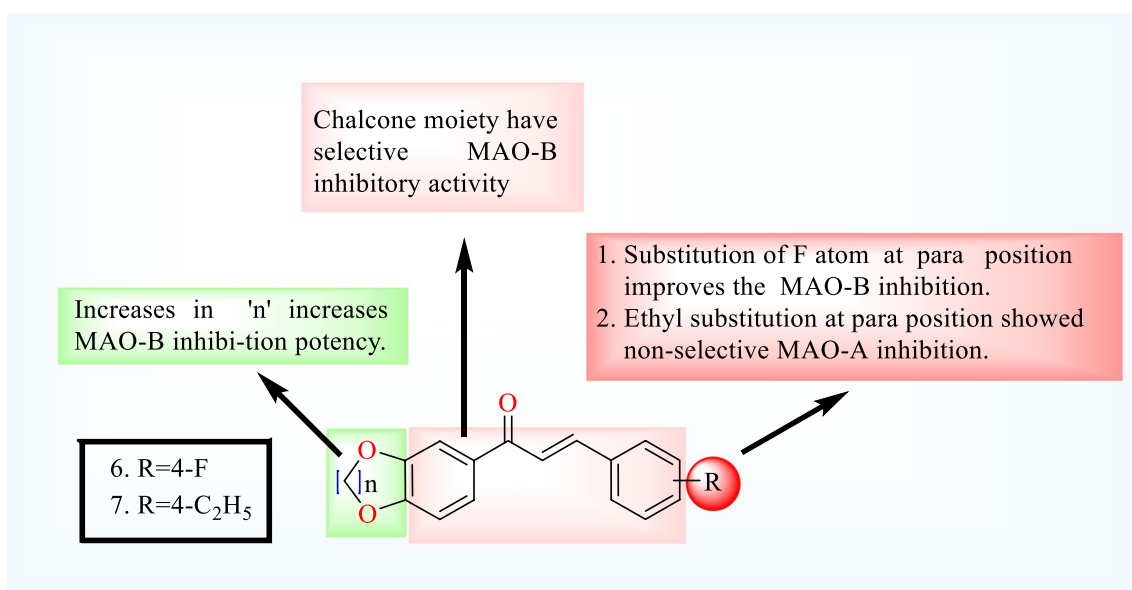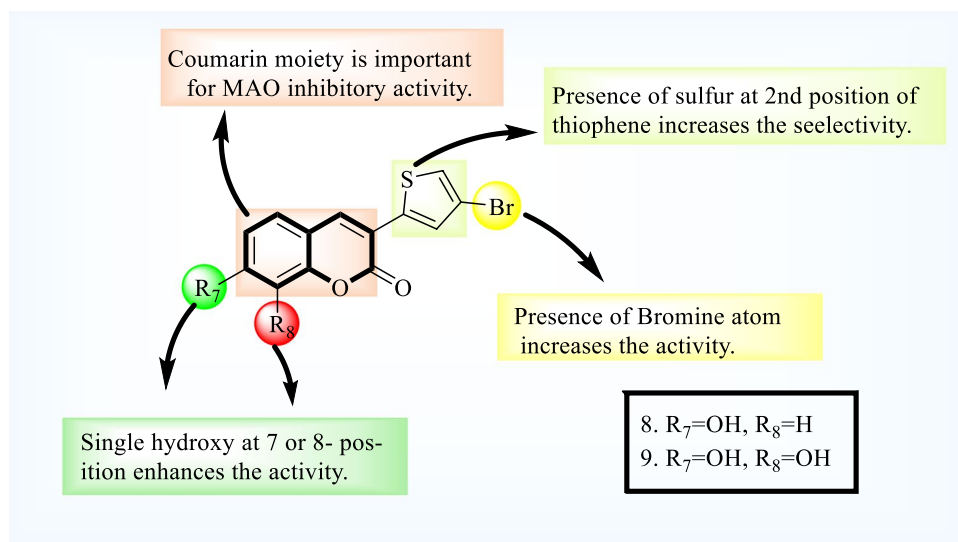


**Fig. 7** Oxygenated chalcone derivatives as MAO-B inhibitors

**Fig. 8** 3-thiophenylcoumarins derivatives as MAO-B inhibitors

in patients who were suffering from Parkinson's Disease according to free radical scavenging assay. In this assay, compound **9** 3-(4-Bromothiophen-2-yl)-7,8-dihydroxy-2H-chromen-2-one displayed an $EC_{50}$ value of 5.82 µM near the $EC_{50}$ value of vitamin C i.e., 5.02 µM. MTT (dimethyl-diphenyltetrazolium bromide) method was used to check the neurotoxicity profile of the compounds, and it found that there is a significant decrease in cell viability. Compound **9** was evaluated against ROS (reactive oxygen species) in SH-SY5Y using DCFDA assay (conversion of dichlorofluo-rescindiacetate to fluorescence dye dichlorofluorescein) and found that the compounds showed a significant effect against ROS formation. In vivo studies on the most potent compound **8** revealed an increased locomotor activity, time percentage in movement, and movement velocity compared to reference compound selegiline. All the compounds showed a good pharmacokinetic profile and suitable physicochemical parameters in silico methods to be used as a candidate for lead optimization [90].

The same research group synthesized twelve novel Coumarin-pyridazine derivatives as MAO-B inhibitors. In vitro studies showed compound **3** was the most potent compound with an $IC_{50}$ value of 60 nM against MAO-B. In vivo studies suggested compound **10** 7-Bromo-3-(6-bromopyridazin-3-yl)-2H-chromen-2-one was a promising anti-parkinsonian agent. In structure–activity relationship studies, it was found that the presence of a bromine atom at C6 of pyridazine was good for the activity, and an additional increase in the inhibitory potency and selectivity was observed when bromine atom was present at the coumarin fragment, particularly at C7 (Fig. 9). In silico (by ADME-Tox prediction) study suggested that all the compounds exhibited drug-like properties [91]. The molecular docking studies disclosed some critical amino acid residues, such as Tyr60, Ile198, and Ile199, responsible for the activity of these coumarin-pyridazine derivatives [91].

Saglik et al. designed and synthesized a series of novel Benzylamine-sulphonamide derivatives for MAO-B. The structure was determined using spectroscopic methods such as $^1$H-NMR, $^{13}$C-NMR, and HRMS. In vitro studies revealed that all the compounds selectively inhibit the MAO-B enzyme and compounds **11** N-benzyl-2-((5-chlorobenzo[d]thiazol-2-yl)thio)-N-(4-sulfamoylphenyl)acetamide and compound **12** 2-((5-chlorobenzo[d]thiazol-2-yl)thio)-N-(3-methylbenzyl)-N-(4-sulfamoylphenyl)acetamide were found to be most potent with $IC_{50}$ values of 0.041 µM and 0.065 µM, respectively. In contrast, the reference compound selegiline had an $IC_{50}$ value of 0.037 µM. Additionally, structure–activity relationship studies showed that the Presence of the sulfonamide group increased the inhibitory activity, the presence of the electron-withdrawing group ($NO_2$) decreased the activity, and the Presence of the Benzothiazole enhanced the MAO-B inhibitory activity (Fig. 10). Kinetics studies revealed that compounds **11** and **12** showed a reversible and non-competitive inhibition in contrast to the conventional MAO inhibitors which were irreversible. Cytotoxicity assay was performed against the NIH3T3 cell line and found that compounds **11** and **12** showed an $IC_{50}$ value of greater than 1000 which is significantly higher than the effective concentration, and it can be concluded that these compounds were non-cytotoxic at their effective concentration. Molecular docking studies were performed for compound **11,** and found that it has a good binding affinity with the MAO-B enzyme [92].

In a study, Mathew et al. synthesized ten derivatives of methylthiosemicarbazones and evaluated them against MAOs and acetylcholinesterase. The most potent activity was shown by compounds **13** (E)-2-(1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)ethylidene)-N-methylhydrazine-1-carbothioamide**, compound **14** (E)-N-methyl-2-(1-(4-morpholinophenyl)ethylidene)hydrazine-1-carbothioamide**, and compound **15** (E)-2-(1-(4-ethoxyphenyl)ethylidene)-N-

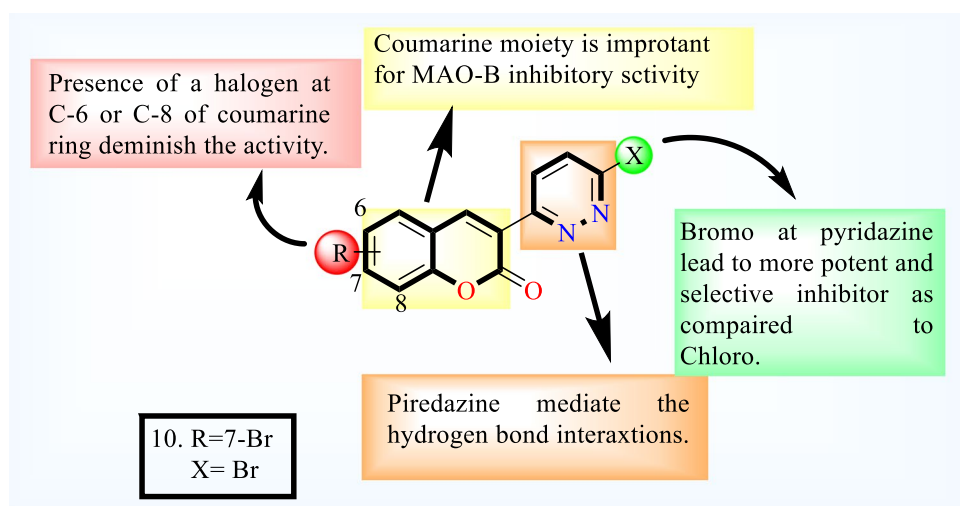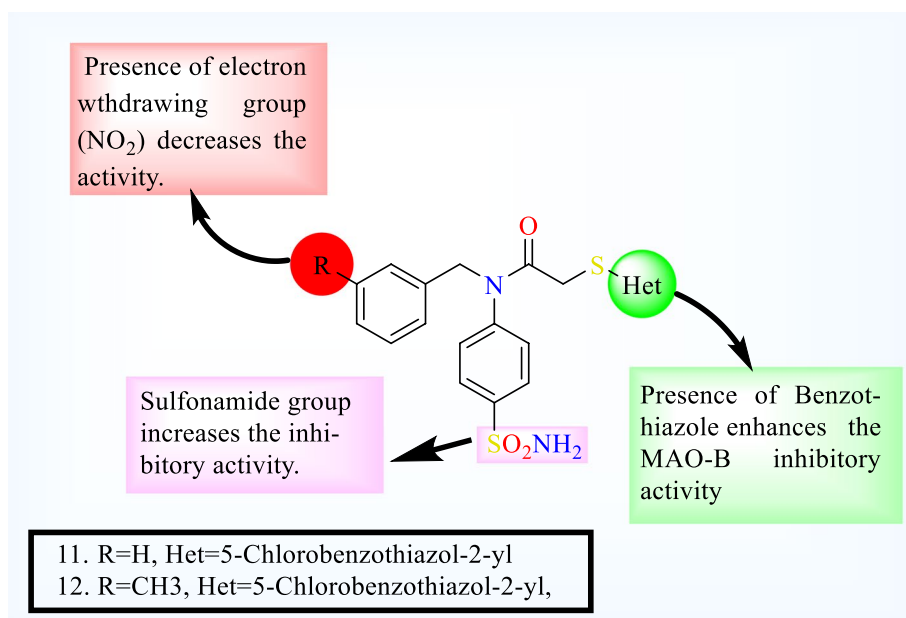**Fig. 9** Coumarin-pyridazine derivatives as MAO-B inhibitors

**Fig. 10** Benzylamine-sulphon-amide derivatives as MAO-B inhibitors

Presence of electron wthdrawing group ($NO_2$) decreases the activity.

Presence of Benzothiazole enhances the MAO-B inhibitory activity

Sulfonamide group increases the inhibitory activity.

$SO_2NH_2$

11. R=H, Het=5-Chlorobenzothiazol-2-yl
12. R=CH3, Het=5-Chlorobenzothiazol-2-yl,

methylhydrazine-1-carbothioamide with $IC_{50}$ values 5.48, 7.06, and 8.03 μM, respectively. Additionally, SARs studies showed that the Presence of morpholine moiety is important for activity, compounds which contain five-membered attachments were less potent than the compounds which contain a six-membered attachment, and the introduction of methylenedioxy ring increases the activity (Fig. 11). Kinetics studies which were performed on compound **14**, revealed that compound **14** is a competitive and reversible inhibitor of MAO-B with a mean $K_i$ value of 2.39 μM. Cytotoxicity

studies revealed that **14** is non-toxic to (African green monkey kidney cells) Vero cells ($IC_{50}$ = 198.95 μg/mL). In silico studies revealed that compound **14** interacted with Tyr326 of MAO-B with pi-pi interactions and hydrophobic interactions, which played a vital role in holding the phenyl system in the entrance cavity of monoamine oxidase B enzyme [93, 94].

Lazewska et al. reported a novel series of 27 compounds based on 1-(3-(4-*tert*-butylphenoxy)propyl)piperidine ( compound **16b**) as MAO-B inhibitors. Compound
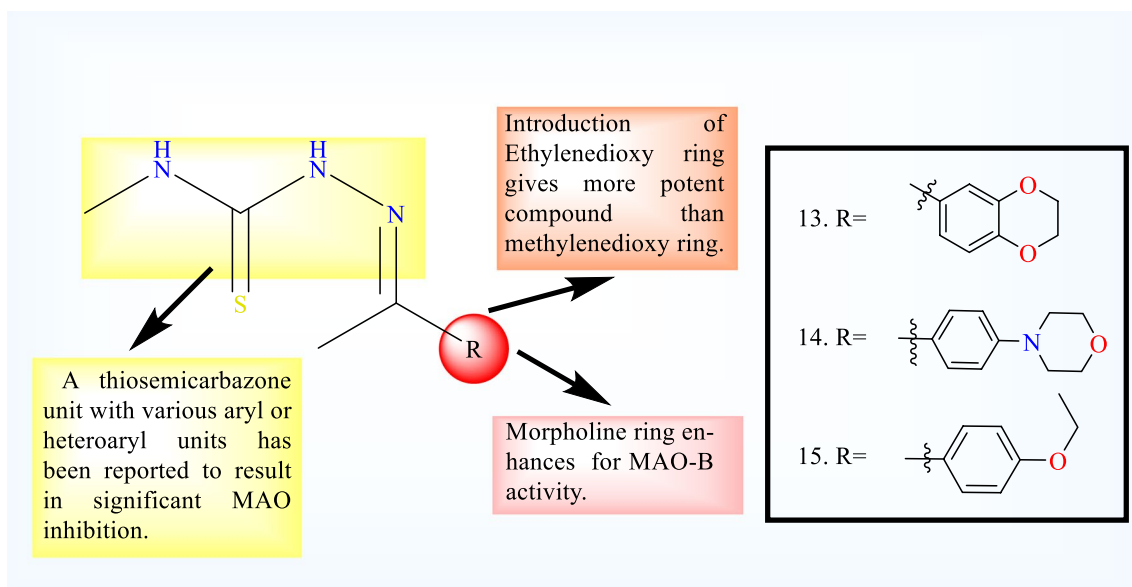
Introduction of Ethylenedioxy ring gives more potent compound than methylenedioxy ring.

A thiosemicarbazone unit with various aryl or heteroaryl units has been reported to result in significant MAO inhibition.

Morpholine ring enhances for MAO-B activity.

13. R=

14. R=

15. R=

**Fig. 11** Methylthiosemicarbazone derivatives as MAO-B inhibitors

**16a** 1-(3-(4-(tert-butyl)phenoxy)propyl)pyrrolidine was the most potent (IC$_{50}$ = 2.7 nM), even higher than the reference compounds rasagiline and safinamide. The Structure–activity relationship studies showed that compounds that contain a cyclic amine moiety (such as pyrrolidine and piperidine) played a very significant role in hMAO-B inhibition. A decrease in activity was observed with an increase in the length of the linker carbon chain (Fig. 12). According to reversibility studies it was found that all the tested compounds are reversible inhibitors. The Kinetic studies suggested that the compounds have a mixed mode of inhibition. In vitro toxicity studies in the HER293 cell line revealed that **16b** is safe at 50 μM concentration. In vivo studies showed that **16b** possesses significant anti-parkinsonian as observed in the cross-leg position test, but a low positive effect was seen in the bar test [95].

In a recent study, Panova et al. synthesized a series of pyrazolo[1,5-a]qunoxalin-4-ones derivatives as MAOs inhibitors. Compound **17** 2-(4-methoxyphenyl)-4-oxo-1l2,10l4-pyrazolo[2,3-a]quinoxaline-5(4H)-carbonitrile (IC$_{50}$ = 0.763 μM) and compound **18** 5-acetamido-4-oxo-2-phenyl-4,5-dihydro-1l2,10l4-pyrazolo[2,3-a]quinoxalin-7-yl acetate (IC$_{50}$ = 0.181 μM) were specific inhibitors of MAO-A and MAO-B respectively. Compound **19** 5-acetamido-2-(4-chlorophenyl)-4-oxo-4,5-dihydro-1l2,10l4-pyrazolo[2,3-a]quinoxalin-7-yl acetate (IC$_{50}$ = 0.028 μM) was found to be the most potent inhibitor of MAO-A.
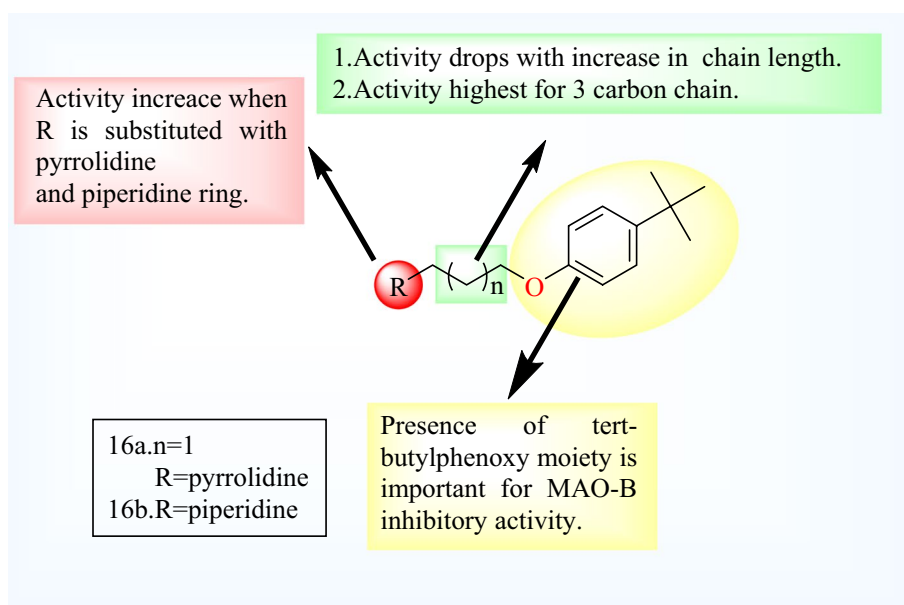
Additionally, SAR studies showed that the substituted chlorophenyl group at R$_1$ is suitable for MAO-A inhibition, the Presence of the CN group at R$_2$ improves the MAO-B specificity, and the acetyl group at R$_3$ is essential for inhibitory activity (Fig. 13) [96].

Li et al. designed and synthesized pyridoxine-resveratrol derivatives as MAO-B inhibitors. In vitro studies revealed that compounds **20** (E)-3-(2-(2,2,8-trimethyl-4H-[1,3] dioxino[4,5-c]pyridin-5-yl)vinyl)phenol, compound **21** (E)-N-methyl-N-(prop-2-yn-1-yl)-4-(2-(2,2,8-trimethyl-4H-[1,3] dioxino[4,5-c]pyridin-5-yl)vinyl)aniline**, and **22** (E)-2,2,8-trimethyl-5-(4-(4-methylpiperazin-1-yl)styryl)-4H-[1,3] dioxino[4,5-c]pyridine were the most potent inhibitors with IC$_{50}$ values 0.01 μM, 0.01 μM, and 0.02 μM, respectively.

The Structure–activity relationship studies revealed that a decrease in the ability of electron-donating substituent would decrease the inhibitory activity, significant reduction of the activity observed when N-methyl-N-propargylamine is replaced with N, N-propargylamine. No change in activity when there is an extension of the carbon chain. The Presence of a cyclic amine group was found on the aromatic ring (Fig. 14). According to reversibility studies, it was found that compounds **20** and **22** were reversible inhibitors, but compound **21** was an irreversible inhibitor. Molecular docking of the most potent compound with the MAO enzyme revealed modes of interaction such as hydrogen bonds, hydrophobic interactions, and π–π interactions. The binding energy of compound **20** was found to be − 9.44 kcal/mol and − 11.65 kcal/mol for MAO-A and MAO-B, respectively. Synthesized compounds were checked for antioxidant activity, and results revealed that the compounds have good antioxidant activity and antioxidant capacity index between 1.98 and 2.89. All three derivatives showed a high blood–brain barrier permeability and the neuroprotective effect on H$_2$O$_2$-induced PC-12 cell injury. So they can become excellent MAO-B inhibitors [97].

In a study, Osmaniye et al. reported a new series of thiosemicarbazide derivatives and evaluated them



**Fig. 12** 1-(3-(4-*tert*-butylphenoxy)propyl)piperidine derivatives as MAO-B inhibitors
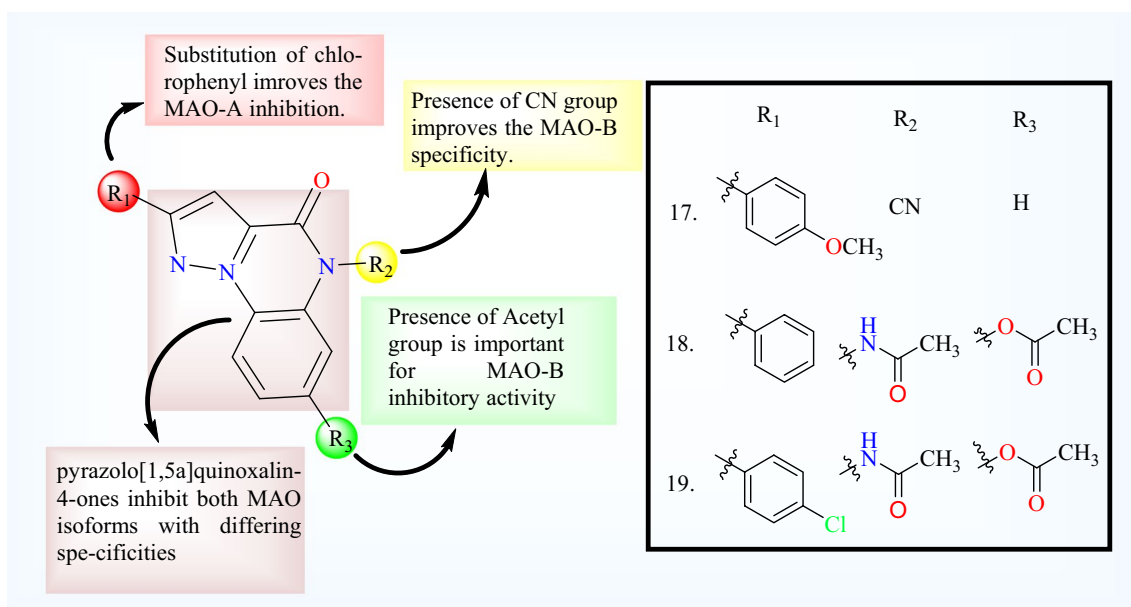
Activity increace when R is substituted with pyrrolidine and piperidine ring.

1. Activity drops with increase in chain length.
2. Activity highest for 3 carbon chain.

Presence of tert-butylphenoxy moiety is important for MAO-B inhibitory activity.

16a.n=1
R=pyrrolidine
16b.R=piperidine

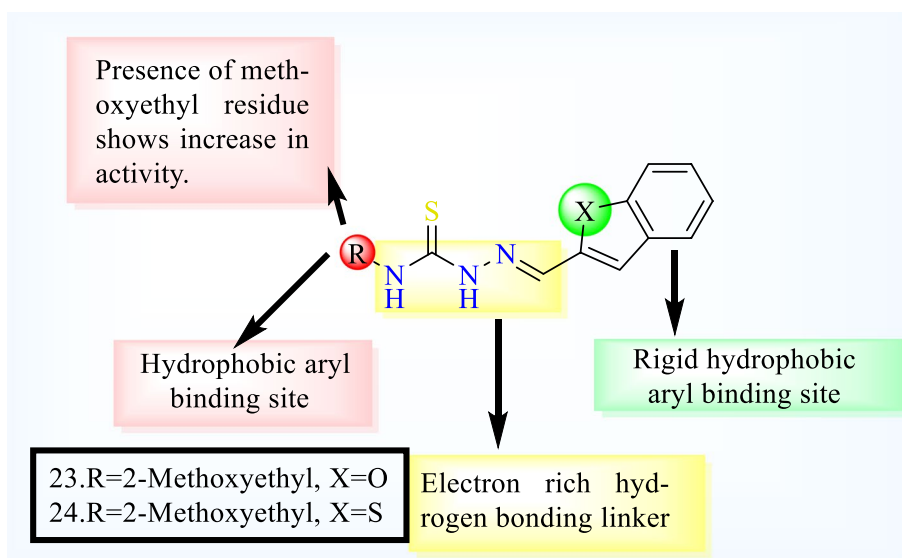**Fig. 13** Pyrazolo[1,5-a]qunoxalin-4-ones derivatives as MAO-B inhibitors

**Fig. 14** Pyridoxine-resveratrol derivatives as MAO-B inhibitors
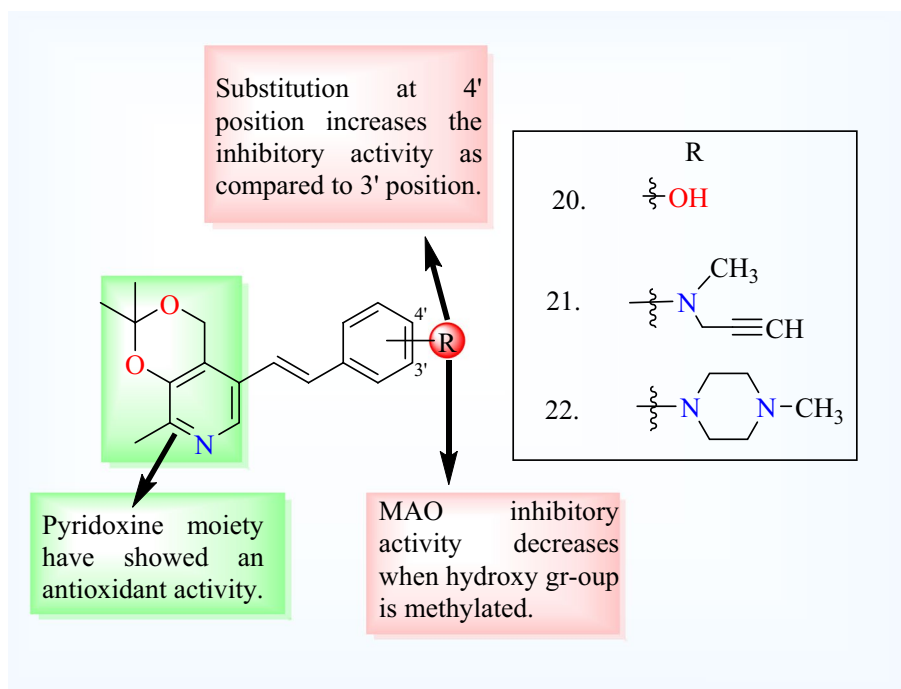


against the MAO-B enzyme. Compounds **23** (E)-2-(benzofuran-2-ylmethylene)-N-(2-methoxyethyl)hydrazine-1-carbothioamide and compound **24** (E)-2-(benzo[b]thiophen-2-ylmethylene)-N-(2-methoxyethyl)hydrazine-1-carbothioamide were the most effective agent with an IC$_{50}$ value of 0.042 μM and 0.056 μM, respectively. These compounds showed a similar inhibitory effect as Selegiline (reference compound). The SAR studies (Fig. 15) revealed

that the methoxyethyl group increased the MAO-B inhibitory activity, and benzofuran was more active than benzothiophene. The Kinetic studies disclosed that compounds were reversible and non-competitive, and K$_i$ values of compounds **23** and **24** were 0.035 μM and 0.046 μM, respectively. Cytotoxicity assay revealed that compounds **23** and **24** were non-cytotoxic at therapeutic concentration against MAO-B. According to molecular docking studies,

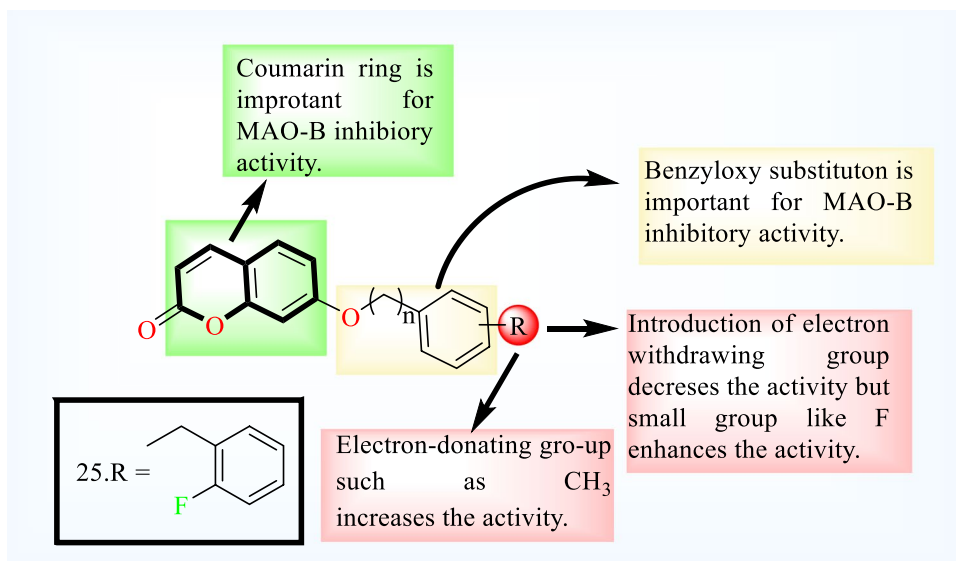**Fig. 15** Thiosemicarbazide derivatives as MAO-B inhibitors



Presence of methoxyethyl residue shows increase in activity.

R — Hydrophobic aryl binding site

X — Rigid hydrophobic aryl binding site

23. R=2-Methoxyethyl, X=O
24. R=2-Methoxyethyl, X=S

Electron rich hydrogen bonding linker

compounds showed various interactions, such as $\pi$–$\pi$ interaction and hydrogen bonds; hydrazine moiety was essentia for polar interactionsl. Compounds showed favorable van der Waals interactions with amino acid residues such as Leu171, Ile198, Cys172, Gln206, Phe343, Tyr326, Tyr398, Tyr435, and FAD molecule. Similarly, electrostatic interactions of these compounds were found with amino acid residues such as Gln65, Tyr188, Cys172, Ile198, Tyr326, Gln206, Tyr435, and FAD molecule [98].

Liu et al. designed and synthesized a series of novel 3,4-dihydrocoumarin derivatives and evaluated their inhibitory activity against the MAO-B enzyme. Compound 25 7-((4-(2-fluorobenzyl)benzyl)oxy)-2H-chromen-2-one was found the most potent with $IC_{50}$ equal to 0.37 nM. This compound was even more potent than reference iproniazid.

The kinetics study showed that compound **25** is a reversible and competitive inhibitor of MAO-B. Additionally, Structure–Activity relationship studies showed that benzyloxy substituent is critical for activity, fluorine at ortho position enhanced the activity, an electron-withdrawing group such as $NO_2$ decreased the activity, electron-donating $CH_3$ increased the activity as shown in (Fig. 16). Molecular modeling studies were done to explain the selectivity toward human monoamine oxidase enzyme. Dihydro coumarin moiety interacted with Lle 198, Leu 171, Gln 206, and Cys 172 amino acid residues. Cytotoxic and neuroprotective studies in the PC12 cell line revealed that compounds showed little toxicity at 200 μM, but most were safe at 50 μM and 100 μM, and compound **25** showed a 48% increase in protection against 6-OHDA treated cells. According to ADMET prediction
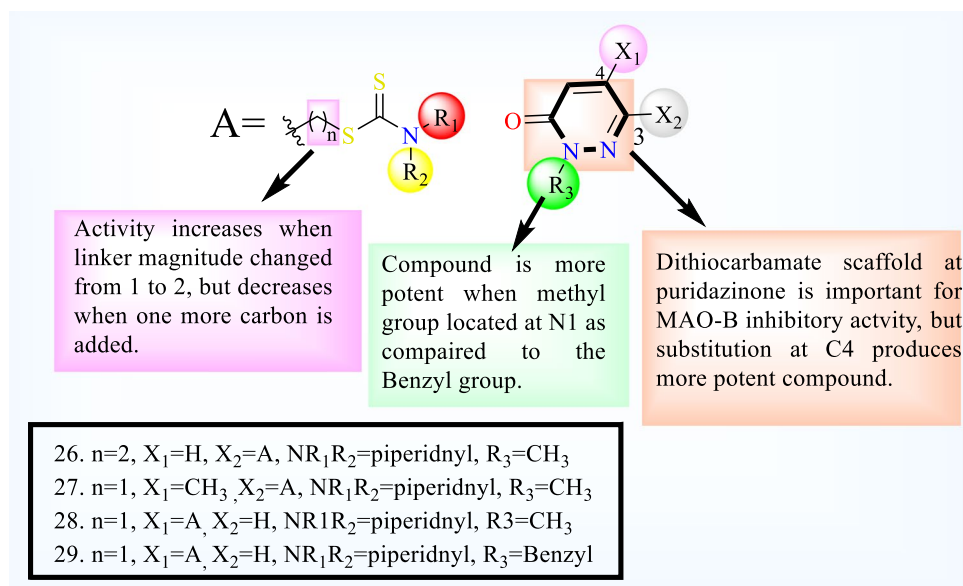
**Fig. 16** The 2,3-dihydro coumarin derivatives as MAO-B inhibitors



Coumarin ring is improtant for MAO-B inhibiory activity.

Benzyloxy substituton is important for MAO-B inhibitory activity.

Introduction of electron withdrawing group decreses the activity but small group like F enhances the activity.

Electron-donating gro-up such as $CH_3$ increases the activity.

25. R =

studies, new compounds showed a good pharmacokinetic profile which exhibits their biological importance [99].

In a recent study, Besada et al. synthesized a series of Pyridazinon-dithiocarbamate hybrids as MAO-B inhibitors. The in vitro studies revealed that all the compounds showed selectivity for the hMAO-B enzyme. The most potent compounds were **26** 2-(1-Methyl-6-oxo-1,6-dihydropyridazin-3-yl)ethyl di(piperidin-1-yl)carbamodithioate, **27** (1,4-Dimethyl-6-oxo-1,6-dihydropyridazin-3-yl)methyl di(piperidin-1-yl)carbamodithioate, **28** (1-Methyl-6-oxo-1,6-dihydropyridazin-4-yl)methyl di(piperidin-1-yl)carbamodithioate, and **29** (1-Benzyl-6-oxo-1,6-dihydropyridazin-4-yl)methyl di(piperidin-1-yl)carbamodithioate with $IC_{50}$ values 11.88 μM, 7.48 μM, 16.51 μM, and 6.71 μM respectively. It has been found that all the potent compounds showed reversible behavior. Additionally, the SAR studies (Fig. 17) revealed that the Presence of dithiocarbamate moiety at different positions of pyridazinone is essential for activity, and the substitution of dithiocarbamate at $C_4$ slightly increased potency. The activity increased when the linker magnitude was increased from 1 to 2, and the Presence of a phenyl ring at the diazaheterocyclic core increased the the inhibition profile and selectivity of the compound. Methyl substitution on nitrogen was more potent than the bulky benzyl group. Furthermore, cell toxicity studies on human cell line SH-SY5V revealed that compounds exhibited no significant cellular toxicity at the effective concentration. The Molecular Docking studies showed two different binding modes for the compounds i.e., the alkyl chain linking both scaffolds and the binding of the dithiocarbamate group in the proximity of the basic residues Phe168, Leu171, and Cys172. Finally, the predicted ADME descriptors showed that the novel pyridazinone/dithiocarbamate derivatives

showed good drug-like properties for oral absorption and BBB permeation [100].

Halaby et al. synthesized 21 new biphenyl piperazine derivatives and screened them against MAOs. In vitro tests were performed, and compound **30** 2-(4-(4-(2-ethoxyphenyl)piperazin-1-yl)phenyl)-5-methyl-1H-benzo[d]imidazole was found to be the most potent compound with an $IC_{50}$ value of 0.053 μM while the reference compound rasagiline and selegiline with $IC_{50}$ value of 0.237 μM and 0.040 μM, respectively. The Structure–activity relationship studies (Fig. 18) revealed that 1,4-biphenylpiperazine moieties were significant for MAO inhibitory activity, the presence of benzimidazole scaffold increased the activity and substitutions with
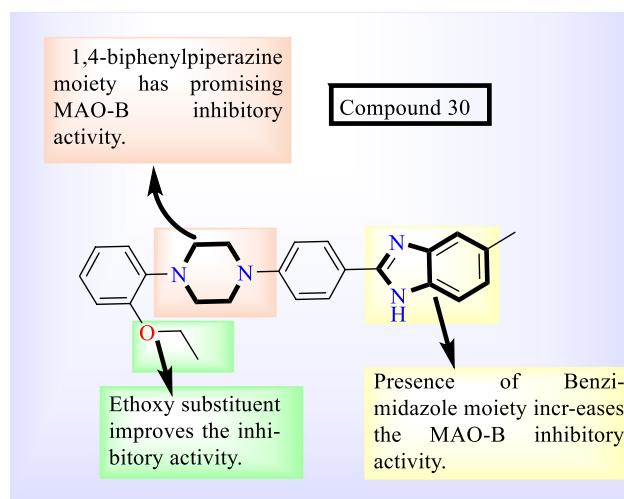


**Fig. 18** Biphenylpiperazine derivatives as MAO-B inhibitors



**Fig. 17** Pyridazinone/dithiocarbamate derivatives as MAO-B inhibitors

electron-donating groups such as methoxy showed more selectivity toward MAO-A enzyme.

Furthermore, the kinetics study revealed that compound **30** is a mixed inhibitor ($K_i = 0.017$ μM). The reversibility studies showed that compound **30** was a reversible inhibitor. According to cytotoxicity studies $IC_{50}$ value was calculated to be 54.45 μM against the SH-SY5Y cell line, which showed that synthesized derivatives were non-toxic at active concentration. The compound **30** showed excellent drug-like properties as per ADME prediction studies. Molecular docking studies showed the binding interactions and essential amino acid residue in the binding cavity. Finally, this information is helpful in developing safe and potent new anti-parkinsonian drugs [101]. The Molecular docking studies revealed that the most potent compound **30** does not correctly fit in the active site of the MAO-A enzyme, so the compound may bind due to displacement of conserved water molecules and the reason for the significant affinity of the compound for the MAO-A enzyme. ADME parameters were predicted using the swissADME tool by calculations of various physicochemical parameters such as lipophilicity, molecular weight, solubility, polarity, and polar surface area, etc., and concluded that these compounds may have good brain penetration and oral bioavailability and can be potential MAO-B inhibitors.

Tok et al. designed and synthesized thirty novel 2,5-disubstituted-1,3,4-oxadiazole derivatives and evaluated their inhibitory activity against MAOs enzyme. In vitro studies showed that none of the compounds were active against MAO-A, but compound **31** 1-(4-Chlorophenyl)-3-(5-(5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl)pyridin-2-yl)urea**, compound **32** 1-(4-Chlorophenyl)-3-(5-(5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl)pyridin-2-yl)urea**, and compound **33**

1-(4-Chlorophenyl)-3-(5-(5-(4-methoxyphenyl)-1,3,4-oxadiazol-2-yl)pyridin-2-yl)urea were the most potent compounds with $IC_{50}$ values 0.039, 0.066, and 0.045 μM, respectively against the MAO-B isoform. Additionally, structure–activity relationship studies revealed that the presence of 1,3,4-oxadiazole ring was necessary for the activity, substitution of phenyl ring with chloro-group enhanced the activity and replacing with nitro group decreased the activity as compared to chloro-group (Fig. 19). Furthermore, the Docking studies were performed to determine the interaction between compound H8 and active site of the enzyme. A halogen bond was formed between the chlorine atom of the 4-chlorophenyl ring attached to the urea group of compound **31** with the carbonyl of Leu164 amino acid, and a hydrogen bond was established between the amino group and the carbonyl of Pro102. So, all this information provides us with lead i.e. Compound **31** which is a potent and selective MAO-B inhibitor that can be used for further development of the treatment for Parkinson's Disease [102].

Ozdemir et al. designed and synthesized a series of pyridazinone derivatives as MAO-B inhibitors in a recent study. In vitro assay was carried out to check the MAO-inhibitory activity and selectivity of synthesized derivatives and found that compound **34** 2-(3-(4-(4-Chlorophenyl)piperazin-1-yl)-6-oxopyridin-1(6H)-yl)acetohydrazide was the most effective MAO-B inhibitor with $K_i$ and selectivity index equal to 0.022 μM and 206.82, respectively. Furthermore, structure–activity relationship studies showed that piperazine-linked pyridazinone is necessary for the activity, the substituted phenyl at the piperazine ring enhanced the hMAO-B inhibitory activity, and halogen substitutions are significant for the activity. In contrast, the addition of a second halogen decreased the activity (Fig. 20). Additionally, the Docking

**Fig. 19** 1,3,4-oxadiazole derivatives as MAO-B inhibitors



Phenyl ring created a pi-pi interaction with the phenyl ring of active site amino acids.

Presence of 1,3,4-Oxadiazole moiety is important for the MAO-B inhibitory activity.

Chlorine substituted phenyl enhances the inhibitory activity.

31. $R_1$=4-Cl, $R_2$=4-Cl
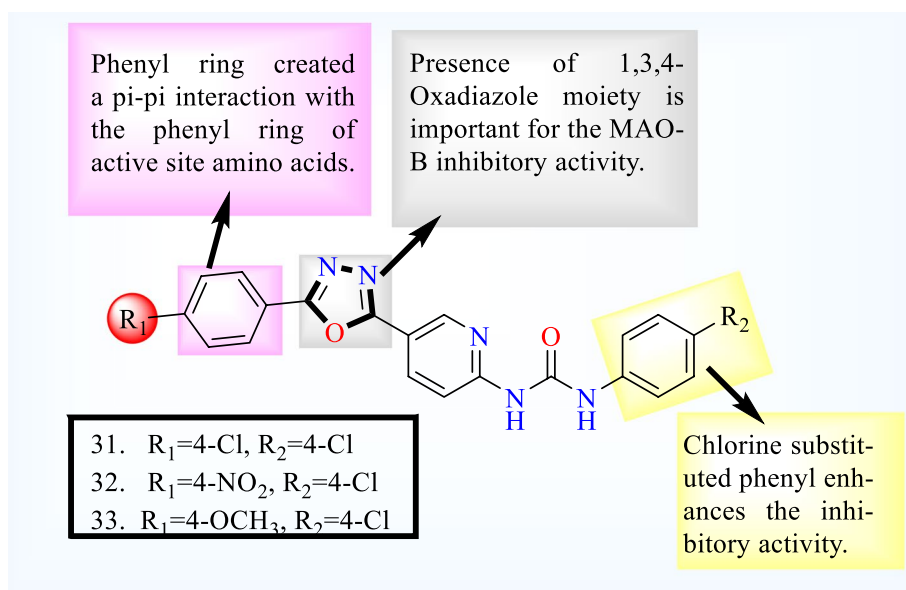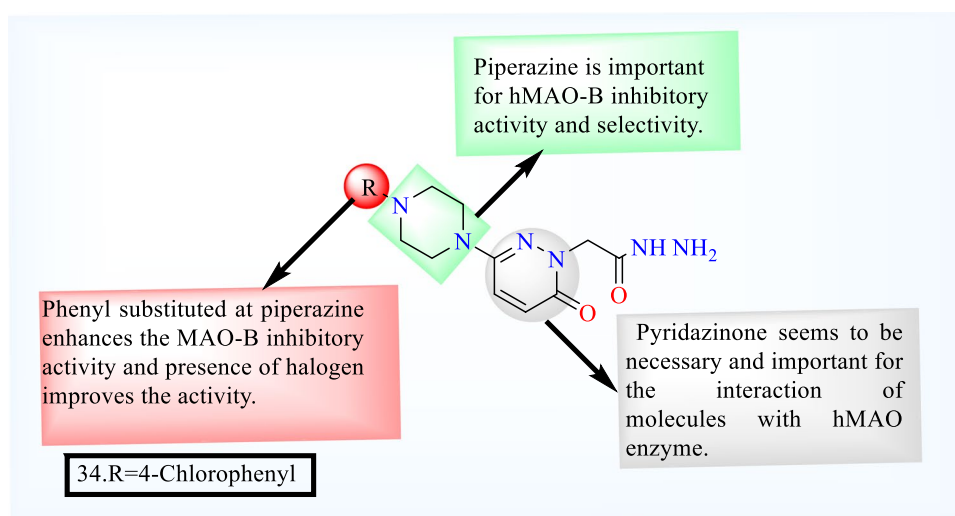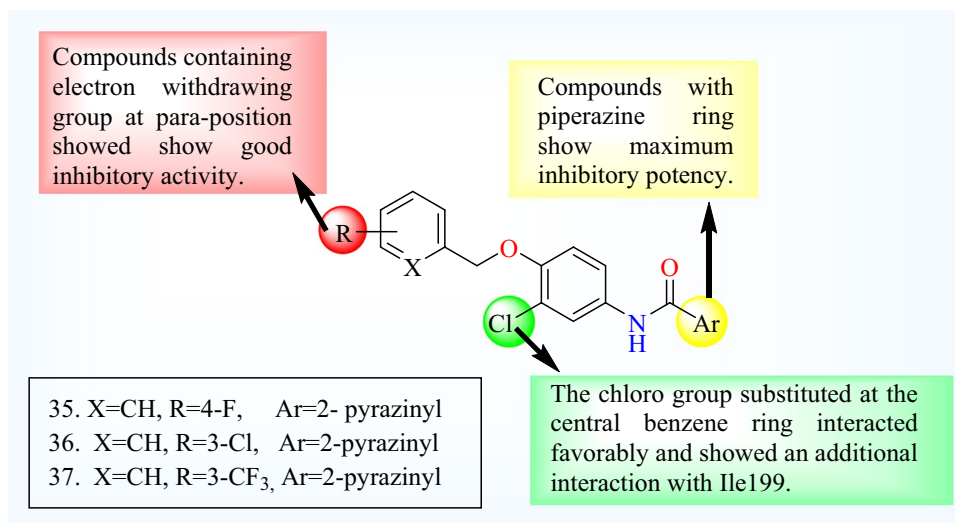32. $R_1$=4-NO$_2$, $R_2$=4-Cl
33. $R_1$=4-OCH$_3$, $R_2$=4-Cl

**Fig. 20** Pyridazinone derivatives as MAO-B inhibitors



studies revealed that pyridazinone and hydrazine group are essential for the interaction between the compound and active site of the enzyme. According to in silico ADME prediction studies, the compounds were drug-like for various physicochemical parameters [103].

Elkamhawy et al. synthesized 36 novel Safinamide derivatives and evaluated them against MAO-B. Compound **35** N-(3-chloro-4-((4-fluorobenzyl)oxy)phenyl)pyrazine-2-carboxamide, compound **36** N-(3-chloro-4-((3-chlorobenzyl)oxy)phenyl)pyrazine-2-carboxamide, and compound **37** N-(3-chloro-4-((3-(trifluoromethyl)benzyl)oxy)phenyl)pyrazine-2-carboxamide showed the most potent inhibitory activity with IC$_{50}$ values of 9.7 nM, 5.1 nM, and 3.9 nM, respectively. Additionally, the SAR studies revealed that the presence of carboxamide moiety (2-pyrazinyl) enhanced the activity, and the presence of halogen at the 3,4-position enhanced the MAO-B inhibitory activity as shown in

(Fig. 21). Furthermore, the Docking studies provided knowledge about the interaction between the inhibitor and enzyme. In vivo studies showed that the nigrostriatal dopaminergic neurons were significantly protected by oral administration of **37**, so compound **37** can be considered a novel, potent, and selective hMAO-B inhibitor for treating Parkinson's disease [104].

In a study, Rehuman et al. designed and synthesized two series of dimethoxy-halogenated chalcone derivatives and evaluated their MAO inhibitory activity. In vitro studies showed that compound **38** (E)-3-(4-Chlorophenyl)-1-(2,4-dimethoxyphenyl)prop-2-en-1-one was the most potent inhibitor of MAO-B with an IC$_{50}$ value of 0.067 μM and followed by compound **39** (E)-1-(2,3-dimethoxyphenyl)-3-(4-fluorophenyl)prop-2-en-1-one with an IC$_{50}$ value of 0.118 μM. Additionally, structure–activity relationship studies revealed that different orientation of halogen atoms

**Fig. 21** Safinamide derivatives as MAO-B inhibitors



35. X=CH, R=4-F,     Ar=2- pyrazinyl
36. X=CH, R=3-Cl,   Ar=2-pyrazinyl
37. X=CH, R=3-CF$_3$, Ar=2-pyrazinyl

at different locations of B ring changed the activity of the compounds, such as chloro at ortho position was more potent as compared to meta or para position (Fig. 22). According to kinetics study, compounds **38** and **39** show competitive and reversible inhibition with $K_i$ value 0.032 and 0.045 μM, respectively. Cytotoxicity was checked using the MTT assay method on the Vero epithelial cell line, and it found that **38** was non-toxic below 100 μg/ml. Induced fit docking simulations were performed to determine the binding mode between the synthesized compounds and MAO-B enzyme and found the two compounds with similar binding pockets with ortho-chlorine and ortho-fluorine interact with Y326 and F168, and hydrogen bond stabilized the side chain of Y188 within the binding pocket. It was concluded that compounds **38** and **39** were good candidates for the development of the new class of MAO-B inhibitors [105].

Alagoz et al. reported the synthesis of 16 novel compounds and evaluated their MAO inhibitory activity against two isoforms of the enzyme, i.e., MAO-A and MAO-B. The most potent compound found to be **40** (E)-N'-(4-chlorobenzylidene)-2-(3-(4-(4-methoxyphenyl)piperazin-1-yl)-6-oxopyridazin-1(6H)-yl)acetohydrazide with an $IC_{50}$ value of 0.17 μM followed by compound **41** (E)-N'-(4-chlorobenzylidene)-2-(3-morpholino-6-oxopyridazin-1(6H)-yl)acetohydrazide ($IC_{50} = 0.27$ μM). Additionally, structure–activity relationship studies revealed that para-chloro substitution increased the MAO-B inhibitory activity, and the substitution of $R_1$ with -$OCH_3$ showed higher activity than -$CF_3$ substitution (Fig. 23). These compounds were reversible and competitive inhibitors with $K_i$ value 0.230 and 0.146 μM, respectively. According to the PAMPA test, it is revealed that compounds **40** and **41** transverse the blood–brain barrier very quickly as it has good CNS permeability. The docking studies revealed that the reason for the potent inhibitory efficiency of compounds **40** and **41** might be due to interaction with some essential residue i.e., E84 and Y326 in MAO-B. Bioavailability prediction studies showed that compounds **40** and **41** have drug-like properties, so they can be considered a candidate for developing MAO-B inhibitors [106].

## Drugs in clinical trial for Parkinson's disease

The MAO-B inhibitors and therapy under clinical trial in past years are listed in Table 1. Rasagiline, an irreversible inhibitor of monoamine oxidase B, has completed a clinical trial in which change in the cognitive brain biomarker was compared over 2.5 years in 12 patients, assessed by MRI in Parkinson's disease (NCT02278588). In another phase two trials Brain and Motor behavior changes were investigated in Parkinson's disease in response to the drug (NCT02789020). In a different clinical trial study effect of rasagiline was determined on gait treatment (NCT01098396). Rasagiline's effect was evaluated on cognition in the early stages of PD and entered in phase 4 clinical trial (NCT01382342). Completed the clinical trial for the effect of rasagiline on sleep disturbance in Parkinson's disease and showed a positive effect on sleep disturbance by reducing nocturnal akinesia (NCT01442610). In another study under phase 4, rasagiline as an add-on dopamine agonist in the treatment of Parkinson's disease was evaluated, and it found that it is not optimally controlled on dopamine as compared to placebo (NCT01049984).

Safinamide, a reversible MAO-B inhibitor, completed the clinical trial for the study of the overnight switch from
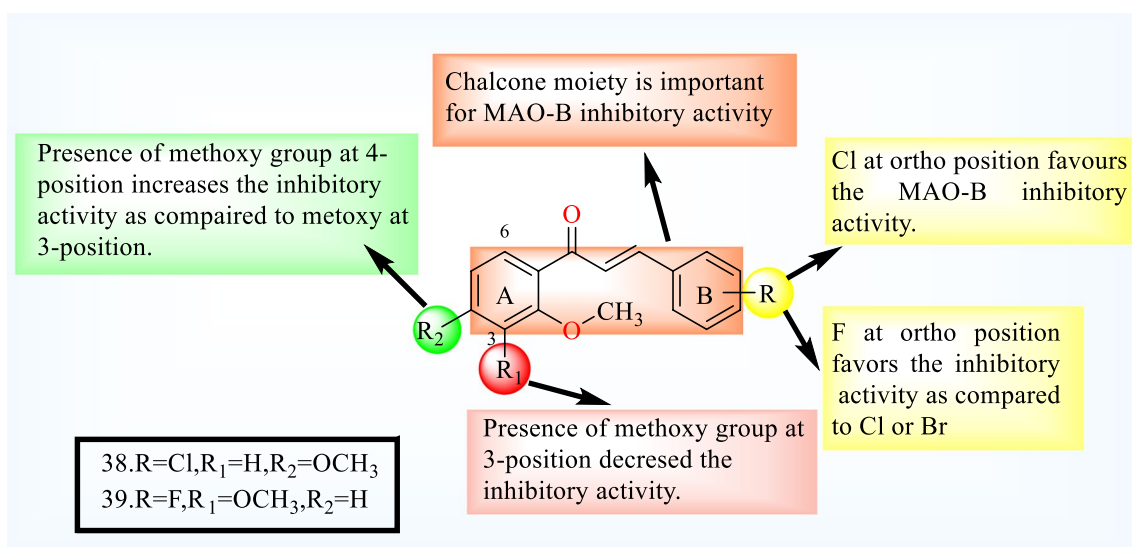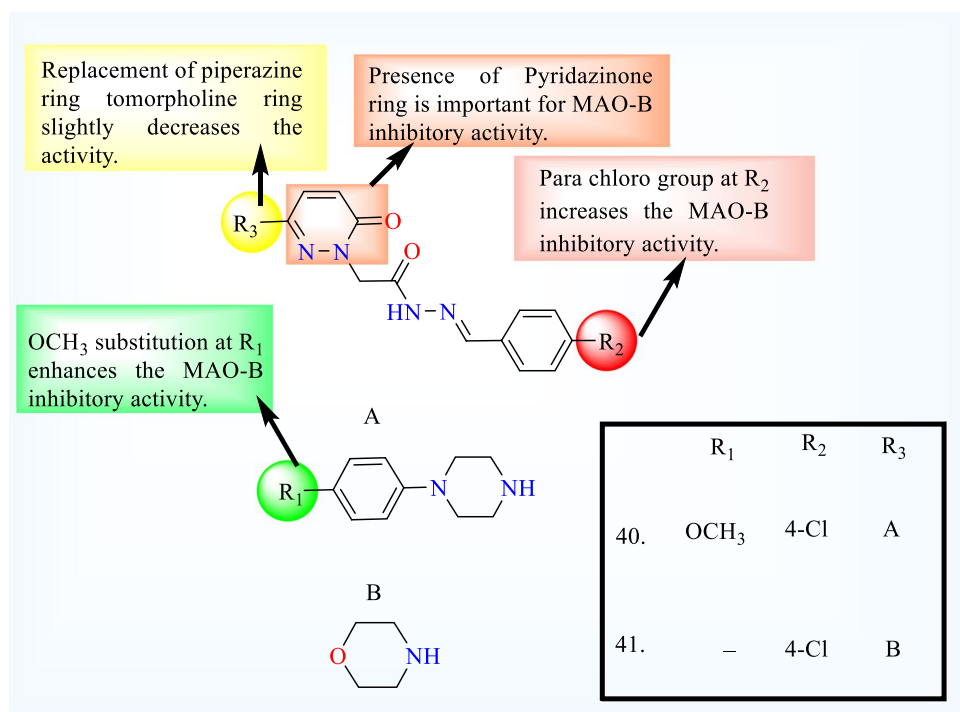


**Fig. 22** Dimethoxy-halogenated chalcone derivatives as MAO-B inhibitors

**Fig. 23** Pyridazinone derivatives as MAO-B inhibitors



Replacement of piperazine ring tomorpholine ring slightly decreases the activity.

Presence of Pyridazinone ring is important for MAO-B inhibitory activity.

Para chloro group at $R_2$ increases the MAO-B inhibitory activity.

$OCH_3$ substitution at $R_1$ enhances the MAO-B inhibitory activity.

| | $R_1$ | $R_2$ | $R_3$ |
|---|---|---|---|
| 40. | $OCH_3$ | 4-Cl | A |
| 41. | – | 4-Cl | B |

Rasagiline to Safinamide, and safety and tolerability were checked when there was a sudden switch from one medication to another (NCT03843944). A different study showed that clinical outcome assessment of Parkinson's disease with XADAGO (Safinamide) in Phase 4 of the clinical trial. In this study, the effect of XADAGO on motor and non-motor symptoms in Parkinson's disease was evaluated (NCT03944785).

Zelapar (orally disintegrating Selegiline), an irreversible MAO-B inhibitor, completed the clinical trial titled efficacy of orally disintegrating selegiline in Parkinson's patients experiencing adverse effects with dopamine agonists. This study was performed to evaluate the side effects of dopamine, such as swelling of lower limbs or feet or hallucinations during the addition of orally disintegrating selegiline which can reduce the adverse effect and maintain the symptoms of Parkinson's disease (NCT00443872).

Treatment by Chinese herbal medicine as adjuvant therapy for the treatment of Parkinson's disease is in Phase 2 for conventional medicine and Phase 3 for Chinese herbal medicine. This study explores the effect of Chinese herbal medicine on Parkinson's disease parameters (NCT05001217).

Apomorphine, a non-selective dopamine agonist, is in a Phase 3 clinical trial to determine the safety and tolerability of continuous subcutaneous infusion (NCT02339064).
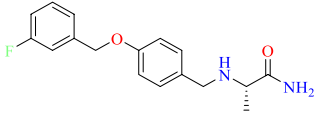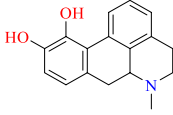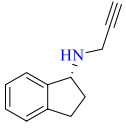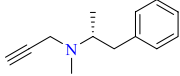
## Data from patents documents

Some patents on MAO-B inhibitors that were published last few years are listed in Table 2. The Data of patent literature focuses structure of various compounds which may be used for Parkinson's disease and other neurological disorders. Papers that were published were added to this review.

## Conclusion

Parkinson's disease (PD) is the second most common age-related complex, idiopathic neurological disorder. Although there are several treatments available, none of them are very successful in preventing the loss of dopaminergic neurons and restoring DA levels in the striatum. Thus, the development of novel anti-parkinsonians is the requirement of the present era. In-depth information on the design and synthesis of various MAO-B inhibitors that are currently being developed (as of 2018) is presented in this review. We have also gone through SAR analyses for these derivatives, which
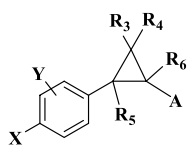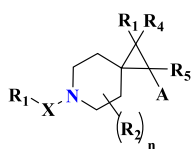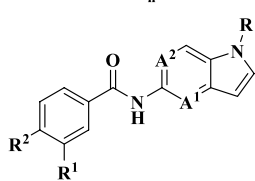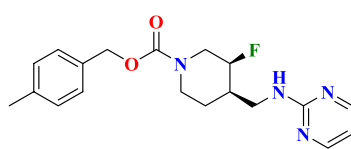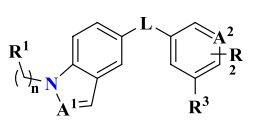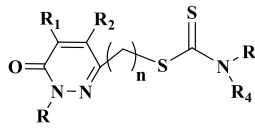
**Table 1** Drugs under clinical trial for the treatment of Parkinson's disease

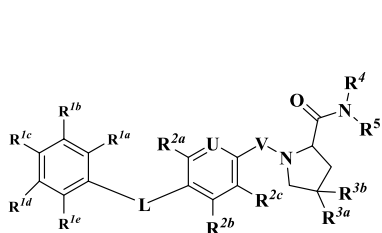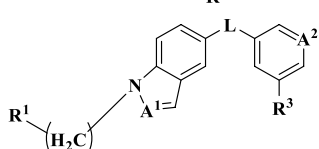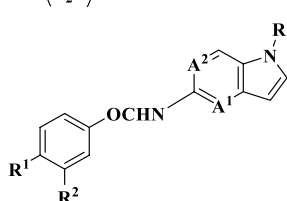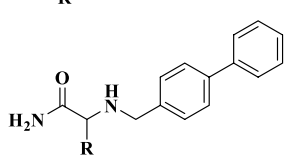| S.no | Drug | Study | Last entry | Phase | Clinical trial number | References |
|---|---|---|---|---|---|---|
| 1 | Safinamide | Overnight switch from Rasagiline to Safinamide | 2022 | Phase 4 | NCT03843944 | [107] |
| | | Clinical outcome assessment of Parkinson's disease patients treated with XADAGO (Safinamide) | 2021 | Completed | NCT03944785 | [108] |
| 2 | Apomorphine | Infusion of Apomorphine: Long-term safety study | 2020 | Phase 3 | NCT02339064 | [109] |
| 3 | Chinese herbal medicine | Chinese herbal medicine treatment based on subgroups differentiation as an adjunct therapy for Parkinson's disease: a pilot adds on randomized, controlled, Pragmatic clinical trial | 2021 | Phase2 Drug conventional medicine | NCT05001217 | [110] |
| 4 | Rasagiline | Image Parkinson's disease progression study | 2021 | Phase 2 | NCT02789020 | [111] |
| | | Effect of 2.5 years of Rasagiline therapy on progression of cognitive biomarkers assessed by MRI in Parkinson's disease | 2019 | Completed | NCT02278588 | [112] |
| | | Effect of Rasagiline on sleep disturbance in Parkinson's disease | 2016 | Phase 4 | NCT01442610 | [113] |
| | | Rasagiline as add on to dopamine agonist in the treatment of Parkinson's disease | 2015 | Phase 4 | NCT01049984 | [114] |
| | | The effect of Rasagiline on cognition in Parkinson's disease | | Phase 4 | NCT01382342 | [115] |
| | | Rasagiline for Gait treatment | 2010 | Unknown | NCT01098396 | [116] |
| 5 | Zelapar | Efficacy of orally disintegrating selegiline in Parkinson's Patients experiencing adverse effects with dopamine agonist | 2014 | Phase 4 | NCT00443872 | [117] |

showed the importance of various substituents on the basic moieties. The coumarin derivatives showed the presence of hydroxy in the seventh position enhances the activity, and halogen-substituted heterocyclics or substituted benzoxy group increases the activity. The chalcone moiety-containing compounds showed important for the activity in which the A ring may be substituted by the prenyl group of the methoxy group for good activity and ring B to be substituted by electron-withdrawing groups at ortho position for better MAO-B inhibitory activity. Piperazine-linked pyridazinone is necessary for the activity, phenyl substituted at piperazine enhances the MAO-B inhibitory activity, and the presence of halogen improves the activity. This knowledge can be used as a springboard for creating novel anti-parkinsonian drugs. A multitarget approach is more beneficial than compared to single target approach for the treatment of the neurodegenerative disorder. MDLTs show an effective outcome for the treatment of PD by targeting sigma receptors. The multi-target disease modification approach can be used in the modification of misfolded alpha-syn in the treatment of

**Table 2** Patent documents surveyed in this review

| S. no | Patent number | Applicant | Priority date | Publication date | Markush claim | References |
|---|---|---|---|---|---|---|
| 1 | US 11,332,463 B2 | Merck Sharp & Dohme Corp., Rahway, NJ (US) | 29 April 2019 | 17 May 2022 |  | [118] |
| 2 | US 10,870,630 B2 | Merck Sharp & Dohme Corp., Rahway, NJ (US) | 30 October 2017 | 22 December 2020 |  | [119] |
| 3 | US 9,738,640 B2 | "NTZ LAB" Ltd., Sofia (BG) | 11 July 2014 | 22 August 2017 |  | [120] |
| 4 | US 11,479,542 B2 | CERECOR, INC., Rockvill, MD (US); MERCK SHARP & DOHME CORP., Rahway, NJ (US) | 27 May 2020 | 25 October |  | [121] |
| 5 | US 9,643,930 B2 | NTZ LAB.,Sofia (BG) | 5 June 2013 | 9 May 2017 |  | [122] |
| 6 | US 10,253,000 B2 | UNIVERSIDADE DE, Vigo (Pontevedra)(ES); UNIVERSIDADE DE SANTIAGO DE COMPOSTELA, Santiago de Compostela (La Coruna) (ES) | 3 March 2015 | 9 April 2019 |  | [123] |
| 7 | US 11,225,460 B2 | SUNHINE LAKE PHARMA CO., LTD., Guangdong (CN) | 7 March 2019 | 18 January 2022 |  | [124] |
| 8 | EP 2,964,219 B1 | "NTZ Lab" Ltd 1618 Sofia (BG) | 14 January 2013 | 13 January 2016 |  | [125] |
| 9 | EP 2991986 B1 | "NTZ Lab" Ltd 1618 Sofia (BG) | 29 January 2013 | 3 March 2016 |  | [126] |
| 10 | EP 3202759 B1 | Megabiowood Co., Ltd. Jeollanam-do, 58141 (KR) | 18 September 2015 | 9 August 2017 |  | [127] |

PD. The multi-target approach is very effective to predict the effectiveness of MAO-B inhibitors. For the treatment of PD, deep brain stimulation by the multi-target approach is very beneficial. Dual- acetylcholinesterase inhibitors and mono-amine oxidase can be used as a multi-target approach for the treatment of PD. The monoaminergic and histaminergic systems both can also be targeted by the multi-target approach for PD. Therefore, a multi-target approach can be used for the potential treatment of PD. This review also highlights that drug in the early or late stages of clinical trials for Parkinson's disease. This review provides useful information for developing new drugs with minimum side effects and better effectiveness for treatment of Parkinson's disease.

## Declarations

**Conflict of interest** The authors declare no conflict of interest.

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