



Monoamine Oxidase Inhibitors: From Classic to New Clinical Approaches

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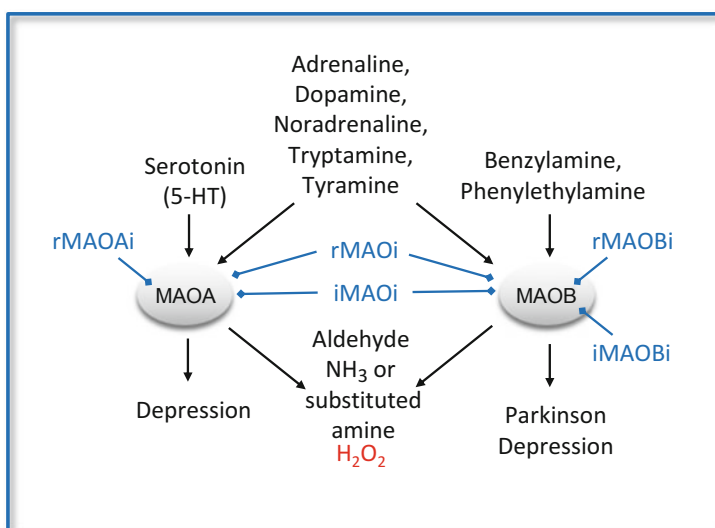
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Abstract

Monoamine oxidases (MAOs) are involved in the oxidative deamination of different amines and neurotransmitters. This pointed them as potential targets for several disorders and along the last 70 years a wide variety of MAO inhibitors have been developed as successful drugs for the treatment of complex diseases, being the first drugs approved for depression in the late 1950s. The discovery of two MAO isozymes (MAO-A and B) with different substrate selectivity and tissue expression patterns led to novel therapeutic approaches and to the development of new classes of inhibitors, such as selective irreversible and reversible MAO-B inhibitors and reversible MAO-A inhibitors. Significantly, MAO-B inhibitors constitute a widely studied group of compounds, some of them approved for the treatment of Parkinson's disease. Further applications are under development for the treatment of Alzheimer's disease, amyotrophic lateral sclerosis, and cardiovascular diseases, among others. This review summarizes the most important aspects regarding the development and clinical use of MAO inhibitors, going through mechanistic and structural details, new indications, and future perspectives.

Graphical Abstract



Monoamine oxidases (MAOs) catalyze the oxidative deamination of different amines and neurotransmitters. The two different isozymes, MAO-A and MAO-B, are located at the outer mitochondrial membrane in different tissues. The enzymatic reaction involves formation of the corresponding aldehyde and releasing hydrogen peroxide (H₂O₂) and ammonia or a substituted amine depending on the substrate. MAO's role in neurotransmitter metabolism made them targets for major depression

and Parkinson's disease, among other neurodegenerative diseases. Currently, these compounds are being studied for other diseases such as cardiovascular ones.

Keywords

Depression · MAO-A · MAO-B · Monoamine oxidases · Neurodegeneration · Oxidative stress · Parkinson

1 Overview

Monoamine oxidases (MAOs) are part of the family of flavin adenine dinucleotide (FAD)-dependent enzymes that catalyze the oxidative deamination of different amines and neurotransmitters. There are two different isozymes that are well characterized (MAO-A and MAO-B), and they are located at the outer mitochondrial membrane in most mammalian tissues with different expression patterns. MAOs are responsible of neurotransmitters regulation by their degradation in which the enzymatic reaction involves formation of the corresponding aldehyde from the neurotransmitter to form the oxidized FAD and releasing hydrogen peroxide resulting from reduction of molecular oxygen and ammonia or a substituted amine depending on the substrate. The production of H_2O_2 by these enzymes might lead to the generation of free radicals that can exert cytotoxicity under pathological conditions. The relationship of MAOs with the neurotransmitter metabolism pointed them as potential target for different disorders including major depression, Parkinson's disease (PD), Alzheimer's disease (AD), Lewy body diseases with dementia, and amyotrophic lateral sclerosis (ALS), and currently they are used in clinics for some of these disorders.

In general, MAO inhibition has a long history since first drug was approved in the late 1950s. Initially, iproniazid was tested as a treatment for tuberculosis; although it was not effective, it showed an improvement in patient emotional state. It would be later described as a non-selective irreversible MAO inhibitor of the hydrazine group and approved in 1958 for depression. Nevertheless, those drugs showed high liver toxicity and were associated to hypertensive crisis, secondary effects that resulted in market removal of some of them. Thereafter, non-hydrazine MAO inhibitors were developed as an alternative to avoid liver toxicity (i.e., tranylcypromine, early 1960s); however, hypertensive crisis as secondary effect was still present. Therefore, some initially approved MAO inhibitors were retired as antidepressants and substituted by other drugs directed to novel targets (Shulman et al. 2013; Youdim et al. 2006; Edmondson and Binda 2018).

The discovery of two different MAO isozymes (MAO-A and B) with different substrate selectivity and expression pattern in different tissues led to novel therapeutic approaches and the development of new classes of inhibitors, such as selective irreversible and reversible MAO-B inhibitors and reversible MAO-A inhibitors. Typically, MAO-A is related to the oxidative deamination of serotonin, while MAO-B catalyzes preferentially benzylamine and 2-Phenethylamine. Dopamine, noradrenaline, adrenaline, tryptamine and tyramine exhibit similar substrate

specificities for both isozymes. Hypertensive crises suffered by patients treated with MAO inhibitors were then associated with a strong MAO-A inhibition, since this enzyme metabolizes tyramine in the small intestine due to its higher expression compared to MAO-B in that organ. The toxic effect is related with the ingestion of food containing tyramine coupled to MAO-A inhibitors. This combination induces tyramine accumulation leading to high blood pressure due to the displacement of norepinephrine from neuronal storage, extremely increasing its concentration in the bloodstream (Anderson et al. 1993). The related toxic effect is known as the “cheese effect” (tyramine-induced hypertensive crisis of MAO-A inhibitors). In this sense, selective MAO-B inhibitors provide an improved pharmacological profile avoiding this effects; also reversible inhibitors of MAO-A (RIMAs) obtaining in some cases a sufficient blockade without toxicity (Da Prada et al. 1988).

MAO-B inhibitors were extensively studied after the case of intoxication with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) in 1980. It was discovered that the toxicity induced by MPTP was related to its conversion to 1-methyl-4-phenylpyridinium (MPP+) by MAO-B, a metabolite that induced Parkinsonian symptoms. These symptoms were reversed by pargyline, a selective and irreversible MAO-B inhibitor (Langston et al. 1984). This correlation induced an intensive investigation of MAO-B inhibitors as potential therapeutics for the treatment PD. Nowadays, three selective MAO-B inhibitors are approved for the treatment of this disease: selegiline, rasagiline, and safinamide.

2 Structure and Binding Site of MAO

Human MAO proteins are flavoenzymes constituted by 527 and 520 amino acids for MAO-A and MAO-B isozymes, respectively. They are attached to the mitochondrial outer membrane as dimer structures (Fig. 1a) (Upadhyay et al. 2008). Both isozymes share about 70% aminoacidic sequence with a flavin adenine dinucleotide (FAD) coenzyme covalently bonded by $\delta\alpha$ -methylene to Cys397 in MAO-B and Cys406 in MAO-A (Hubalek et al. 2003). Studies on their crystal structures suggest that the C-terminal α -helix would be related to the anchoring at the outer mitochondrial membrane of each monomer of the dimer. Substrate entry to the catalytic site of each monomer is independent from each other (Binda et al. 2002; Edmondson et al. 2009). Human MAO-A is demonstrated to be also a dimer, but it crystallizes as a monomer due to its higher instability (Edmondson and Binda 2018).

The catalytic mechanism is similar in both enzymes; however, different binding site structures revealed important aspects for substrate selectivity and inhibitors binding. One of the most important differences is a unique 550 \AA^3 substrate cavity present in MAO-A opposite to FAD coenzyme. MAO-B isozyme presents two cavities, an entry cavity and a reactive site cavity, with total combined volume of about 700 \AA^3 (Fig. 1b). MAO-B cavity exhibits an entrance cavity (290 \AA^3) that precedes the flat hydrophobic substrate cavity (490 \AA^3) (Binda et al. 2002; De Colibus et al. 2005). Open or closed conformation of Ile199 side chain in MAO-B determines the connectivity between cavities, flanked by other important residues as

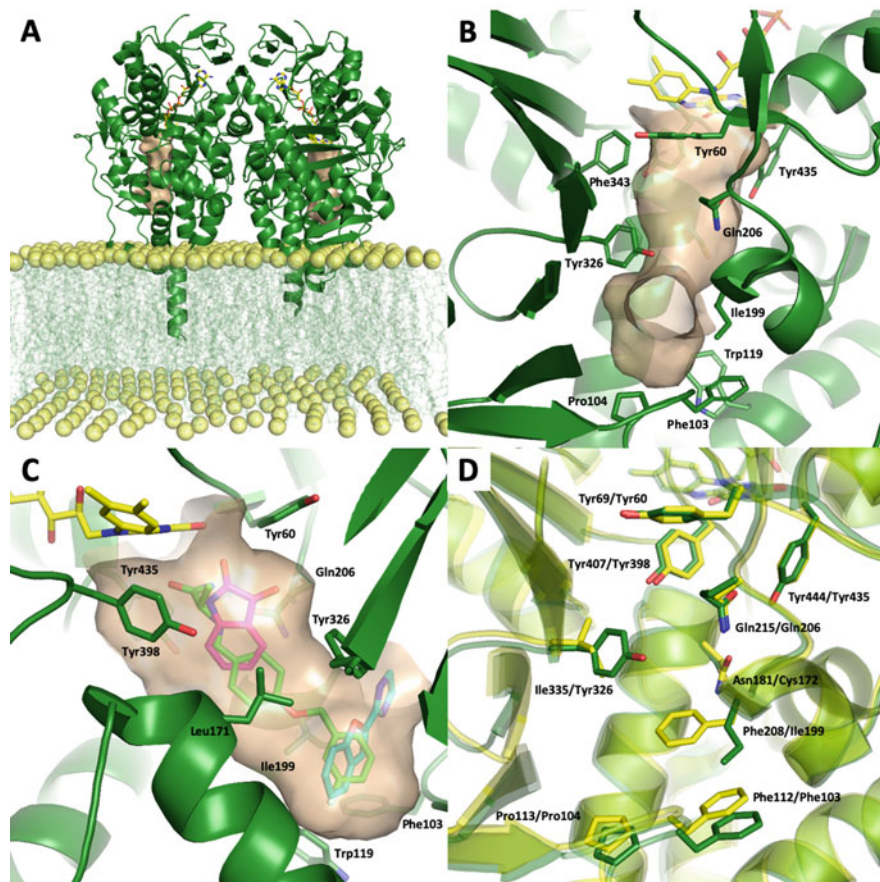


Fig. 1 Structural details about MAO enzymes. (a) Schematic model of the human MAO-B crystal structure PDB-ID 2V5Z (Binda et al. 2007) as a dimer inserted in a phospholipid bilayer shown as sphere-stick representation. MAO-B protein is represented as dark green cartoon with FAD coenzyme of each monomer as yellow sticks and binding site cavity as light orange surface. (b) Zoom of the human MAO-B binding site with key residues as dark green sticks. (c) Detail of different inhibitor binding modes. Isatin represented as pink sticks is located in the substrate cavity near FAD coenzyme, 2-(2-benzofuranyl)-2-imidazoline represented as blue sticks is located in the entrance cavity at the other end of the binding site, and safinamide represented as light green sticks fits along the bipartite cavity. Isatin and 2-(2-benzofuranyl)-2-imidazoline come from crystal structures (PDB-ID 1OJA and 2XFN) (Bonivento et al. 2010; Binda et al. 2003) aligned to 2V5Z structure in complex with safinamide. (d) Comparison between binding site key residues of human MAO-A (PDB-ID 2Z5X) (Son et al. 2008) and MAO-B (PDB-ID 2V5Z) isoforms represented as yellow and dark green cartoon, respectively. Most of the residues are conserved and show equivalent positions of the side chains, except for Phe208/Ile199 and Ile335/Tyr326 (MAO-A/MAO-B), key residues for substrate and inhibitor specificity. All images were constructed using PyMOL software [*The PyMOL Molecular Graphics System, Version 2.2 Schrödinger, LLC*]

Tyr326 or Phe168 (Hubalek et al. 2005). In spite of the higher total pocket volume for MAO-B, narrowness and stiffness of the bipartite cavity limit size of ligands in comparison with the A isozyme, and depending on its nature, they will bind in different positions along the cavity (Fig. 1c, discussed in the next section). The main differences of both isozymes can be found in these residues: Ile199 and Tyr326 of MAO-B instead of Phe208 and Ile335 of MAO-A. In this sense, MAO-A Phe208 side chain prevents the possibility of establishing a double cavity. The human mutant I199F MAO-B protein showed no binding for some selective MAO-B inhibitors stating the importance of Ile199 gate as a determinant for MAO-B specificity (Hubalek et al. 2005). Likewise, double I199A/Y326A human MAO-B mutation led to a protein that exhibits binding properties closer to MAO-A, highlighting the importance of Ile199 and Tyr326 side chains for selectivity (Milczek et al. 2011). In addition, the hydrophobic environment near FAD and some polar residues as Gln206 in MAO-B are important for substrate recognition and, therefore, inhibitor orientation at the coenzyme surroundings (Bonivento et al. 2010; Dasgupta et al. 2018). Furthermore, the presence of aromatic amino acid residues such as Tyr398 and Tyr435 in MAO-B oriented perpendicular to the flavin ring has been suggested as important for catalysis (Tyr407 and Tyr444 form a similar aromatic cavity in MAO-A, see Fig. 1d). Mutations in Tyr435 residue revealed differences in catalysis and function of this aromatic cage for substrate specificity (Li et al. 2006). Besides that, Y407F/Y444F mutant MAO-A enzymes also led to modified catalytic properties (Nandigama et al. 2001). Altogether, there are many structural evidences and information about what are the most influential residues in relationship with MAO activity and, therefore, crucial for inhibitor performance and design (for review, see Edmondson and Binda (2018)). Structural knowledge and binding site details are summarized in Fig. 1.

2.1 Mechanisms of MAO Catalysis and Inhibition

Compounds targeting MAO inhibition can be generally classified as irreversible or reversible inhibitors. This refers to the ability to react covalently or not with the enzyme, in particular with FAD coenzyme involved in catalysis. Irreversible inhibitors block the enzyme, and they are not released from binding site over time as a covalent bond is established. Conversely, reversible inhibitors are stabilized by weaker interactions in the pocket for inhibition. Depending on the therapeutic approach, reversible or irreversible inhibition will be desired. Classically, irreversible MAO inhibitors were associated with higher toxicity, although the development of specific isozyme selective compounds would reduce these complications (Youdim et al. 2006; Edmondson and Binda 2018; Anderson et al. 1993). In general, irreversible inhibitors can be classified into different classes attending to its chemical structure: hydrazines, cyclopropylamines, and propargylamines, among others. Irreversible inhibitors permanently deactivate the enzyme, and its action can only be recovered by the expression of new enzyme. The formation of the enzyme-inhibitor

adduct has been related to increased secondary effects and potential immunogenicity of these adducts.

From a structural point of view, there are some important details to mention, particularly for MAO-B inhibitors. Related to the well-known architecture of MAO-B cavities, nature of the inhibitor will determine different binding site conformations. Larger compounds will occupy both, entrance and substrate cavity, inducing an open conformation of Ile199 side chain (i.e., safinamide, approved drug for the treatment of PD). In this case, this compound guides its amine moieties to flavin ring mimicking natural substrate orientation and establishing hydrogen bonds with Gln206 (Binda et al. 2007). This situation, with both cavities engaged, is found also with other compounds (Binda et al. 2003). In turn, smaller compounds can bind in the substrate cavity with a close conformation of Ile199 gate. Thus, depending on the inhibitor size, connection between cavities will vary, regardless of nature of inhibition (Fig. 1c) (Binda et al. 2003). Considering mechanistic details, known irreversible inhibitors such as rasagiline establish a covalent bond with N5 atom of the flavin ring (Binda et al. 2004, 2005). Other mechanisms have been described for other compounds as tranylcypromine, one of the first antidepressants, consisting in covalent linkage in this case with C4A atom of the flavin ring (Bonivento et al. 2010).

Considering selectivity, compounds can exhibit different levels of inhibition towards A or B isozyme. Apart from this, it is important to mention brain selectivity. Some compounds, regardless its affinity for A or B enzymes, can exhibit preferential brain activity and no peripheral MAO activities. Ladostigil, a compound that has completed phase II clinical trials for mild cognitive impairment as dual neuroprotective agent with cholinesterase and brain-selective MAO activity (Schneider et al. 2019) is a good example of this situation. This compound did not show intestinal MAO-A inhibition upon oral administration in rabbits, exhibiting brain selectivity for MAO inhibition (Weinreb et al. 2012).

3 Therapeutic Value of MAO Inhibitors

Several chemical structures are described as MAO inhibitors, and many new compounds are being developed. An extensive review about privileged scaffolds as MAO inhibitors is described in Tripathi et al. (Tripathi et al. 2018). Here we focused on preclinical and clinical studies with MAO inhibitors targeting several diseases from classical to new therapeutic approaches.

3.1 Affective Diseases

Classically, the effectiveness of MAO inhibitors as antidepressants raised the hypothesis of a potential overexpression of MAO enzymes as the cause of some forms of depression, and on the opposite, reduced MAO activity has been related to violent behavior (Alia-Klein et al. 2008). MAO inhibitors have been typically used

for the treatment of depression and related disorders, and they were the first antidepressant drugs developed (Ramachandraith et al. 2011). The therapeutic value for this and other related affective diseases is, in general, related to MAO-A inhibition in the central nervous system (CNS), leading to increased levels of serotonin among other neurotransmitters such as noradrenaline (Youdim et al. 2006; Finberg 2014; Finberg and Rabey 2016). In addition, the selective MAO-A inhibitor ^{11}C -harmine was used for brain imaging and gave evidence of increased MAO-A levels in striatal, mid-brain, and cortical locations of major depressive disorder patients (Meyer et al. 2006). In this line, MAO-A activity is potentiated upon chronic glucocorticoid treatment in several experimental models, thus indicating relationship between stress and increased MAO-A activity (Soliman et al. 2012). MAO-A overactivity results in a decrease in monoamine neurotransmitters supporting the idea of using MAO inhibitors for the treatment of this kind of diseases, in line with classic biogenic amine hypothesis of depression (Ramachandraith et al. 2011; Finberg 2014). In addition, different MAO-A gene polymorphisms have been connected with behavioral traits, associating reduced MAO-A expression to aggressive mood and overexpression to depression (Alia-Klein et al. 2008). Most relevant MAO inhibitors for the treatment of affective disorders are summarized in Table 1.

Some of the first non-selective irreversible MAO inhibitors are still being used in clinic (i.e., phenelzine and tranylcypromine). Nevertheless, the abovementioned medical complications lead to new compound profiles. In this sense, reversible and selective MAO-A inhibitors (RIMAs) appeared from 1980s to deal with “cheese effect” among other complications. In relation with it, the safety of these compounds was assessed by several clinical studies with tyramine combination (Finberg 2014; Finberg and Rabey 2016). Also, a potential secondary effect is related to the combination of irreversible MAO inhibitors and drugs with the ability to elevate 5-HT, such as serotonin reuptake inhibitors (SSRIs), leading to the serotonin toxicity syndrome (Gillman 2006). Thus, in the case of needing a serotonin reuptake inhibitor, it is necessary a washout period between 7 and 10 days for complete recovery of MAO activity. The reversible mechanism of action facilitates the competition of concentrated substrate with the inhibitor; thus, in case of high inhibition, the substrate is able to displace the inhibitor from the catalytic site limiting the secondary effects.

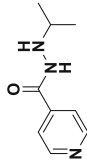
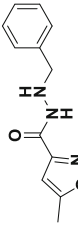
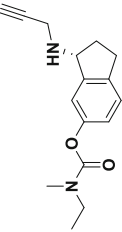
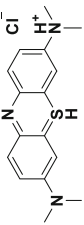
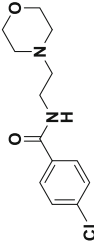
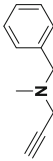
Moclobemide is the most important RIMA available for clinical use (approved in several western countries such as United Kingdom) also pirlindole (available in Russia) (Fasipe 2019; Lotufo-Neto et al. 1999). Other RIMAs were marketed; however, most of them were rejected. They are valuable in the treatment of depression associated to aged people and also other affective disorders such as bulimia or hypersomnia (Zisook 1985). In this line, compound CX157 was developed to achieve higher levels of brain MAO-A inhibition, and it is the first RIMA with documented reversible brain MAO-A inhibition which correlates to its plasma concentration (Fowler et al. 2010). It ended phase II clinical trials for major depressive disorder (NCT00739908); however, no more clinical studies have been documented to date. Novel compounds targeting MAO-A are still being developed, i.e., pyrazoline and hydrazone derivatives, that led to more potent MAO-A inhibitors

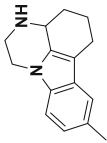
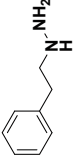
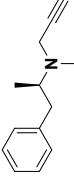
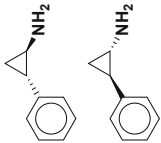
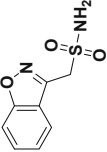
Table 1 MAO inhibitors for the treatment of affective disorders

Compound	MAO inhibition and state of development	Comments	Structure
Befloxadone	Reversible A; Not approved	Research and clinical use for brain positron emission tomography (PET) imaging of MAO-A with [¹¹ C]befloxadone radioligand (Curet et al. 1996; Zanotti-Fregonara and Bottlaender 2014; Zanotti-Fregonara et al. 2014)	
Brofaromine	Reversible A; Not approved	It is also a modest inhibitor of serotonin reuptake. Broadly studied and clinical trials although not approved, probably due to the limited market (Lotufo-Neto et al. 1999; Chouinard et al. 1993)	
Clorgyline	Irreversible A; Not approved	Crystal structure of MAO-A with clorgyline is one of the only two available for this isozyme (De Colibus et al. 2005). Improved affective phenotypes in a mouse model of Huntington's disease (HD) and antidepressant effects demonstrated in humans (Finberg and Rabey 2016; Garcia-Miralles et al. 2016)	
CX157	Reversible A; Not approved	Potent brain MAO-A inhibition observed in humans and first RIMA with documented reversible brain MAO-A inhibition which correlates to its plasma concentration (Fowler et al. 2010). Completed phase II clinical trials for major depressive disorder (NCT00739908)	
Harmine	Reversible A; Not approved	Research and clinical use for brain PET imaging of MAO-A with [¹¹ C]harmine radioligand (Zanderigo et al. 2018). Crystal structure of MAO-A in complex with harmine (Son et al. 2008). Harmine is related with stimulation of human neural progenitors and restoration of astrocytic functions, which could be linked with its antidepressant potential (Dakic et al. 2016; Liu et al. 2017a). Clinical trials for resistant depression with Ayahuasca, a botanical hallucinogenic brew (NCT02914769) (Sanches et al. 2016)	

(continued)

Table 1 (continued)

Compound	MAO inhibition and state of development	Comments	Structure
Iproniazid	Irreversible A and B; Not approved (removed from market)	Strong liver toxicity associated to hydrazine compounds (Youdim et al. 2006; Edmondson and Binda 2018)	
Isocarboxacid	Irreversible A and B; Approved	Rarely use due to dietary restrictions and toxicity associated to hydrazine compounds (Youdim et al. 2006; Edmondson and Binda 2018)	
Ladostigil	Irreversible A and B; Not approved	Potential antidepressant activity showed in rats. Brain selectivity towards MAO inhibition, avoiding dietary restrictions (Weinreb et al. 2012)	
Methylene blue	Reversible A; Approved for the treatment of methemoglobinemia	It is also a non-selective inhibitor of nitric oxide synthase, guanylate cyclase, and selective reversible MAO-A inhibitor. It has completed phase III clinical trials for bipolar disorder showing improved symptoms of depression and anxiety (NCT00214877) (Alda et al. 2017)	
Moclobemide	Reversible A; Approved	Evaluated for nicotine dependence (Berlin et al. 1995). Compared efficacy to SSRIs for the treatment of depression. The first RIMA approved in Europe (Loufo-Neto et al. 1999)	
Pargyline	Irreversible B; Not approved	Antidepressant and antihypertensive activities (Finberg and Rabey 2016)	

Pirlindole	Reversible A; Approved	Promotes hippocampal adult neurogenesis and prevent stress-associated dendritic atrophy of granule neurons in a chronic stress rat model (Morais et al. 2014)	
Phenelzine	Irreversible A and B; Approved	One of the first developed antidepressants. Needs dietary control for tyramine ingestion, hepatotoxicity (Finberg and Rabey 2016)	
Selegiline	Irreversible B; Approved	Approved for the treatment of major depressive disorder in a transdermal patch to avoid "cheese effect" (Lee and Chen 2007)	
Tranylcypromine	Irreversible A and B; Approved	Needs dietary control for tyramine ingestion (Finberg and Rabey 2016)	
Zonisamide	Reversible B; Approved for the treatment of epilepsy	Clinical trials conducted for sleep apnea (NCT01765608), alcohol use (several clinical trials available; one phase IV study for the treatment of alcohol dependence NCT00595556), bipolar disorder (NCT00047567), post-traumatic stress disorder (NCT01847469, NCT03376139), and cocaine dependence (NCT01137890)	

than moclobemide that exerted antidepressant properties in behavioral in vivo tests (Evranos-Aksoz et al. 2017).

Development of selective MAO-B inhibitors, accelerated for their use in PD, leads to their evaluation in depression, considering that they do not induce hypertensive crisis (“cheese effect”). A prominent example was selegiline, a selective irreversible MAO-B inhibitor, approved for major depressive disorder (Finberg and Rabey 2016; Lee and Chen 2007). In order to increase CNS levels, it was administered as transdermal patch, a formulation that increased its brain distribution. Its high brain concentration inhibited both isozymes (A and B), since it is a selective MAO-B inhibitor only at low concentrations. Therefore, under this administration regime, MAO-A inhibition was observed at CNS level without hepatic or intestinal effects (Mawhinney et al. 2003). Selegiline was further evaluated clinically for the treatment of attention deficit hyperactivity disorder (ADHD) in children where it showed increased levels of attention similar to those achieved with methylphenidate (first-line treatment) (Akhondzadeh et al. 2003; Rubinstein et al. 2006). Rasagiline and safinamide, other selective irreversible and reversible MAO-B inhibitors, respectively, were also found to be effective in the treatment of depression associated to PD patients, as shown in different clinical trials (Barone et al. 2015; Korchounov et al. 2012; Ryan et al. 2019; Smith et al. 2015) (Table 1).

3.2 Parkinson’s Disease

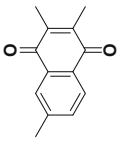
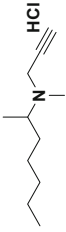
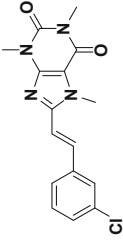

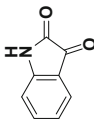
PD is a chronic and fatal neurodegenerative disease that affects mainly the nigrostriatal dopaminergic neurons, resulting in tremor, muscle rigidity, bradykinesia, and instability. Following the development of MAO inhibitors as treatments for depression and other affective disorders, and considering the implication of MAO enzymes in the metabolism of dopamine, their application for the treatment of PD started to be clinically tested. Furthermore, the target in this case was MAO-B inhibition that also led to reduced toxicity risk. In general, MAO-B inhibitors are indicated for patients showing mild motor deficits as results in clinical trials in early PD demonstrated mobility scores improvement compared to levodopa. These compounds showed benefits in the rate of motor fluctuations with reduced adverse effects compared to other dopaminergic agents (Caslake et al. 2009). In that sense, the application of MAO-B inhibitors for PD relies on several observations: (1) both MAO-A and MAO-B isozymes show similar rates for dopamine metabolism (Youdim et al. 2006); (2) levels of MAO-B are increased in PD conditions as consequence of gliosis, considering that this enzyme is mainly present in glial cells (Nagatsu and Sawada 2006); (3) human basal ganglia dysfunction is closely related to PD, and these structures contain higher levels of MAO-B isozyme. In this sense, MAO-B activity has been found to be increased in PD affected areas as *substantia nigra* (Youdim et al. 2006; Mallajosyula et al. 2008); (4) aging is the most important PD risk factor, and MAO-B levels increase with age, as observed in human brain postmortem studies. Thus, MAO-B overactivity might be related to

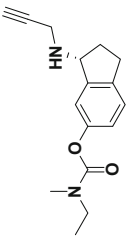
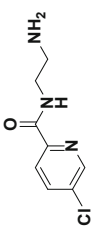
neurodegeneration as a consequence increased ROS levels (Mallajosyula et al. 2008; Fowler et al. 1997).

ROS are considered to play a central role on the onset and progression of the disease. In PD there is a selective loss of dopaminergic neurons in the *substantia nigra* pars compacta, and this neuronal death is considered to be linked to oxidative stress due to dopamine metabolism (Segura-Aguilar et al. 2014). In brief, tyrosine is converted into L-DOPA by tyrosine hydroxylase (TH) and then decarboxylated by the DOPA-decarboxylase to generate dopamine in the brain (Meiser et al. 2013). The metabolism of dopamine by MAO enzymes, or its auto-oxidation, leads to the production of reactive oxygen species (ROS) (Blesa et al. 2015). On the one hand, the auto-oxidized form of dopamine, a quinone-related structure, is a powerful electrophile that exerts high toxicity to the cell. On the other hand, MAO metabolism of dopamine releases hydrogen peroxide that decomposes to generate ROS, thus, exacerbating cellular damage. In this line, dopaminergic neurons present in *substantia nigra* are surrounded by astrocytes containing high levels of MAO-B enzyme; thus, they are exposed to increased oxidative stress, as previously described. In general, neurons contain lower levels of glutathione (GSH) than astrocytes to control oxidative stress; therefore, they are highly susceptible to this toxic stimulus (Mallajosyula et al. 2008; Sian et al. 1994). In fact, decreased levels of GSH increase neuronal vulnerability to free radicals that induce mitochondrial dysfunction and maintain α -synuclein in a protofibril state. α -Synuclein protofibril finally aggregates to form Lewy bodies observed in postmortem brain of PD patients (Croisier et al. 2005; Poewe et al. 2017). Most relevant MAO inhibitors for PD treatment are summarized in Table 2.

The first MAO inhibitor approved for the treatment of PD was selegiline (L-deprenyl), a selective irreversible MAO-B inhibitor. This compound was marketed on the 1980s and used in combination with L-DOPA or levodopa, a dopamine precursor that was the main treatment for PD symptoms. This inhibitor belongs to propargylamine class of compounds, in general, acting through covalent bonding to N5 atom of flavin ring of FAD coenzyme, as previously mentioned. It suffers first-pass metabolism to generate amphetamine and methamphetamine (Yasar et al. 2006), related with potential CNS and cardiovascular secondary effects (Gal et al. 2005). Nevertheless, there is no reported toxicity derived from selegiline metabolites probably due to the safer clinical doses used, although it could contribute to sleep disturbances (Muller et al. 2013; Yasar et al. 1996). Conversely, it has been reported a psychostimulant-like behavioral effects related with production of selegiline-derived amphetamine metabolites at higher doses (Yasar et al. 2006). Although it can be used in monotherapy (Youdim et al. 2006), clinical trials demonstrated that levodopa dosing can be reduced 30–40% when combined with selegiline (Myllyla et al. 1997); additionally, the DATATOP study demonstrated that only 26% of selegiline treated patients needed levodopa combination after 12 months compared to 47% of placebo group (Parkinson Study 1989). Thereafter, the SELEDO study demonstrated that the mean time delay for an increase of 50% of levodopa dosage in selegiline treated patients was 4.9 years, compared to 2.6 years

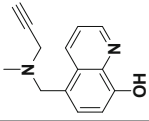
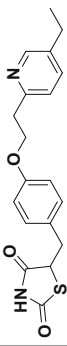
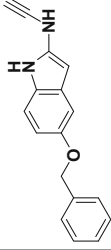
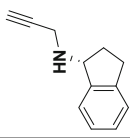
Table 2 MAO inhibitors for the treatment of PD

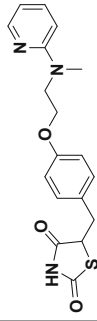
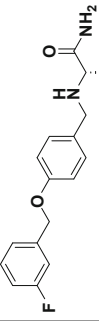
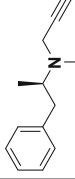
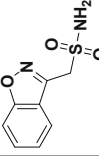
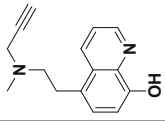
Compound	MAO inhibition and state of development	Comments	Structure
2,3,6-Trimethyl-1,4-naphthoquinone (TMN)	Reversible A and B; Not approved	Present in tobacco plant. Increased dopamine levels in the striatum observed in TMN pre-treated MPTP mice (Castagnoli et al. 2003). Similar structures such as 1,4-naphthoquinones also showed MAO inhibition (Coelho Cerqueira et al. 2011)	
2-HMP (N-(2-heptyl)-N-methylpropargylamine)	Irreversible B; Not approved	Showed in vivo selective and brain specific MAO-B inhibition. Neuroprotection and antiapoptotic activity, MAO-B independent (Berry 1999)	
(E)-8-(3-Chlorostyryl)caffeine (CSC)	Reversible B; Not approved	Dual adenosine A _{2A} receptor antagonist and MAO-B inhibitor developed as xanthine derivative. Protective profile against 6-hydroxydopamine (6-OHDA) in rats (Aguiar et al. 2008)	
Farnesol	Reversible B; Not approved	Showed in vivo rat brain MAO-B inhibition (Khalil et al. 2006). Reported neuroprotective activities in LPS mice model by regulating apoptotic cascade through antioxidant effects (Santhasabapathy and Sudhandiran 2015)	
Isatin	Reversible B; Not approved	An endogenous indole with MAO inhibitory properties, more selective for B isozyme. Isatin is able to increase brain dopamine levels upon striatal administration in rat (Justo et al. 2016). It improves bradykinesia and striatum dopamine levels in rat model of PD induced by the Japanese encephalitis virus (Ogata et al. 2003). It improves apomorphine (APO)-induced rotations	

		<p>in a 6-OHDA rat model, although this effect seems to be MAO independent as caudate putamen dopamine levels do not change (Zhou et al. 2001). Isatin pre-treatment in MPTP mice improved locomotor activity and profile of ubiquitinated brain mitochondrial proteins, related with mitochondrial dysfunction elicited by the toxin (Buneeva et al. 2018)</p>	
Ladostigil	Irreversible A and B; Not approved	<p>Ladostigil showed brain-selective MAO inhibition. It inhibits hippocampal and striatal MAO isozymes in rats upon chronic treatment, increases striatal dopamine levels, and inhibits behavioral hyperactivity following L-DOPA treatment (Sagi et al. 2005). Ladostigil also avoids nigrostriatal neurodegeneration in MPTP mice model (Youdim 2013)</p>	
Lazabemide	Reversible B; Not approved	<p>Shows higher potency than selegiline (Henriot et al. 1994). Clinical trials in levodopa-treated PD patients were carried out without improvement in clinical features of the disease (Parkinson Study 1994). Some lazabemide derivatives are currently being developed for further research (i.e., an L-DOPA-lazabemide prodrug composed by L-DOPA linked with lazabemide via an amide) (Hoon et al. 2017; Zhou et al. 2018)</p>	

(continued)

Table 2 (continued)

Compound	MAO inhibition and state of development	Comments	Structure
M30	Irreversible A and B; Not approved	The propargyl moiety of the compound is thought to be responsible of neuroprotective properties observed, related to interaction with Bcl-2 and Bcl-x1 apoptotic proteins (Youdim 2013; Zheng et al. 2005). Limited actuation of M30 on cardiovascular effect of oral tyramine in rats in comparison with tranylcypromine as control, related to its brain selectivity (Gal et al. 2010)	
Pioglitazone	Reversible B; Not approved	Antidiabetic drug under repurposing studies for PD treatment. Phase II clinical trials in early PD patients was carried out although pioglitazone was not found to modify progression of the disease (NCT01280123) (Neuro 2015)	
PF9601N (N-(2-propynyl)-2-(5-benzoyloxy-indolyl)methylamine)	Irreversible B; Not approved	Tryptamine derivative (Pérez et al. 1999). It showed nigrostriatal dopamine neurons protection in MPTP mice and rats under 6-OHDA striatal lesion (Cutillas et al. 2002; Perez and Unzeta 2003). As other propargylamine inhibitors, neuroprotective effects are in part related with antiapoptotic properties MAO-independent (Sanz et al. 2008)	
Rasagiline	Irreversible B; Approved	Approved for the treatment of PD	

Rosiglitazone	Reversible A and B; Not approved	Antidiabetic drug under repurposing studies for PD treatment. Low selectivity for MAO-B inhibition (Binda et al. 2011a)	
Safinamide	Reversible B; Approved	Approved for the treatment of PD	
Selegiline	Irreversible B; Approved	Approved for the treatment of PD	
Zonisamide	Reversible B; Approved (not in United States, but available in Japan)	Antiepileptic drug repurposed for PD treatment and approved in 2009 in Japan	
VAR103039	Irreversible A and B; Not approved	Multitarget compound that achieves iron chelation, iron-induced lipid-peroxidation inhibition, and brain-selective MAO inhibition, structurally related with M30. It showed neuroprotective profile in MPTP mice and 6-OHDA rats, attenuating striatal dopamine loss and increasing tyrosine hydroxylase levels. Chronic treatment in aged rats led to an increase in neurotrophic factors (BDNF, GDNF) and Bcl-2 family proteins (Bar-Am et al. 2015)	

of placebo patients (Przuntek et al. 1999). This is important for reducing levodopa-induced dyskinesia observed in levodopa-treated PD patients.

Another propargylamine potent selective irreversible MAO-B inhibitor, rasagiline, was then developed on the 2000s and approved for the treatment of PD. This compound is not metabolized into amphetamine as selegiline, offering an improved profile in terms of potential neurotoxicity (Edmondson and Binda 2018). Rasagiline can improve motor behavior, motor complications, mood, and sleep disorders due to its additional glutamate antagonizing properties (Muller et al. 2013; Dong et al. 2016). After satisfactory safety clinical trials, rasagiline showed reduced PD advance (Rabey et al. 2000), and this observation was further evaluated in the TEMPO study. Results from this study suggested a potential disease modifying activity of rasagiline that reduced the disease progression and increased patient quality of life (Parkinson Study 2002, 2004). Considering these encouraging results, a new clinical trial was designed to evaluate the effectiveness of rasagiline in combination with levodopa in advanced PD patients, the LARGO study (Rascol et al. 2005). In this case, rasagiline showed reduced off-time duration intraday and improved clinical global improvement and motor function on patients. More recently, a new double-blind clinical trial was conducted to further evaluate the potential disease modifying ability of rasagiline in PD, the ADAGIO study (Olanow et al. 2009). The results showed a possible disease modifying effect of rasagiline given at 1 mg daily dosage; however, it did not show this effect at 2 mg daily dosage; thus, these divergent results are not conclusive (Rascol et al. 2011; Jankovic et al. 2014).

As previously depicted, irreversible inhibitors led to strong and long-lasting inhibition, and new enzyme has to be synthesized. In that sense, reversible inhibition appears to be more manageable, maintaining selectivity to the B isozyme. Safinamide, a reversible and highly selective MAO-B inhibitor, was then developed following this idea and has been recently approved as an adjunctive treatment to L-DOPA for mild- to late-stage PD (Borghain et al. 2014). Separately from selective reversible MAO-B inhibition, this drug acts through multiple mechanisms of action. It is able to block sodium and calcium channels and reduce excessive glutamate release (Stocchi et al. 2006). It has shown a safer profile, and there is evidence of improved motor symptoms in early PD patients (Edmondson and Binda 2018; Bette et al. 2018; Fabbri et al. 2015). Initial clinical studies (study 015 and continued in study 017) showed improved motor scores in safinamide treated patients as well as improved quality of life (Schapira et al. 2013). Thereafter, the MOTION study also demonstrated benefits in the ADL score, health-related quality of life, better cognition, and increased rate of responders (Stocchi and Torti 2016). Thereafter, the SETTLE trial (in combination with levodopa) demonstrated a significant increase in the on-time and improved motor symptoms (Schapira et al. 2013) (For a critical review of safinamide clinical evidence in PD, see Bette et al. (2018)). In addition, a recent post hoc analysis of the 2-year study 018 revealed a reduction on chronic pain suffered by PD patients with a reduction on pain drugs usage (Cattaneo et al. 2018). Finally, the recent SIN-DEP-PAR and SELEDO clinical studies further

confirm the beneficial effects of selegiline for the management of PD (Muller and Mohr 2019).

Apart from MAO-B inhibition-related aspects, this kind of inhibitors exhibit MAO-independent activities, also responsible of its beneficial effects as mentioned for safinamide. It has been demonstrated that selegiline exerts neuroprotective activities against MPTP toxicity also in cell lines lacking MAO-B (Le et al. 1997). In this sense, rasagiline and selegiline have been effective in several neuroprotection models of disease, and they have demonstrated antiapoptotic properties, an effect attributed to the propargylamine moiety (Szoko et al. 2018).

During the last years, new multitarget drugs derived from rasagiline have been developed for the treatment of PD among other neurodegenerative diseases. Ladostigil, an example of rasagiline multitarget derivative, inhibits brain acetylcholinesterase, butyrylcholinesterase, and brain MAO-A and MAO-B isozymes after chronic treatment in rats. Furthermore, it exerts neuroprotection against MPTP toxicity in mice, among other activities (Youdim 2013). Related to its neuroprotective profile in preclinical models, ladostigil has completed phase IIb clinical trials for mild cognitive impairment and Alzheimer's disease (AD) (NCT01354691, NCT01429623) (discussed below). M30, another rasagiline derivative, is a multitarget iron chelator that exhibits brain-selective MAO inhibition and neuroprotection against MPTP, lacatcystin, and 6-hydroxydopamine in animal models of PD. The protective properties of M30 were also dependent to the ability of the drug to activate the hypoxia-induced factor (HIF) and derived induction of neurotrophins as brain-derived neurotrophic factor (BDNF), vascular endothelial growth factor (VEGF), erythropoietin, and glia-derived neurotrophic factor (GDNF) (Youdim 2013). Finally, it was demonstrated that M30 elevated dopaminergic and transferrin receptor cell count in the *substantia nigra* of MPTP-treated mice (Youdim 2012). Apart from the previously mentioned increase in MAO activity with PD and ageing, iron was also observed to increase in such conditions stating the promising future of multitarget iron chelators (Youdim et al. 2014).

Last years, repurposing programs are being used for the development of new treatments for complex diseases, due to their interesting cost reduction. In that sense, glitazones, used as antidiabetic drugs, were evaluated for PD as they showed MAO-B inhibition properties. This is the case of pioglitazone and rosiglitazone. Crystal structure of pioglitazone in complex with MAO-B explained binding mode through both the entrance and substrate cavities (Binda et al. 2011a). Several studies position this compound for potential PD treatment: (1) acute treatment of MPTP mice led to the absence of striatal dopamine reduction and improved motor behaviors (Barbiero et al. 2011); (2) beneficial effects on rotenone model of PD in rats related to recovery of striatal dopamine levels and locomotion (Ulusoy et al. 2011); (3) improvements in the 6-OHDA model in rats: reduced mortality rate, attenuated microglial activation, exerted antidepressant-like effects, induction of hippocampal neurogenesis (often associated with depression in PD patients), and protection against hypolocomotion (Bonato et al. 2018; Machado et al. 2019); and (4) decreased neuroinflammation in the midbrain and striatum and improved motor phenotype in Cox10/DAT-cre mice (dopaminergic neuron knockout of Cox10

essential for maturation of COXI, catalytic subunit of Complex IV of mitochondrial respiratory chain) (Pinto et al. 2016). Phase II clinical trials in early PD patients was carried out although pioglitazone was not found to modify progression of the disease (NCT01280123) (Neurol 2015). On the other hand, rosiglitazone showed low selectivity for MAO-B inhibition (Binda et al. 2011a) and also reported properties of this drug in PD models: (1) pre-treatment with rosiglitazone prior to 6-OHDA insult in rats leads to protection against striatal dopaminergic death and decrease in some pro-inflammatory markers as TNF- α (Lee et al. 2012) and (2) partial recovery of striatal dopamine content and dopamine neuron degeneration in *substantia nigra* after rosiglitazone treatment in MPTP mice (Carta et al. 2011). The protective effects of this kind of compounds may be MAO-independent, at least in part, as demonstrated by importance of peroxisome proliferator-activated receptor γ (PPAR γ) activation by glitazones for neuroprotection in *substantia nigra* and its related anti-inflammatory actions (Martin et al. 2012).

Another important example of repurposing is the case of the antiepileptic drug zonisamide, compound approved for the treatment of PD in Japan. Its binding mode was elucidated in the substrate cavity in complex with MAO-B (Binda et al. 2011b). Among several results in PD-related models, it has been demonstrated implication of zonisamide as MAO inhibitor, showing an attenuation of striatal dopamine and tyrosine hydroxylase reduction in MPTP mice (Sonsalla et al. 2010). Zonisamide has also showed a neuroprotective profile in a genetic mouse model of PD, reducing motor symptoms (Sano et al. 2015), enhancing L-DOPA treatment (Nishijima et al. 2018), and exhibiting a reduction in associated dyskinesia in 6-OHDA rats (Oki et al. 2017). In this line, zonisamide has been evaluated in several clinical trials, most of them in Japan (Murata et al. 2015, 2016, 2018), and there is one recent open study in advanced PD in Egyptian population (NCT04182399). As previously mentioned, it was approved in Japan for use as anti-PD agent in 2009, in patients treated with other drugs in combination with L-DOPA that show inadequate responses (Grover et al. 2013) (Table 2).

3.3 Other Neurodegenerative Disorders

Given the neuroprotective profile of several MAO inhibitors, they could be useful for treatment of other neurodegenerative diseases. These complex diseases share many physiopathological mechanisms, in which MAO enzymes are involved, such as oxidative stress and neuroinflammation.

In this sense, several MAO-B inhibitors have been evaluated as potential treatments of AD. This is the most prevalent neurodegenerative disease, and it is characterized by progressive memory loss and incapacitation for daily task. AD major symptoms are accompanied by depression, agitation, delusions, and hallucinations. AD patients showed higher levels of MAO-B activity, and this may lead to an exacerbated oxidative stress condition in this disease (Kennedy et al. 2003). MAO activation has also been related to cognitive impairment, altering balance of neurotransmitters, and the formation of amyloid plaques through the

modulation of amyloid precursor protein (APP) processing by MAO (for review, see Cai (2014)). These evidences prompted the application of MAO inhibitors as potential treatments of AD. In this line, selegiline and rasagiline have been evaluated in clinical trials for AD (NCT01701089, NCT00104273, NCT02359552). Initial clinical trials with selegiline pointed to a potential cognitive and behavioral improvement after 3–6 months treatment (Campi et al. 1990; Filip and Kolibas 1999); however, these results were not corroborated in other cases (Tariot et al. 1987; Burke et al. 1993). Further post hoc analysis determined that selegiline might have a short-term beneficial effect with no clinical relevance.

Given the potential protective effects of these compounds, also novel rasagiline derivatives have been tested. This is the case of M30 and ladostigil, previously introduced in this review for the treatment of PD. These compounds were developed as multitarget drugs combining interesting activities for the treatment of neurodegenerative diseases (see Sect. 3.2). M30 has been observed to be involved in regulation of amyloid β ($A\beta$), inhibiting its accumulation in APP/presenilin 1 mice, neurogenesis, suppression of oxidative stress, pro-cognitive, and anti-inflammatory effects (improvement in a rat model of AD with amyloid pathology McGill-R-Thy1-APP transgenic rats) (Cai 2014; Kupersmidt et al. 2012; Pimentel et al. 2015; Zheng et al. 2010). Ladostigil was shown to be related with APP translation and processing (Yogev-Falach et al. 2006) and neuroinflammation in a model of aged rats (Panarsky et al. 2012). These among other properties such as its acetylcholinesterase inhibition point out ladostigil as a new candidate for AD treatment, and phase II clinical trials has been conducted (NCT01354691, NCT01429623). Although it was safe and well tolerated, ladostigil did not delay progression to dementia. In spite of its failure, ladostigil treatment was associated with reduced brain and hippocampus volume loss (Schneider et al. 2019).

Apart from the abovementioned compounds, many others have shown potential therapeutic value for AD: (1) *harmine* improved memory and learning in animal models and exerted anti-inflammatory properties in LPS-mouse model (Dos Santos and Hallak 2017; Liu et al. 2017b); (2) *methylene blue* relationship between serotonin levels and psychological symptoms of AD could be an approach for this compound. Apart from this, methylene blue has shown attenuation of the formation of amyloid plaques, neurofibrillary tangles of tau protein, and involvement in mitochondrial function restoration, among others (Oz et al. 2009). It is currently under clinical trials (NCT02380573); (3) *KDS2010* is a novel compound highly potent and selective reversible MAO-B inhibitor (Fig. 2). It has demonstrated learning and memory improvements, promotion of synaptic transmission, and reduction of astrogliosis and astrocytic GABA levels in APP/presenilin 1 mice (Park et al. 2019). Importantly, abundant GABA production by MAO-B in reactive astrocytes has been linked to AD-like pathology in animal models of AD (Jo et al. 2014); (4) *ASS234* is a multitarget compound that inhibits acetylcholinesterase, butyrylcholinesterase, and MAO enzymes (Fig. 2). From crystal structure in complex with MAO-B, it is known that it acts as irreversible inhibitor binding to the FAD coenzyme (Esteban et al. 2014). It has been shown that ASS234 is able to restore scopolamine-induced cognitive impairment and prevent $A\beta$ aggregation in animal

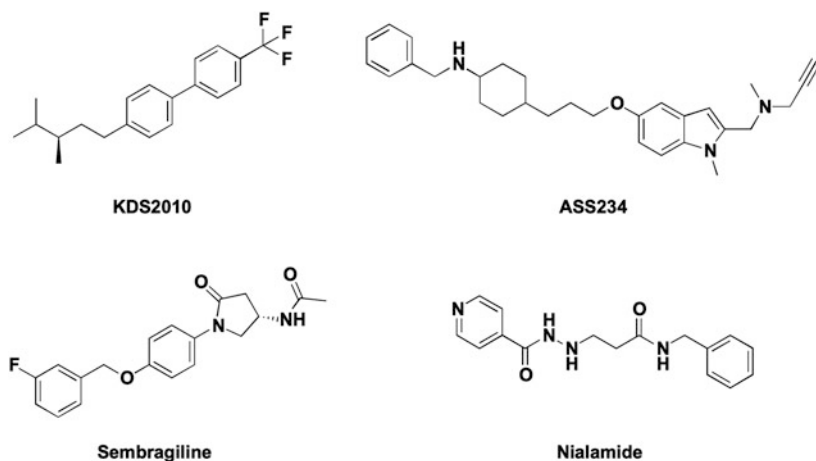


Fig. 2 Chemical structure of novel MAO inhibitors for the treatment of AD (KDS2010, ASS234, sembragiline) and ischemic stroke (nialamide)

models of AD (Marco-Contelles et al. 2016); (5) *sembragiline* has shown potent and reversible MAO-B inhibition with an improved safety profile, regarding serotonin syndrome and the “cheese effect” observed with other MAO inhibitors (Fig. 2). Interestingly, this compound was protective against oxidative stress and astrogliosis in transgenic mice overexpressing MAO-B in astroglia (Borroni et al. 2017). In accordance with these promising results and after phase I trials, *sembragiline* was evaluated in phase II clinical trials for AD (MAYflOwer RoAD study) suggesting potential benefits on behavioral symptoms in some subpopulations (NCT01677754) (Nave et al. 2017). No differences were found between treated groups and placebo in ADAS-Cog11 scale performance, missing the primary endpoint. Positron emission tomography measurements have demonstrated that same dose used in phase II clinical trial (NCT01677754) achieved near-complete brain MAO-B inhibition in AD patients daily treated with *sembragiline* (NCT01701089) (Sturm et al. 2017).

Amyotrophic lateral sclerosis (ALS) and Huntington’s disease (HD) share many of the pathophysiological characteristics of PD and AD. Although selegiline was shown to be ineffective in clinical trials for ALS (Lange et al. 1998), other MAO inhibitors have demonstrated potential properties. Previously mentioned iron chelator M30 was evaluated in SOD1-G93A transgenic mouse model of ALS in combination with high-calorie energy supplemented diet, and it has been related with protective effects on motor performance and increased survival, with brain MAO inhibition and reduction in dopamine metabolism (Golko-Perez et al. 2016). Other MAO inhibitors such as rasagiline have been evaluated in clinical trials for ALS. This compound was safe in ALS patients, also suggesting potential disease modifying properties in some subpopulations of the study when co-administered with riluzole (NCT01879241) (Ludolph et al. 2018). However, when administered alone it did not show any alteration of the disease progression when compared to control after 12 months (Statland et al. 2019).

Regarding dopamine imbalance present in HD (Chen et al. 2013), MAO inhibitors have been evaluated for this condition. MAO activity is increased in brain tissue from HD patients and mouse striatal neural cells expressing huntingtin. Treatment with MAO inhibitors (clorgyline, phenelzine, selegiline) improved oxidative stress condition and survival of these cells (Ooi et al. 2015). In this line, clorgyline treatment of YAC128 HD mice restored dopamine, serotonin, and norepinephrine levels in the striatum (Garcia-Miralles et al. 2016).

Other related diseases such as cerebral ischemia have been postulated for MAO inhibition treatment. Probably related to its neuroprotective activities, selegiline treatment within 48 h after stroke improved patient recovery in a phase II study (Sivenius et al. 2001; Bartolo et al. 2015). Recently, the MAO inhibitor nialamide has shown to be protective in terms of improved functional recovery and survival after post-ischemic administration in a stroke mouse model (Liu et al. 2019) (Fig. 2).

3.4 Cardiac Diseases

Apart from the deeply discussed role of oxidative stress in neurodegenerative diseases, it also appears as an important factor for cardiovascular diseases. Serotonin and norepinephrine, which are MAO-A substrates, are related with cardiac function. On the one hand, variations in serotonin levels can lead to cardiovascular dysfunction, being important regulator of heart function (Cote et al. 2004). On the other hand, norepinephrine metabolism by MAO-A is increased in mice subjected to hemodynamic stress leading to enhanced oxidative stress, hypertrophy, chamber dilation, and reduced systolic function; clorgyline treatment of these animals showed beneficial effects on cardiac function (Kaludercic et al. 2010). Levels of MAO-A are increased in several models of cardiomyopathies, and cardiac-specific MAO-A overexpression in transgenic mice was related with oxidative mitochondrial damage, cardiomyocyte necrosis, and chronic ventricular dysfunction (Villeneuve et al. 2013). Recent studies with reversible MAO-A inhibitor moclobemide exhibited myocardium protection in rats submitted to acute volume overload (Huuskonen et al. 2019). There are some studies in the same way with MAO-B demonstrating a role of enhance activity of this isozyme in cardiac injuries after chronic hemodynamic stress (Kaludercic et al. 2014). All this shows the potential for the future clinical use of MAO inhibitors for the treatment of heart disease.

4 Summary and Future Prospects

MAO inhibitors have provided a number of successful drugs for the treatment of complex diseases, being the first drugs approved for depression. During the last 70 years, the advances on the knowledge of the crystal structures of both isozymes, MAO-A and MAO-B, tissue distribution, and substrate selectivity have led to the development of a plethora of highly selective reversible and irreversible inhibitors with clinical application. These advances overcome the deleterious side effects

improving the efficacy and security of these classes of advanced drugs. Novel therapeutics as MAO inhibitors included classical applications such as major depressive disorder, transient resistant depression, bipolar depression, etc., and it is expected as exponential growth of their application in this therapeutic area. Nonetheless, novel therapeutic areas are under use due to the development of selective MAO-B inhibitors such as the treatment of neurodegenerative diseases. In particular, the treatment of Parkinson's disease is a prominent example with four compounds in clinical use. Further applications are under development for the treatment of Alzheimer's disease, amyotrophic lateral sclerosis, and cardiovascular diseases. The ubiquitous distribution of MAO enzymes ensures future exciting development of novel therapeutics including the development of novel and safer formulations.

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