Introduction

Monoamine oxidases (MAOs) are mitochondrial outer membrane-bound flavoenzymes that catalyze the degradation of biogenic amines, more specifically the oxidative deamination of several important neurotransmitters, including 5-hydroxytryptamine (5-HT) (or serotonin), histamine, and the catecholamines dopamine, noradrenaline, and adrenaline. There are two isoforms
of MAO, MAO-A and -B, which differ with respect to amino acid sequence, distribution in the body tissues, and substrate/inhibitor specificity. MAOs play an important role in several neurodegenerative diseases such as Huntington’s disease, Alzheimer’s disease, Parkinson’s disease, and amyotrophic lateral sclerosis, as well as in depression. Furthermore, they are suspected to be inhibited in cigarette smokers and in alcoholic subjects.

Several classes of natural products can modulate MAO activity. One of these classes is the alkaloids, which are nitrogenous secondary metabolites essentially from plant origin. They are one of the largest groups of chemicals found in nature. Most alkaloids are quite toxic and produced by the plants as a defense against herbivores. This class of compounds is not only characterized by a great structural diversity but also by a great diversity of pharmacological effects. Many varieties of alkaloids have remarkable structural similarities with neurotransmitters in the central nervous system (CNS), including dopamine, serotonin, and acetylcholine. They can either mimic (agonists) or block (antagonists) the activity of neurotransmitters leading to numerous physiological and psychological effects. Among the alkaloids with activity on the CNS are those able to inhibit MAO-A and -B with various potencies, such as indole, isoquinoline, piperidine, quinazoline, tetrahydroisoquinoline, tropane, and tryptamine derivatives.

The aim of this chapter is to summarize the MAO inhibitory profiles of several of these alkaloids and highlight their importance in the search for novel MAO inhibitors to treat neurodegenerative diseases and neuropsychiatric disorders. They might be particularly promising lead compounds for discovering and developing novel clinical drugs.

THERAPEUTIC POTENTIAL OF MONOAMINE OXIDASE INHIBITION IN NEUROLOGICAL DISORDERS

Monoamine oxidases (MAOs, EC 1.4.3.4) are a family of flavin-dependent metabolic enzymes that catalyze the oxidative deamination of biogenic and xenobiotic amines. They play an important role in motor and mood control, as well as in the regulation of motivation and other brain functions. Two isoenzymes, MAO-A and -B, are distinguishable on the basis of their in vitro substrate specificity and inhibitor sensitivity [1]. MAO-A has a higher affinity for 5-HT, and to lesser extent, for noradrenaline and dopamine. It is inhibited by low concentrations of clorgyline, whereas MAO-B is more specific toward benzylamine, 2-phenylethylamine, and is inhibited by selegiline (Deprenyl) [2,3].

The reaction catalyzed by MAO generates hydrogen peroxide (H₂O₂), the corresponding aldehyde, and ammonia (from primary amines) as shown in Fig. 1 or a substituted amine (from secondary amines).

Both MAO-A and -B are tightly associated with the outer membrane of the mitochondria, and only a small part of both enzymes is found within the microsomal fraction. While MAOs located in peripheral tissues and in the blood–brain barrier seem to exert a protective role through the oxidation of
amines in the blood (metabolic barrier), MAO isoenzymes in the CNS have more specific functions [2].

As low levels of MAO-A were detected in serotonergic neurons, selective MAO-A inhibitors were shown to increase brain 5-HT and to exert an antidepressant effect. MAO-B is also present in serotoninergic neurons and, by degrading other amines, it may contribute to the purity of 5-HT delivered to the synaptic cleft. Both MAO-A and -B are found in noradrenergic neurons. Within synaptosomes of these neurons, MAO-A plays an important role in the deamination of noradrenaline and dopamine in the hypothalamus and striatum, respectively. On the other hand, MAO-B exerts a major role in the extraneuronal dopamine metabolism when dopamine uptake is impaired [2].

MAO inhibitors can be used for the treatment of neurodegenerative diseases, depression, and stroke, as well as tissue damage associated with oxidative stress, nicotine (smoking), and alcohol addiction [2]. Selectivity and reversibility are the main factors to consider while determining the usefulness of MAO inhibitors to treat neurological diseases. For instance, nonselective inhibitors have been avoided in the treatment of extraneuronal MAO-B-dependent pathologies (e.g., Parkinson’s disease) because of the “cheese reaction.” This reaction consists of a marked hypertensive response due to the increase of unchanged tyramine levels in the blood following the ingestion of food rich in tyramine, such as cheese. This is a consequence of the inhibition of MAO-A, the predominant isofom in the stomach and intestine responsible for the metabolization of dietary pressor amines [4]. However, the common trend to avoid the prescription of MAO-A inhibitors is now undergoing some changes since the discovery that these inhibitors can also improve the motor function in patients suffering from Parkinson’s disease [5,6].

MAO-B levels are up to fivefold higher in the brain of the aging population, corroborating the use of MAO-B inhibitors in age-related neurodegenerative diseases. An increase in MAO-B levels results in dopamine depletion and increases in toxic and reactive catalytic by-products, such as dopanal and H$_2$O$_2$ [1].

**Depression**

Selective MAO-A inhibition in the CNS is responsible for the antidepressant effect of MAO inhibitors clinically used, leading to increased levels of dopamine, 5-HT, and noradrenaline [1]. Reversible MAO-A inhibitors have
demonstrated particular efficacy in the treatment of depression in elderly patients [7]. Despite the efficacy of MAO-A inhibitors as antidepressants, these drugs are usually reserved for patients who failed to respond to the first-line therapy (tricyclic antidepressants), due to the risk of hypertensive crisis (the cheese reaction) and the interaction with serotonergic drugs (serotonin syndrome) [6].

MAO-B inhibitors do not have antidepressant activity and are devoid of the cheese reaction side effect, unless concentrations are high enough to also inhibit MAO-A [2].

**Parkinson’s Disease**

MAO-B inhibitors are currently used as monotherapy in the treatment of Parkinson’s disease, mainly at the early stages following the diagnosis. This increases the endogenous dopamine levels in the affected regions of the brain and postpones the beginning of levodopa treatment (which carries the risk of motor complications). Along with disease progression, the use or association of other drugs, such as dopaminergic agonists, levodopa, and COMT inhibitors, is considered [8–10]. While the MAO-B selective inhibitors are still recommended for the clinical management of Parkinson’s disease, their use has been recently revisited by several authors. Studies showed that the selective inhibition of MAO-A or -B did not alter the steady-state dopamine levels in brain. However, increases in dopamine activity and the subsequent behavioral changes are observed when both isoforms are almost completely inhibited [11]. Acute and chronic treatments with MAO-A and MAO-B inhibitors have similar effects on enzyme activity. The chronic treatment with the selective MAO-B inhibitor L-deprenyl further increases dopamine release due to the action of one of its metabolites, L-amphetamine [11–13].

**Other Neurodegenerative Diseases**

Several neurodegenerative diseases such as Huntington’s disease, Alzheimer’s disease, Parkinson’s disease, and amyotrophic lateral sclerosis have pathological characteristics in common. These include misfolding of proteins that tend to aggregate, impairment of the ubiquitin–proteasome system responsible for the elimination of highly ubiquitinated toxic protein aggregates, oxidative stress, excitotoxicity, and inflammatory processes. Few studies have shown that MAO inhibitors could counteract some of these processes through various neuroprotective mechanisms, such as the interaction with the mitochondrial outer membrane, as well as the upregulation of antiapoptotic proteins and neurotrophic factors [2,6].

Human MAO-A and -B were shown to be upregulated in the basal ganglia of the brain of Huntington’s disease patients. The increase of MAO activity correlated with the severity of the pathology [14]. A mouse model of Huntington’s
disease was also used to demonstrate that specific MAO-A knockout and the intrastralatal administration of the specific inhibitor clorgyline were both able to reduce striatal damage and oxidative stress. One possible explanation was that dopamine contributed to striatal damage caused by impaired mitochondrial function via its metabolization by MAO, followed by the production of toxic oxygen-based free radicals [15,16].

Smoke and Alcohol Cessation

MAO-A and -B were shown to be inhibited in cigarette smokers. This is one of the reasons why MAO inhibitors were suggested to be useful in smoking cessation and continued abstinence [17,18]. This effect might be related to the maintenance of a level of MAO inhibition to which smokers were exposed [2]. As a matter of fact, an increase in dopamine levels was detected in the limbic system of smokers, contributing to the reinforcement of nicotine and other addictive drugs [19].

Clinical trials with MAO-B specific inhibitors (selegiline and EVT302) failed to improve smoking abstinence rates compared to placebo [20,21]. On the other hand, the study of the polymorphism in the promoter region of the MAOA gene in alcohol-dependent, heavily smoking men showed that there was evidence for a MAOA gene-associated effect on the quantity of cigarettes smoked. Longer alleles in the promoter region are associated with increased MAO-A activity. Individuals with the 4-repeat alleles MAOA genotype consume more cigarettes per day than those with the 3-repeat allele genotype \( p < 0.05 \) [22]. Moreover, a recent study demonstrated an increase in MAO-A binding in the prefrontal and anterior cingulate cortex during acute withdrawal from heavy cigarette smoking. These findings revive the interest in the use of selective MAO-A inhibitors for smoking cessation, which needs further investigation [23].

Regarding alcoholism, some studies showed low MAO activity levels in alcoholic subjects, but these results could not be confirmed by subsequent studies. Several other factors such as gender, metabolic profile, and concomitant smoking may alter MAO activity [19]. Interestingly, a study showed that the levels of MAO-B activity were significantly increased in dependent subjects submitted to alcohol withdrawal, even after bias correction for smoking and gender [24]. Further studies are needed to better understand the role of alcohol abuse on MAOs inhibition and their implications on alcohol withdrawal.

ALKALOIDS AS MONOAMINE OXIDASE INHIBITORS

Alkaloids have been extensively investigated for their effects on MAO-A and -B. Several classes of these secondary metabolites are known as potent MAO inhibitors. Among those able to inhibit MAO-A and -B with various potencies are the indoles, isoquinolines, piperidines, quinazolines, tetrahydroisoquinolines,
tropanes, and tryptamines. Several projects on the optimization of original scaffolds of natural origin by chemical synthesis have already been started and have produced interesting and very potent mono- and multifunctional inhibitors [25–27]. However, the pharmacomodulation of these natural scaffolds generally based on local (quantitative) structure–activity relationship ((Q)SAR) and molecular modeling approaches are beyond the scope of this chapter centered on natural alkaloids.

Indole Alkaloids

β-Carbol ine Alkaloids

The β-carboline alkaloids are a large group of natural and synthetic indole alkaloids that possess a common tricyclic pyrido[3,4-b]indole ring structure. These molecules can be categorized according to the saturation of their N-containing six-membered ring and, consequently, they present marked differences in the basicity of this nitrogen atom. Unsaturated members are named as fully aromatic β-carbolines (βCs; Fig. 2A), whereas the partially or completely saturated ones are known as dihydro-β-carbolines (DHβCs; Fig. 2B) and tetrahydro-β-carbolines (THβCs; Fig. 2C), respectively [28]. Regarding their biological effects, the β-carboline alkaloids may interact selectively with specific enzymatic targets leading to a variety of pharmacological activities [29].

The inhibitory effects of βCs on MAO-A and -B have been evaluated in enzymes obtained from various organisms revealing details related to their potency, selectivity, and modes of action. The harmala alkaloids were able to inhibit both MAO isoenzymes, possessing various potency and selectivity according to the saturation of the six-membered ring containing one nitrogen atom and substituents of the β-carboline system [30–32]. In nature, these compounds are reported to occur in a number of plants, including Banisteriopsis caapi and Peganum harmala, the extracts of which are traditionally used for their medicinal and psychotropic properties [33]. The main harmala alkaloids (1–12) and their IC_{50} values for MAO-A and -B inhibition are summarized in Table 1. The mode of inhibition of both MAO-A and -B by βC alkaloids is reversible and competitive, according to kinetic studies [30,34] using human (hMAOs) and rat (rMAOs) enzymes [32,34].

![FIGURE 2 Building blocks ring systems of β-carboline alkaloids.](image)
Regarding SAR, the experimental data of MAO-A and -B inhibition by β-carboline alkaloids indicate that the fully aromatic βCs (harmine, 1), and the DHβCs (harmaline, 6) are more potent inhibitors than the THβCs (tetrahydro-harmine, 8) [30,31]. Compounds 1 and 6 displayed about the same potency for inhibiting the oxidative deamination of 5-HT by rat liver MAOs, with IC₅₀ values of 0.013 and 0.016 μM, respectively (see Table 1) [30]. These data are corroborated by studies using hMAO-A, in which 1 and 6 inhibited this enzyme with IC₅₀ of 0.002 and 0.003 μM, respectively (see Table 1) [31]. The diminution of the inhibitory activity of THβCs may be a consequence of variations in the 3D structure of the N-containing six-membered ring: a flat geometry seems to be more adequate to interact with the different parts of the MAOs active sites [36].

Additionally, it was demonstrated that 8 was about 30-fold less potent in inhibiting hMAO-A (IC₅₀ of 1.77 μM) than 1 and 6 (see Table 1) [31]. The substituent at C-7 also seems to be important for MAO-A inhibition. Compound 1,
which possesses a methoxy group at C-7, was a more potent MAO-A inhibitor than harmol (3) and harmane (4), which contain a hydroxyl group and a hydrogen at this position, respectively (see Table 1) [30,31]. Moreover, the 7-substituted βCs (1 and 6) presented higher affinity for MAO-A than the corresponding 6-substituted analogues (6-MeO-harmane, 2 and 6-MeO-harmalan, 7) (see Table 1) [30]. The lack of the methyl substituent at C-1, such as in norharmane (5), seemed to reduce about 10-fold the inhibitory activity on MAO-A. Although 5 was a weaker MAO-A inhibitor than 4, it inhibited MAO-B with IC$_{50}$ values close to those able to inhibit MAO-A, opposite to other harmala alkaloids, which seem to be selective for inhibition of the A isoform [34]. Finally, the presence of a seven-membered ring at C-1 and N-2, such as in banisteroside A (11) and B (12) [31], seems to be another feature causing the lack of MAO-A activity. The subtle variations in activity reported here could suggest that the selectivity of substrates and inhibitors for MAO-A or -B can be determined at two levels. The first one is the access to the substrate binding site through the hydrophobic entrance cavity (MAO-B) and the putative channel (MAO-A). The second possibility is by differential interactions (hydrophobic stacking and/or H-bonds) with specific residues once the molecule has entered the substrate binding site [36].

\[
\begin{align*}
1 & \quad R_1 = \text{CH}_3; R_2 = \text{OCH}_3; R_3 = \text{H} \\
2 & \quad R_1 = \text{CH}_3; R_2 = \text{H}; R_3 = \text{OCH}_3 \\
3 & \quad R_1 = \text{CH}_3; R_2 = \text{OH}; R_3 = \text{H} \\
4 & \quad R_1 = \text{CH}_3; R_2 = R_3 = \text{H} \\
5 & \quad R_1 = R_2 = R_3 = \text{H} \\
6 & \quad R_1 = \text{CH}_3; R_2 = \text{OCH}_3; R_3 = \text{H} \\
7 & \quad R_1 = \text{CH}_3; R_2 = \text{H}; R_3 = \text{OCH}_3 \\
8 & \quad R_1 = \text{CH}_3; R_2 = \text{OCH}_3; R_3 = \text{H}; R_4 = \text{H} \\
9 & \quad R_1 = R_2 = R_3 = R_4 = \text{H} \\
10 & \quad R_1 = \text{CH}_3; R_2 = R_3 = R_4 = \text{H} \\
11 & \quad R_1 = (\alpha)\text{OGluc}; R_2 = \text{OCH}_3; R_3 = \text{H}; R_4 = (\beta)\text{OH} \\
12 & \quad R_1 = (\beta)\text{OGluc}; R_2 = \text{OCH}_3; R_3 = \text{H}; R_4 = (\alpha)\text{OH}
\end{align*}
\]
Deeper structural studies by crystallography, molecular modeling, and SAR were performed until recently to modulate the potency and the selectivity of synthetic harmine (1) derivatives (see e.g., [37]). These studies showed that lipophilic substituents, replacing the methyl group of the methoxy moiety at C-7, increased the potency for MAO-A inhibition in comparison with 1. Additionally, it was found that synthetic compounds containing a cyclohexyl group as substituent at C-7 were more potent MAO-B inhibitors than 1. Docking simulations demonstrated that this cyclohexyl chain points to a lipophilic pocket in the “entrance cavity” of the human MAO-B active site.

THβC are also described as constituents of spider venom. The major THβC isolated from Parawixia bistriata venom was identified as 6-hydroxytrypargine (13), being also named PwTX-I. This compound occurs at low abundance in spider venom, and this is the reason why Saidemberg et al. [38] proposed a Pictet–Spengler synthesis of 13 for its complete functional characterization. The two synthetic enantiomers resulting from this synthesis, (+)-PwTX-I and (−)-PwTX-I, were analyzed for MAO-A and -B inhibition displaying IC\textsubscript{50} values ranging from 8 to 39 μM. The results demonstrated no significant differences in the inhibitory effects of these two enantiomers on MAO-A and -B activity. Moreover, these THβCs seemed to be slightly selective for MAO-B inhibition. The kinetic studies showed that (+)-PwTX-I and (−)-PwTX-I were noncompetitive inhibitors on both MAO-A and -B, differing from the competitive inhibition described for the harmala alkaloids [38].

![Diagram of 13](image)

### Monoterpene Indole Alkaloids

Some monoterpene indole alkaloids (MIAs) have been evaluated regarding their inhibitory activity on MAOs. Yohimbine (14) displayed a weak rMAO inhibition obtained with a partially purified liver mitochondrial preparation. These effects were observed with concentrations of 100 μM (10–20% inhibition) and 1000 μM (30–40% inhibition) [39]. In another study, isomers of 14, tested at 1000 μM, showed weak inhibition (5–15%) of rMAOs obtained with a hypothalamic tissue homogenate [40]. The antitumour agents vinblastine
(15) and vincristine (16), tested at 200 μM, inhibited the oxidation of benzylamine by rMAOs from brain mitochondria, possessing about the same qualitative potency [41]. Subsequent kinetic experiments indicated that 15 acted as a reversible and competitive MAO-B inhibitor with an estimated $K_i$ of 0.77 μM [41]. Echitovenidine (17) is an indole from Alstonia venenata fruits possessing a vincadiformine skeleton. This compound was able to inhibit 47% of tyramine oxidation by rMAOs from brain mitochondria at 300 μM and 24% at 30 μM [42].

MIAs occurring in Psychotria species from the neotropics have also been evaluated on MAO assays. In experiments using brain mitochondrial fractions as a source of rMAO-A and -B, strictosidinic acid (18), lyaloside (19), and strictosamide (20) showed weak to very weak inhibition of MAO-A and -B with IC$_{50}$ values ranging from 117 to 475 μM for MAO-A inhibition, and 645 to >1000 μM for MAO-B inhibition (see Table 2) [43,44]. Alkaloids 18, 19, and 20, together with other MIAs also isolated from neotropical Psychotria (21–27), were tested on hMAO-A and -B, showing inhibition levels
similar to those verified on the rat enzymes (see Table 2) [45]. Among the MIAs evaluated on hMAOs, angustine (22) inhibited hMAO-A in a reversible and competitive way, while compounds 23–27 behaved as irreversible hMAO-A inhibitors. The IC\textsubscript{50} values calculated for hMAO-A inhibition by \textit{Psychotria} MIAs varied from 0.85 to 182 μM, while the IC\textsubscript{50} values for hMAO-B inhibition ranged from 40 to 316 μM. As observed for most of the harmala alkaloids, MIAs seemed to possess selectivity for the A isoenzyme [45].
Isoquinoline Alkaloids

The protoberberine alkaloids jatrorrhizine (28) and berberine (29) were shown to inhibit rMAOs from brain mitochondria [46]. Compound 28 displayed MAO-A and -B inhibition with IC$_{50}$ values of 4 and 62 μM, respectively. In this same study, berberine (29) inhibited only MAO-A with an IC$_{50}$ of 126 μM [46]. The difference in potencies between 28 and 29 could be explained by the phenol hydroxyl group present at C-2 in jatrorrhizine (28) and absent in berberine (29), which possesses a methylenedioxy moiety between C-2 and C-3 [46]. Compound 29 was also evaluated together with palmatine (30) in assays using brain homogenates from mouse (mMAOs) as an enzyme source. In these experiments, it was demonstrated that both 29 and 30 inhibited MAO activity with IC$_{50}$ values of 98 and 91 μM, respectively [47,48]. Furthermore, 29 and 30 behaved as noncompetitive inhibitors with $K_i$ values of 44 and 59 μM, respectively, in assays using kynuramine as substrate [49]. Another protoberberine isoquinoline alkaloid, coptisine (31), displayed inhibitory effects on mMAO-A from brain, without affecting MAO-B activity. Compound 31 inhibited MAO-A activity in reactions using kynuramine as substrate in a reversible and competitive way, with an IC$_{50}$ of 1.8 μM [50]. The benzophenanthridine alkaloid sanguinarine (32) inhibited
mAOM activity in brain homogenates with an IC50 of 25 μM. The kinetic analysis by Lineweaver–Burk reciprocal plots indicated that 32 behaved as a noncompetitive MAO inhibitor with respect to the substrate kynuramine. The estimated $K_i$ was 22.1 μM [51]. Higienamine (33), a simple tetrahydroisoquinoline (TIQ), inhibited 42% MAO-A activity at 150 μM. The kinetic studies indicated that this inhibition was noncompetitive to kynuramine, with a $K_i$ of 188 μM [47].

Some TIQ, benzyltetrahydroisoquinoline, and tetrahydroxyberberine alkaloids known for their inhibitory activity on MAO can be formed within the human body. An example of such a TIQ is salsolinol (34), a weak MAO inhibitor formed by the direct condensation of acetaldehyde and dopamine. Following the metabolism of alcohol (oxidized to acetaldehyde) and dopamine, 34 can be found in rat brain [52], where it acts as a MAO inhibitor competitive to 5-HT, suggesting selectivity to MAO-A. The estimated $K_i$ values for MAO inhibition by 34 were between 30 and 285 μM (see Table 3) [52–56]. In addition, the potency of 34 for MAO-A inhibition

<table>
<thead>
<tr>
<th>Table 3 MAO-A and -B Inhibition of TIQs Alkaloids</th>
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<tr>
<td>TIQ Alkaloids</td>
</tr>
<tr>
<td>(R) salsolinol (34R)</td>
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<tr>
<td>(S) salsolinol (34S)</td>
</tr>
<tr>
<td>Tetrahydropapaveroline (35)</td>
</tr>
<tr>
<td>2,3,9,11-Tetrahydroxyberberine (36)</td>
</tr>
<tr>
<td>Norsalsolinol (37)</td>
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<td>N-methyl-norsalsolinol (38)</td>
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<td>N-methyl-((R)salsolinol (39R)</td>
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<tr>
<td>N-methyl-((S)salsolinol (39S)</td>
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C, Competitive inhibition; NC, noncompetitive inhibition; M, mixed type inhibition; NI, no inhibition.

$^a$MAOs from brain homogenate. MAO-A activity was evaluated using serotonin as substrate, and MAO-B activity was evaluated with the substrate benzylamine. Experiments performed with racemic mixtures [52].

$^b$MAOs from brain homogenate. MAO-A activity was evaluated using serotonin as substrate. Experiments performed with racemic mixtures [53].

$^c$MAO-A isolated from placenta; hMAO-B isolated from liver; substrate kynuramine in concentrations close to its $K_m$ for MAO-A and -B [54].

$^d$hMAO-A and -B from human brain synaptosomal mitochondria; substrate kynuramine; deprenyl and clorgyline were used as selective inhibitors to differentiate MAO-A from -B [55].

$^e$hMAO-A from placenta [55].

$^f$hMAO-A from liver [55].
varied according to the enantiomeric form: the $R$ enantiomer of 34 was about twofold more potent for MAO-A inhibition than the $S$ enantiomer [54,55].

Meyerson et al. [52] and Minami et al. [55] also evaluated the effects of other TIQ alkaloids (35–39) on the enzymatic oxidation of different substrates by MAOs (see Table 3) [52,55,56]. The in vitro data for MAO inhibition indicated that most of these alkaloids were MAO-A selective, except for compound 35, which seemed to be a nonspecific inhibitor of rMAOs from brain homogenates [52]. The SAR of isoquinoline derivatives was reported in details by Bembrnek et al. [54] and Thull et al. [57]. These studies reinforced that isoquinoline compounds are often selective toward MAO-A and helped to clarify the relative importance of steric, lipophilic, and polar interactions in modulating MAO-A inhibitory activity [49].
Piperidine Alkaloids

Kong et al. [58] demonstrated that the alkaloid piperine (40) could inhibit MAO-A and -B from rat brain mitochondria in a dose-dependent manner, with IC$_{50}$ values of 49 and 91 $\mu$M, respectively. The kinetic experiments with 40 on MAO-A indicated inhibition of mixed type, with $K_i$ and $K_I$ data of 36 and 26 $\mu$M, respectively. On the other hand, the inhibition of MAO-B by 40 was shown to be competitive, with a $K_i$ of 79 $\mu$M. Other studies also evaluated the effects of piperine (40) on MAO-A and -B activity. Lee et al. [59] determined the potential of 40, isolated from *Piper longum* extracts, in inhibiting mMAO-A and -B in brain mitochondrial fractions. In these experiments, 40 competitively inhibited both MAO-A and -B with IC$_{50}$ values of 21 $\mu$M ($K_i = 19 \mu$M) and 7 $\mu$M ($K_i = 3.19 \mu$M), respectively. In addition, the MAO-A and -B inhibition by 40 seemed to be reversible, as demonstrated by the recovery of percentages higher than 95% of MAO-A and -B activity after dialysis experiments [59]. Taken together, the data of Kong et al. [56] and Lee et al. [57] indicate that 40 seemed to be more selective for rMAO-A, and mMAO-B. In a recent study using brain mitochondria as a source of rMAO-A and -B, Mu et al. [60] demonstrated that 40 inhibited both MAO-A and -B with IC$_{50}$ values of 0.40 and 0.26 $\mu$M, respectively. Finally, inhibition studies using human enzymes revealed that 40 was about 100-fold more selective for hMAO-B inhibition: hMAO-A IC$_{50} = 59 \mu$M and hMAO-B IC$_{50} = 0.48 \mu$M [61].
An in vivo study aiming to investigate the antidepressant effect of 40 and of antiepilepsirine (41) showed that both compounds, at doses of 10–20 mg/kg, possessed minor inhibitory activity on MAO-A and -B, when compared with the in vitro enzymatic experiments [62].

Other piperidine alkaloids from Piper longum were also evaluated for MAO inhibition [63]. Guineensine (42) showed significant MAO inhibitory activities with IC₅₀ values of 139.2 μM. The inhibition assays were performed using brain mitochondrial fractions as source of mMAOs, kynuramine as substrate, and clorgyline and deprenyl as selective MAO-A and -B inhibitors, respectively.

Desoxypeganine

Desoxypeganine (43) is a quinazoline alkaloid isolated from Peganum harmala and is able to inhibit the enzymes MAO-A (IC₅₀ = 2.0 μM) [64] and acetylcholinesterase (IC₅₀ = 17 μM) [65]. This compound showed some activity for the pharmacological treatment of alcohol abuse to reduce craving and depression [66,67]. Inhibitor 43 was subjected to clinical trials aiming at the assessment of its oral bioavailability, pharmacokinetics profile, and tolerability in healthy volunteers submitted to a single-dose (50, 100, 150, or 200 mg) [67] and multiple-dose regimens (50 and 100 mg; 3 days) [66]. These preliminary studies indicated that 43 had a linear and dose-proportional pharmacokinetics, oral bioavailability, plasma half-life, renal excretion, and an adequate safety profile. These features led to further clinical investigations with 43.
Other Alkaloids

Quinine (44), cinchonicinol (45), and cinchonaminone (46), isolated from Cinchona succiruba (Rubiaceae), inhibited MAO from bovine plasma in assays using benzylamine as the substrate [68]. The IC$_{50}$ values calculated for MAO inhibition were 16 µM (44), 12 µM (45), and 32 µM (46), and kinetic experiments indicated that quinine (44) acted as a competitive MAO inhibitor.

The tropane alkaloids atropine (47) and hyoscine (48) slightly inhibited MAO when evaluated at 100 µg/mL (inhibition corresponding to 9% for 47, and 15% for 48) and 200 µg/mL (inhibition corresponding to 14% for 47, and 20% for 48) [69].

Seven indoloquinazoline alkaloids isolated from Evodia rutaecarpa inhibited rMAO-A and -B from brain mitochondria: 1-methyl-2-undecyl-4(1H)-quinolone (49), 1-methyl-2-nonyl-4(1H)-quinolone (50), 1-methyl-2-[(Z)-6-undecenyl]-4(1H)-quinolone (51), evocarpine (52), 1-methyl-2-[(6Z,9Z)-6,9-pentadecadienyl]-4(1H)-quinolone (53), dihydroevocarpine (54), and echinopsine (55). The IC$_{50}$ values for MAO-A inhibition ranged from 240 to >400 µM, whereas the IC$_{50}$ values for MAO-B inhibition ranged from 2.3 to >400 µM. Among these compounds, the most potent inhibitor for both MAOs was 50, which displayed a 100-fold selectivity for MAO-B. Alkaloids 49, 50, and 54, which differ from one another by C$_{2}$H$_{4}$ in the length of the C-2 saturated hydrocarbon chain, showed MAO-B inhibitory activities with IC$_{50}$ values of 19, 2.3, and 215 µM, respectively, indicating that the longer the aliphatic side chain is, the weaker the inhibitory effect on MAO-B activity is. Additionally, the SAR comparison of the IC$_{50}$ values among the compounds with same length of the side chain suggested that the presence of double bonds could improve the potency of MAO-B inhibitory activity. Finally, kinetic studies determined that 53 acted as a MAO-B competitive inhibitor, with $K_{i}$ of 3.8 µM [70].
49 \( R = \) \( \text{long alkyl chain} \)

50 \( R = \) \( \text{long alkyl chain} \)

51 \( R = \) \( \text{long alkyl chain with unsaturation} \)

52 \( R = \) \( \text{long alkyl chain with unsaturation} \)

53 \( R = \) \( \text{long alkyl chain with unsaturation} \)

54 \( R = \) \( \text{long alkyl chain with unsaturation} \)

55 \( R = H \)
CONCLUSION

In the important search for new drugs to treat age-related diseases, research on MAOs inhibition plays an important role. In this respect, some classes of alkaloids demonstrated multiple biological activities on CNS. The indole and isoquinoline alkaloids showed particularly interesting activities as competitive and noncompetitive inhibitors. The selectivity between MAO-A and -B inhibition is an important factor to decide on the use of a compound for a specific application. Because several alkaloids with small chemical differences were isolated, it was often possible to retrieve SAR information. Even if the range of activity, selectivity, and mode of inhibition varies greatly between classes of alkaloids and also within those classes, a general trend shows a more important selectivity for MAO-A. Few leads were identified, but recent advances have demonstrated that the most promising MAOs inhibitors have to be multifunctional [71]. Without doubt, nature is an important source of novel scaffolds. Considering the lack of a global in silico strategy to predict MAOs inhibition potency, it is mandatory to perform systematic in vitro assays for the inhibition of MAOs from any new natural compound isolated. As soon as the most promising hits are experimentally identified, the modulation of multifunctional activities becomes easier [72,73]. Indeed, the hit selection and lead optimization techniques are now sufficiently mature to rapidly drive via adequate focused virtual libraries the pharmacomodulation of natural scaffolds toward more potent multifunctional MAOs inhibitors [74–80].

ABBREVIATIONS

5-HT  5-hydroxytryptamine
βCs  β-carbolines
CNS  central nervous system
COMT  catechol-0-methyl transferase
DHβCs  dihydro-β-carbolines
FAD  flavin adenine dinucleotide
H$_2$O$_2$  hydrogen peroxide
hMAO  human monoamine oxidase
hMAO-A  human monoamine oxidase A
hMAO-B  human monoamine oxidase B
MAO-A  monoamine oxidase A
MAO-B  monoamine oxidase B
MAOs  monoamine oxidases
MIAs  monoterpenoid indole alkaloids
mMAO  mouse monoamine oxidase
mMAO-A  mouse monoamine oxidase A
mMAO-B  mouse monoamine oxidase B
PwTX-I  6-Hydroxytrypargine
(Q)SAR  (quantitative) structure-activity relationship
rMAO  rat monoamine oxidase
rMAO-A  rat monoamine oxidase A
rMAO-B  rat monoamine oxidase B
THβCs  tetrahydro-β-carbolines
TIQ  tetrahydroisoquinoline

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References