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New Frontiers in Selective Human MAO-B Inhibitors

Miniperspective

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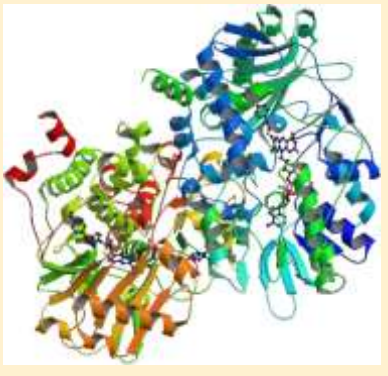
ABSTRACT: Accumulating evidence shows a relationship between the human MAO-B (hMAO-B) enzyme and neuropsychiatric/degenerative disorder, personality traits, type II alcoholism, borderline personality disorders, aggressiveness and violence in crime, obsessive-compulsive disorder, depression, suicide, schizophrenia, anorexia nervosa, migraine, dementia, and PD. Thus, MAO-B represents an attractive target for the treatment of a number of human diseases. The discovery, development, and therapeutic use of drugs that inhibit MAO-B are major challenges for future therapy. Various compounds and drugs that selectively target this isoform have been discovered recently. These agents are synthetic compounds or natural products and their analogues, including chalcones, pyrazoles, chromones, coumarins, xanthines, isatin derivatives, thiazolidin- diones, (thiazol-2-yl)hydrazones, and analogues of marketed drugs. Despite considerable efforts in understanding the binding interaction with specific substrates or inhibitors, structural information available for the rational design of new hMAO-B inhibitors remains unsatisfactory. Therefore, the quest for novel, potent, and selective hMAO-B inhibitors remains of high interest.



1. INTRODUCTION

Monoamine oxidases (MAOs) (EC 1.4.3.4) are FAD-containing enzymes associated with the mitochondrial outer membrane.[1] The monoamine oxidase type A (MAO-A) and type B (MAO-B) isoforms have been characterized on the basis of their tissue distribution[2,3] and specificity for their substrates and inhibitors.[4,5] MAOs are encoded by distinct genes (both with 15 exons) located side-by-side on the X chromosome (Xp11.23−11.4) deriving from a common gene due to their similar exon−intron organization.[4] MAO-A catalyzes the oxidative deamination of serotonin (5-HT), adrenaline (A), and noradrenaline (NA) and clorgyline (1) and moclobemide (2) are selective, irreversible and reversible, respectively, inhibitors of this isoform (Figure 1). On the other hand, MAO-B deaminates preferentially β-phenethylamine and benzylamine and is selectively and irreversibly inhibited by selegiline (3) and rasagiline (4). Kinetics and functions of MAO isoforms have been reviewed by Tipton et al.[6] Because of their fundamental role in key physiological processes, both MAO isoforms are involved in the pathogenesis of various human diseases. The administration of MAO inhibitors results in a benefit in the treatment of several psychiatric and neurological disorders.[7−9] MAO-A inhibitors are used for depression, and MAO-B inhibitors are used in Parkinson's disease (PD) in association with L-DOPA and/or DA agonists.[10] Currently used anti-hMAO-B agents behave as selective and irreversible inhibitors. These compounds display the typical drawbacks of long-lasting enzyme inhibition, namely, de novo enzyme biosynthesis in the human brain and potential immunogenicity of enzyme−inhibitor adducts. In general reversible inhibitors have safer profiles. On the other hand, the irreversible inhibitors show high efficiency to target disruption, less sensitivity toward pharmacokinetic parameters, and increased duration of action.

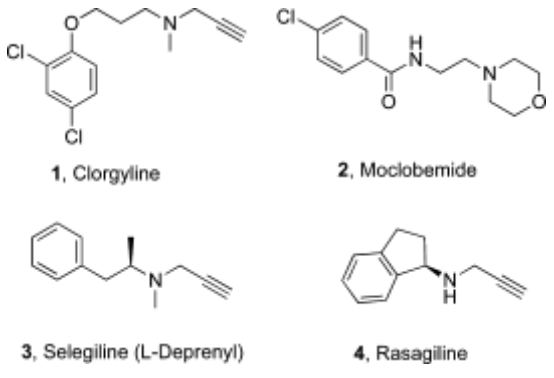


Figure 1. Structures of reference hMAO inhibitors 1−4.

The development of selective hMAO-B inhibitors usually takes advantage of several enzyme/inhibitor and enzyme/substrate complexes deposited in the Protein Data Bank, and their use as pharmacological tools derives from the limited cheese side effect (tyramine-induced hypertensive crisis). This behavior is markedly dependent on selective inhibition and different tissue distribution of the two isoforms. As an example,

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3 at 2 × 5 mg/day does not require dietary restriction and irreversibly inhibits over 90% of hMAO-B in the basal ganglia. Conversely, at higher doses (>20 mg/day) 3 behaves as a nonselective hMAO inhibitor blocking also the enzymatic activity of hMAO-A (as also demonstrated by its effective antidepressant effect).[11] In order to provide a constant dosage avoiding high (and not selective) concentrations of the drug, hMAO-B inhibitors have been also formulated in transdermal systems, which can be useful in those patients not suitable for oral administration. hMAO-B inhibitors have been patented for a number of other pathologies and diseases.[12] Lastly, MAO-B inhibitory activity could be one of the biological properties that characterize multitarget ligands especially for the treatment of multifaceted diseases. Conversely, the structural and functional similarities with hMAO-A isozyme and, to some extent, with LSD1 (lysine specific demethylase 1A) make it difficult to obtain specific "bullets" lacking inhibitory activity against unwanted targets. Despite their safety regarding food−drug interactions, use of current selective hMAO-B inhibitors should include a washout period before or after treatment with other antidepressants in order to avoid the so-called serotonin syndrome.[13] Evidence has demonstrated that some individuals could display genetic polymorphism and altered structure/ inhibitor sensitivity of MAO-B. An absolute B-selectivity could be reduced physiologically by the fact that dopamine is a common substrate for hMAO-A intraneuronally and hMAO-A/ hMAO-B in glial and astrocyte cells. Consequently, the selective inhibition of the B isozyme can be counterbalanced by an increase in the activity of hMAO-A, and sometimes the administration of nonselective MAO inhibitors might result in an unexpected increase of dopamine levels which is not obtained with many hMAO-B-selective inhibitors.

2. hMAO-B INHIBITORS AS NEW THERAPEUTIC OPTIONS

As stated above, selective hMAO-B inhibitors are generally proposed as an option for the early therapy of PD, mostly in combination with the prodrug levodopa, to reduce the metabolic degradation of dopamine. A MAO-B inhibitor may be considered in patients with mild motor symptoms before moving to more potent treatment. Results obtained in clinical trials and meta-analyses of MAO-B inhibitors in early PD demonstrated small persistent symptomatic benefits in mobility scores relative to the agonists levodopa and dopamine. The MAO-B inhibitors may reduce the rate of motor fluctuations compared to initial levodopa therapy with fewer significant adverse effects than the older agonists.[14] An effective rapid onset of disease-modifying effects of 4 at 1 mg has been reported in addition to a better cardiac safety and reduced fatigue symptoms. Strategies for increasing the duration of action of an optimally effective medicine include increasing the dosage of another dopaminergic medication, fractionation of levodopa dosage and adding a catechol-*O*-methyltransferase (COMT) or hMAO-B inhibitor (4 was more effective than entacapone in reducing the motor symptoms).[15] Because of their additional neuroprotective effects, MAO-B inhibitors may be useful for the treatment of other neurodegenerative diseases including Alzheimer's disease (AD). Recently, hMAO-B inhibitors with ancillary activities (effects on cognitive and affective functions, chelating properties)[16] have been proposed as multitarget drugs for the treatment of PD and AD.[17] Beyond this approach, hMAO-B inhibitors have been explored so far for the treatment of other pathologies in which the dysregulation/ overexpression of this enzyme has a crucial role.

A decreased activity of platelet MAO-B has been correlated with altered monoamine metabolite levels in the cerebrospinal fluid (CSF), suggesting this activity as a valid or predictive marker for specific diseases.[18] MAO associated with blood platelets is exclusively of the B type and shows the same amino acid sequence as the B isoform of the enzyme found in the brain.[19] Its catalytic activity has been partly genetically determined: it is stable over time, except for a small increase of activity in people over the age of 40 years, and independent of the clinical condition.

A large number of studies have highlighted a direct involvement of MAO-B activity and expression in the metabolism of dopamine and other biogenic amines in (i) personality traits (sensation seeking, impulsivity, risk taking);
(ii) alcoholism (especially type II alcoholism) and, in general, vulnerability for and early onset of substance abuse. Some studies correlated MAO-B activity only to sex and age with regard to the presence of insomnia in these subjects.[20] Meanwhile other studies aimed to discriminate among subgroups of smoking and nonsmoking patients,[21] as it is well-known that smokers, as well as alcohol drinkers, have low levels of MAO-B activity; (iii) neuropsychological measures (response time in computerized tests, short check time after completing a problem, preference for speed over accuracy). A reduced MAO-B activity could be considered as an indicator of weak frontal inhibitory activity, leading to poor planning and checking capacity and motor disinhibition; (iv) borderline personality disorder, aggressiveness and violence in crime,[22] obsessive-compulsive disorders (the patients show weaker platelet MAO activity than the healthy ones);[23] (v) depression and a positive family history of depression; (vi) suicide; (vii) schizophrenia,[24] anorexia nervosa, migraine, and dementia;
(viii) PD (also idiopathic[25]). A significant increase in platelet MAO-B activity was observed in Parkinson's cases as compared with healthy controls; Parkinson's patients treated with both L- DOPA and MAO-B inhibitors exhibited weaker platelet MAO- B activity than naive- or L-DOPA-treated cases.

The lower platelet MAO-B activity found in alcohol drinkers has been proposed as a marker for alcohol dependence, especially of type 2 alcoholism[26−28] which is associated with characteristic personality traits such as impulsiveness, sensation- seeking behavior, and monotony avoidance. Studies have been carried out to correlate the genetic MAO-B polymorphism with susceptibility to PD.

3. STRUCTURE−ACTIVITY RELATIONSHIPS OF RECENT hMAO-B INHIBITORS

In spite of the considerable progress which has been made in the understanding of the binding interactions of MAO isoforms with their specific substrates or inhibitors, the pharmacological information for the rational design of new potent and selective hMAO-B inhibitors remains unsatisfactory. Privileged struc- tures, such as different families of nitrogen- and/or oxygen- containing heterocycles (pyrazolines, xanthines, coumarins, and their precursors), have been extensively used as scaffolds in the search for novel hMAO-B inhibitors. Moreover, structure- and ligand-based drug designs have been used to achieve structural information on the MAO-B active site cavity by docking of structurally unrelated substrate or inhibitor

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analogues.

3.1. Chalcones and Their Analogues. Chalcones (*trans*- 1,3-diphenyl-2-propen-1-ones) (5) are open-chain flavonoids

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whereby two aromatic rings are linked through a three carbon α,β-unsaturated carbonyl system. These easily accessible compounds are used as synthetic intermediates in the syntheses of hMAO inhibitors (i.e., flavonoids, pyrazolines) mimicking the rigid skeleton of 1,4-diphenyl-2-butene (6).[29] With few exceptions, these compounds display potent hMAO-B inhib- ition and high selectivity over hMAO-A. (Figure 2).

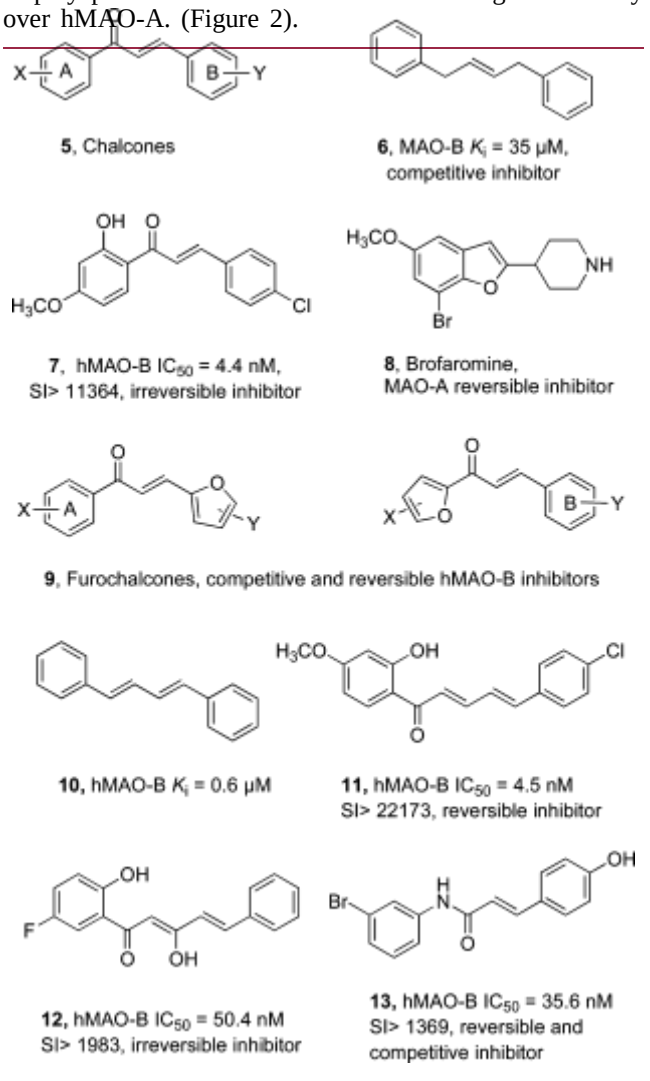

Figure 2. Chalcone derivatives as hMAO-B inhibitors.

The most active chalcones were characterized by the presence of OH and CH_3O substituents at positions 2 and 4, respectively, of the A aromatic ring, and a Cl atom at position 4 of the B ring. These compounds show inhibitory activity in the nanomolar range and good selectivity (compound 7, Figure 2).[30] A major drawback of the chalcone scaffold is the irreversible inhibition of the enzyme. Molecular modeling studies of compound 7 in the hMAO-B active site showed that the A ring of the ligand was oriented toward the FAD cofactor and stabilized by H-bonds, while the CH_3O and OH groups formed interactions with the residues of Tyr326.

The presence of a benzofuran π electron-rich core present in brofaromine (8), a reversible MAO-A inhibitor, suggested the design of a series of furochalcones (9).[31] Introduction of an electron withdrawing group at meta position of either the A or the B ring and a chlorine or bromine atom at the furan nucleus yielded highly potent hMAO-B inhibition. In contrast, these furochalcones exhibited competitive and reversible hMAO-B inhibition.

The potent and selective hMAO-B inhibition displayed by several synthetic chalcones and 1,4-diphenyl-1,3-butadiene (10)[32] prompted the synthesis of structurally related (2*E*,4*E*)- 1-(2-hydroxyphenyl)-5-phenylpenta-2,4-dien-1-ones and (2*Z*,4*E*)-3-hydroxy-1-(2-hydroxyphenyl)-5-phenylpenta-2,4- dien-1-ones (Figure 2).[33] These new compounds selectively inhibited the hMAO-B in the nanomolar or low micromolar range of concentrations. (2*E*,4*E*)-5-(4-Chlorophenyl)-1-(2- hydroxy-4-methoxyphenyl)penta-2,4-dien-1-one (11) showed potent hMAO-B inhibition (hMAO-B IC_{50} = 4.5 nM) and selectivity index (SI) of >22173). Replacement of the CH_3O with an OH group led to a 3-fold reduction in inhibitory activity and a marked reduction in selectivity (hMAO-B IC_{50} = 11.35 nM, SI = 1354). Introduction of an OH group at position 3 of the chain yielded (2*Z*,4*E*)-3-hydroxy-1-(2-hydroxyphenyl)- 5-phenylpenta-2,4-dien-1-ones. Such compounds were dramat- ically less potent than the corresponding unsubstituted pentadienones, with the only exception being (2*Z*,4*E*)-1-(5- fluoro-2-hydroxyphenyl)-3-hydroxy-5-phenylpenta-2,4-dien-1- one (12) that inhibited hMAO-B with IC_{50} = 50.4 nM and SI > 1983.

Interestingly, these two scaffolds showed a different mechanism of action: compound 11 behaved as a reversible hMAO-B inhibitor, and 12 showed an irreversible hMAO-B inhibition. Molecular modeling studies of 11 in the hMAO cavity showed that the phenolic and 4-chlorophenyl rings were positioned toward the FAD and the entrance gorge, respectively, and were surrounded by hydrophobic residues with stacking interactions between the phenolic ring and the Tyr398 and 435 amino acid residues.

Anilide derivatives were designed as structural analogues of chalcones and 1,4-diphenyl-1,3-butadiene.[34] Depending on the length chain, the anilide derivatives fall into three classes: *N*,3- diphenylpropenamides, *N*,5-diphenylpentadienamides, and *N*,4-diphenylbutenamides[35] (Figure 2). These chalcone ana- logues were moderate hMAO-B inhibitors; some derivatives inhibited hMAO-B with IC_{50} values in the submicromolar range. However, Br- and Cl-substituted anilides showed potent hMAO-B inhibition. In general, the styryl anilides were superior to the corresponding phenylbutadienyl anilides. The most potent phenol derivative, (2*E*)-*N*-(3-chlorophenyl)-3-(4-hydroxyphenyl)prop-2-enamide (13), showed a reversible and competitive hMAO-B inhibition. Molecular modeling studies were carried out in the enzymatic active site by means of the LigandFit application of the Discovery Studio 1.7 modeling software (Accelrys). In the case of relatively wide inhibitors, such as 1,4-diphenyl-2-butene, the side chain of Ile199 rotated into an alternative conformation and allowed the inhibitor to cross both cavities. Compound 13 fit the hMAO-B pocket with the 3-chloroanilide moiety within the hydrophobic entrance of the cavity (stabilized to a large degree by van der Waals interactions), while the other ring formed polar interactions with the FAD cofactor. The introduction of halogens at the anilide phenyl ring of the inhibitor was expected to produce favorable interactions within the entrance cavity.

3.2. Pyrazole Derivatives. An exploration of substitutions at positions N1, C3, C4, and C5 of this privileged pharmacophore resulted in the synthesis of pyrazoline derivatives endowed with hMAO inhibitory activity and selectivity comparable or superior to the

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reference compounds.

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Some pyrazolines were evaluated as antidepressant agents by the predictive "forced swimming test" in mice as well as dual MAO-B inhibitors and anti-inflammatory/analgesic agents in order to obtain potential drugs for AD.[36,37] On the other hand, some pyrazolines inhibited acetylcholinesterase (AChE) and butyrrylcholinesterase (BuChE) and have potential as novel dual inhibitors to treat cognitive dysfunction in AD.

N1-unsubstituted pyrazolines as hMAO-B inhibitors were discovered by virtual screening (VS) studies of a focused combinatorial library.[38] The VS studies culminated in the discovery of compounds which combined structural elements of 3,5-diarylpyrazoline and 9-anthracenecarboxaldehyde. The scoring results significantly correlated with the biological data (IC_{50} values for hMAO-B inhibition). Compounds 14 and 15 showed remarkable anti-MAO-B activity at nanomolar concentration with hMAO-B/hMAO-A SIs of 104 and 177, respectively (Figure 3). The substituents at para positions did not affect the anti hMAO-B activity; on the contrary, ortho-monosubstitution, ortho/para-disubstitution, and replacement of the aryl at C5 with a pyridin-2-yl moiety were detrimental to the MAO inhibition. All the structures were superimposed on the active site of hMAO-B, with the anthracene group oriented toward the FAD cofactor.

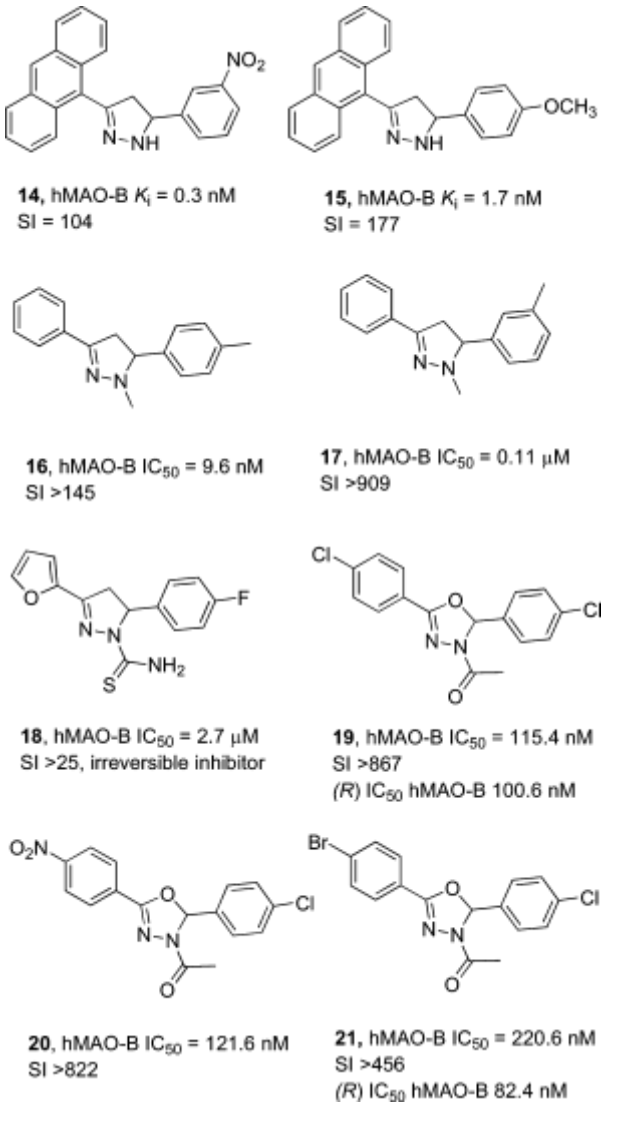

Figure 3. Pyrazoline derivatives as hMAO-B inhibitors.

A number of pyrazoline derivatives bearing different chains at N1 were synthesized with the aim of modulating the interaction of the inhibitor with the B isoform.[39] Introduction of a methyl group at N1 led to hMAO-B inhibitors with IC_{50} values in the submicromolar range (Figure 3). The compounds bearing an unsubstituted 3-phenyl ring (i.e., 16) were potent and selective hMAO-B inhibitors. Shifting of the 4-methyl group to position 3 yielded compound 17 endowed with higher SI. The same authors synthesized N1-acetyl and thiocarbamoylpyrazolines bearing an isoprenoid chain at the 3-aryl group, based on the strong interaction with biological membranes and affinity for target proteins of some natural prenylated compounds.[40] These derivatives showed weak hMAO-B inhibitory activity and did not inhibit hMAO-A. Molecular modeling studies correlated with the biological data of the hMAO-B inhibition (no hMAO- A recognition was reported). The isoprenyloxy moiety pointed toward the FAD cofactor and the C5 pyrazoline substituent toward the outer side of the hMAO-B cleft, while the thioamide group established an H-bond with Ile199 backbone.

A new series hMAO-B inhibitors was obtained by replacing the 3- and 5-aryl groups with heterocycles, i.e., furan, thiophene, and pyrrole.[41] The pendent thiocarbamoyl group at N1 minimized the steric hindrance in the catalytic site and formed strong interactions with the isoalloxazine nucleus of the FAD cofactor, while maintaining cLogP < 5. Compound 18, the most potent and B-selective MAO agent (IC_{50} = 2.7 μM, SI = 25), behaved as an irreversible inhibitor (Figure 3). Comparing the N1-methyl derivatives with N1-thiocarbamoyl/acetyl/propanoyl analogues, it should be noted that the introduction of a small substituent such as a methyl group led to more potent and selective hMAO-B inhibitors. Two series of 1-(*N*- methyl)thiocarbamoyl-3-aryl-4,5-dihydro-1(*H*)-pyrazoles and 1-thiocarbamoyl-3-aryl-4,5-dihydro-1(*H*)-pyrazoles[42] showed good B-selectivity but weak anti-MAO activity, with IC_{50} values ranging from 13.70 to 53.38 μM. A number of 2,5-diaryl-2,3-dihydro-1,3,4-oxadiazoles[43] (19−21) (Figure 3) yielded potent inhibition of the hMAO-B, similar to a series of chalcone derivatives reported above.

3.3. Chromones and Their Analogues. Chromone (benzopyran-4-one) derivatives are naturally occurring hetero- cyclic compounds endowed with important biological activities. On the other hand, experimental evidence supported an interest in simple coumarin (benzopyran-2-one) analogues as MAO inhibitors (see section 3.4). The chromone scaffold can be easily functionalized by appropriate substitution patterns to obtain potent and selective MAO-B inhibitors.

Early studies focused on two chromone isomers, compounds 22 and 23 (Figure 4).[44] Results in screening assays revealed the key position of the carboxylic acid of the γ-pyrone nucleus. With the carboxylic acid moiety at position 3 of the chromone nucleus, compound 22 displayed selective hMAO-B inhibition with IC_{50} of 48 nM. The isomer 23 bearing this functional group at position 2 inhibited both MAO isoforms at higher concentrations only (Figure 4). In binding mode studies, compound 22 established an H-bond with Tyr326 (Ile335 in the hMAO-A site), the aromatic moiety pointed toward the inner side, and the carboxylate formed an H-bond with Tyr326. New chromone derivatives bearing a

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carboxamide at position 2 or 3 were synthesized with the aim of improving the interactions within the enzyme catalytic site.[45−47] Chromones bearing the carboxamide at position 3 of the pyrone nucleus

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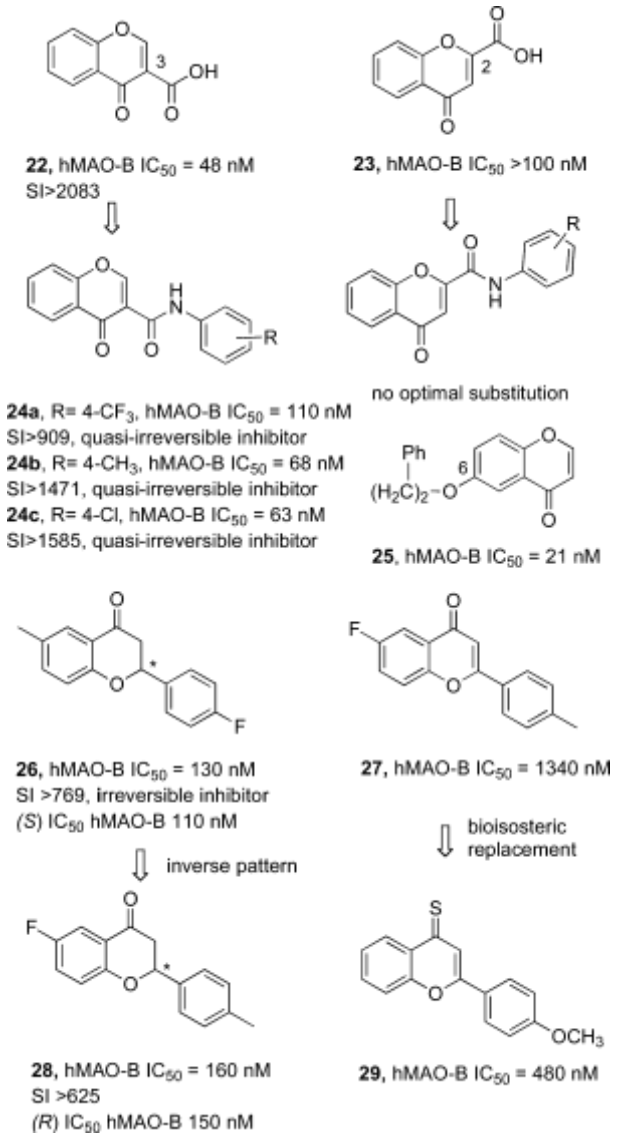

Figure 4. Chromone derivatives as hMAO-B inhibitors.

were selective MAO-B inhibitors with IC_{50} values in the micro- or nanomolar range (compounds 24a−c, Figure 4). The nature and position of the substituents of the aromatic ring at the carboxamide nitrogen modulated a*ffi*nity and selectivity for the hMAO-B. The highest B-selectivity correlated with the presence of a Cl, I atom or a CF_3 group at the para position
of the exocyclic aromatic nucleus. The OH and SCH_3 groups gave good results, whereas the introduction of OCH_3 and NO_2 had a little e*ff*ect on MAO inhibition. Chromone derivatives bearing an unsubstituted exocyclic aromatic group were more active than the corresponding cyclohexyl derivatives. The lackof the phenyl ring led to a dramatic drop of activity. Both electron withdrawing nature, and in particular the resonance e*ff*ect (weak donating), and spatial volume of the substituent at the aromatic ring a*ff*ected the binding mode. Compound 24c formed binding interactions with the FAD, the para-
chloroanilide established contacts with the loop formed by residues 99−112 at the entrance cavity, the carboxamide and the chromone oxygen formed H-bonds with Cys172 and Tyr326, respectively.

A large number of chromones substituted with functionalized arylalkyloxy (benzyloxy, phenylethoxy, and phenylpropoxy)

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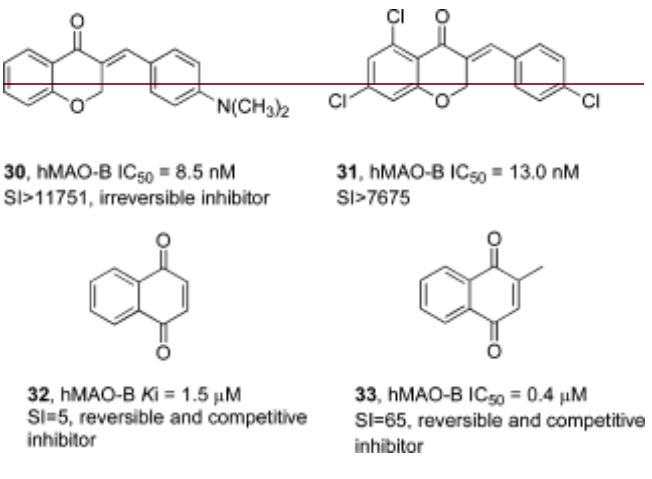
groups at position 6 of the benzopyrone ring were synthesized as hMAO-B inhibitors.[48] The introduction of a benzyloxy group in coumarin congeners provided compounds endowed with remarkable hMAO binding affinities (see section 3.4). The C6-substituted chromone derivatives were highly potent and selective hMAO-B inhibitors with IC_{50} values ranging from 2 to 76 nM. As an hMAO-B inhibitor, the 6-phenylethoxychromone 25 (IC_{50} = 21 nM) was more potent than the benzyloxy and phenylpropoxy counterparts. Introduction of halogens at para or meta positions of the phenyl of the benzyloxy group yielded IC_{50} values in the nanomolar range. Similar to the other chromone derivatives, this scaffold fit the hMAO-B model[49] of safinamide, an agent currently in phase III as an add-on therapy to dopamine agonists or to levodopa in PD patients with motor fluctuations.

Natural flavones, thioflavones, and flavanones (Figure 4)[50] can be viewed as constrained trans analogues of the chalcones (see section 3.1). Derivatives 26−29 showed potent hMAO-B inhibition and no anti-hMAO-A activity. Introduction of a double bond or a sulfur atom yielded flavone and thioflavone derivatives, respectively, which showed weak hMAO-B inhibitory activity and retained some B-selectivity (29).

The same research group synthesized homoisoflavonoids as chalcone−chromone hybrids. These compounds can be viewed as falling in three classes: (*E*)-3-benzylidenechroman-4-ones, 3- benzyl-4*H*-chromen-4-ones, and 3-benzylchroman-4-ones. Natural and synthetic homoisoflavonoids showed a variety of biological properties. However, this class of compounds was not exhaustively explored for MAO inhibition.[51] The (*E*)-3- benzylidenechroman-4-ones may be also considered to be rigid analogues of chalcones (Figure 5).

Figure 5. Benzylidenechromanones and naphthoquinones as hMAO-B inhibitors.

Most of these homoisoflavonoids inhibited the hMAO-B in the nano- or micromolar range and showed different degrees of B-selectivity. (*E*)-3-[4-(Dimethylamino)benzylidene]chroman- 4-one (30, IC_{50} of 8.5 nM and SI > 11751) was the most potent and selective hMAO-B inhibitor within this series. Replacement of the dimethylamino group with an amino or acetylamino group resulted in a dramatic drop in potency and selectivity. (*E*)-5,7-Dichloro-3-(4-chlorobenzylidene)chroman-4-one (31) showed potent hMAO-B affinity and selectivity (IC_{50} = 13.03 nM, SI > 7675). The hMAO-B/30 complex revealed a strong H-bond between the carbonyl oxygen of and the OH of Tyr326 and a large network of hydrophobic contacts, while the



30, hMAO-B IC_{50} = 8.5 nM
SI>11751, irreversible inhibitor

31, hMAO-B IC_{50} = 13.0 nM
SI>7675

32, hMAO-B *Ki* = 1.5 μM
SI=5, reversible and competitive inhibitor

33, hMAO-B IC_{50} = 0.4 μM
SI=65, reversible and competitive inhibitor

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chromone ring was surrounded by a lipophilic cage. Ring contraction of the chromone scaffold to a benzofuran-3-one led to compounds endowed with good, albeit not selective, MAO inhibition.[52]

The low incidence of PD in tobacco smokers as compared with nonsmokers suggested that a reduced hMAO activity could play a protective effect in the brain. 2,3,6-Trimethyl-1,4- naphthoquinone (TMN), a component of flue-cured tobacco leaves and smoke, was identified as a nonselective and competitive MAO inhibitor endowed with protective properties against 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) toxicity in mice.[53,54] Compound 32, a naturally occurring 1,4- naphthoquinone (1,4-NQ) and menadione (33) inhibited hMAO-B with K_i values of 1.5 and 0.4 μM, respectively, in a dose-dependent manner (Figure 5). Kinetic, docking, and fluorescence studies demonstrated the interaction with the FAD cofactor of the enzyme.[55] In fact, inhibitors that interact at the active site usually modify the fluorescence properties of the FAD at different wavelengths. Both 32 and 33 altered the flavin fluorescence by interaction with hMAO-B residues close to the flavin or by direct binding to flavin. In complex with hMAO-B, 33 forms an H-bond with the flavin of the FAD and contacts with Gln206, Tyr326, Phe343, Tyr398, and Tyr435. In contrast, 1,4-NQ does not interact with Tyr326 and forms a new contact with Tyr60. The same authors synthesized polyamine−1,4-NQ hybrids containing a spermidine analogue, lapachol, or *nor*-lapachol.[53,54] These compounds inhibited the hMAO isoforms competitively and bound at the catalytic site close to the flavin.

3.4. Coumarins and Their Analogues. 3-Arylcoumarins

have been designed as hMAO-B inhibitors based on the biological properties of *trans*-resveratrol (3,5,4′-trihydroxy- *trans*-stilbene).[56] The resveratrol/coumarin hybrids showed high selectivity for hMAO-B, with differences depending on the nature and position of the susbtituents at the phenyl rings.[56−62] The unsubstituted 3-arylcoumarin 34 showed moderate hMAO-B inhibition. Introduction of substituents at position 6 or 8 afforded highly potent hMAO-B inhibitors, while the presence of an OH group at C4 had detrimental consequences for hMAO-B inhibition.[63] Preferred substituents at the 3-aryl ring were OCH_3, CH_3, and Br (compounds 35−37) in decreasing order meta > para > ortho (Figure 6). The presence of a bromine atom at position 8 and one/two methoxy group(s) at the 3-phenyl ring increased the anti-hMAO-B activity of 6-methyl-3-phenylcoumarins. Coumarin 36, with the methyl groups at positions 6 and 4′ of the 3-phenyl ring, was the most potent and selective hMAO-B inhibitor within this series (SI > 30 000; 63-fold superior to 3). No reversibility studies were conducted. Docking studies of compound 36 with the DOCK vs 6.3 package showed that the substituent at C6 pointed toward the FAD cofactor, Phe343, and Tyr60. The coumarin ring occupied the bottom of the substrate cavity, interacting with the FAD cofactor, and formed van der Waals and hydrophobic contacts with Tyr398, Tyr435, and Gln206. This orientation allowed the oxygen atom of the coumarin to form an H-bond with Cys172.

The effects of a carbonyl bridging group between the coumarin and the 3-phenyl ring were explored.[64,65] 3-Benzoylcoumarins, considered semirigid chalcones including an α,β-unsaturated double bond in the coumarin skeleton, showed weak hMAO-B inhibition with IC_{50} values in the micromolar range (38, Figure 6). Replacement of the 3-phenyl ring with a thiophen-2-yl, thiophen-3-yl, or indol-3-yl (39) nucleus yielded a new series of hMAO-B inhibitors. These

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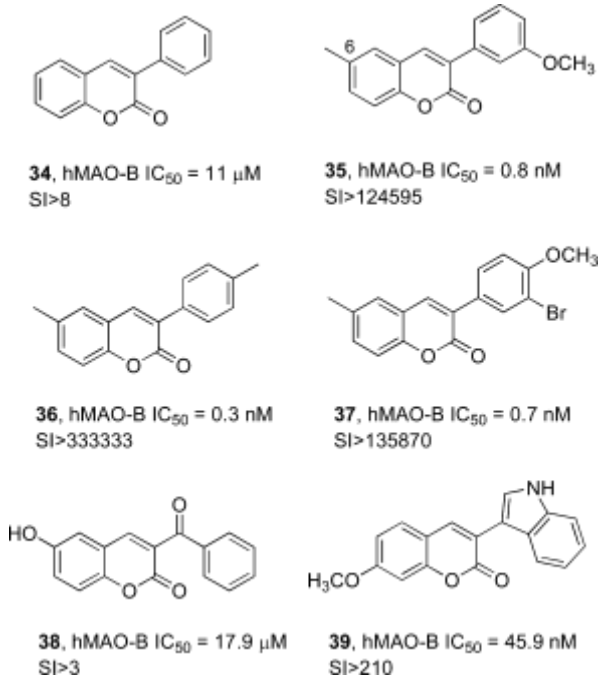

Figure 6. 3-Arylcoumarins and 3-aroylcoumarins as hMAO-B inhibitors.

compounds inhibited the hMAO-B at nanomolar concen- trations only in the presence of a methoxy group at position 7 of the coumarin nucleus.[66] In the hMAO-B cavity the indole ring pointed toward the FAD between the aromatic residues of Tyr398 and Tyr435, and the indole NH formed an H-bond with the N5 of the cofactor.

Secci and co-workers designed a large number of coumarin derivatives[65,67] bearing a methylketone, ethyl ester, carboxylic acid, or carbohydrazido group at position 3 and a variety of substituents at positions 5, 6, 7, and 8 of the coumarin nucleus (Figure 7). The 3-acetylcoumarins showed better anti-hMAO-B activity and selectivity than the corresponding aroyl derivatives. The dihalo derivatives displayed the best hMAO-B inhibition, with IC_{50} values in the nanomolar range (40). Coumarins bearing a 3-ethoxycarbonyl function and a benzyloxy group at C7 showed high B-selectivity and inhibitory activity in the nanomolar range (41). The carboxylic acids were less potent than the corresponding esters, except for derivatives bearing a 3′,4′-dichlorobenzyloxy group at position C7 (42). Carbohy- drazide derivatives (i.e., 43) also showed good hMAO-B inhibition. These findings prompted the synthesis of 3- carboxamidocoumarin derivatives. Introduction of a phenyl ring at the carboxamide nitrogen resulted in an improvement in hMAO-B inhibitory activity. Compound 44, with a meth- ansulfonyl group at para position of the *N*-phenyl ring, showed potent and selective hMAO-B inhibition (Figure 7).[68]

A series of 3-aminocarbonylcoumarins bearing an inverse carboxamide function (i.e., compound 45) showed moderate anti-MAO-B activity.[69] The hMAO-B inhibitory activity of some coumarin-3-ylcarbamates (Figure 7) was dependent on the size (Me < Et < *i*-Pr < *i*-Bu) of the group at the carbamate oxygen.[70] Introduction of a benzyl at the carbamate oxygen gave compound 46 (hMAO-B IC_{50} = 45 nM). This compound was essentially equipotent with 3 and 4. These coumarin derivatives showed lipophilic (log *P*) and topological polar surface area (TPSA) properties according to Lipinski's rules

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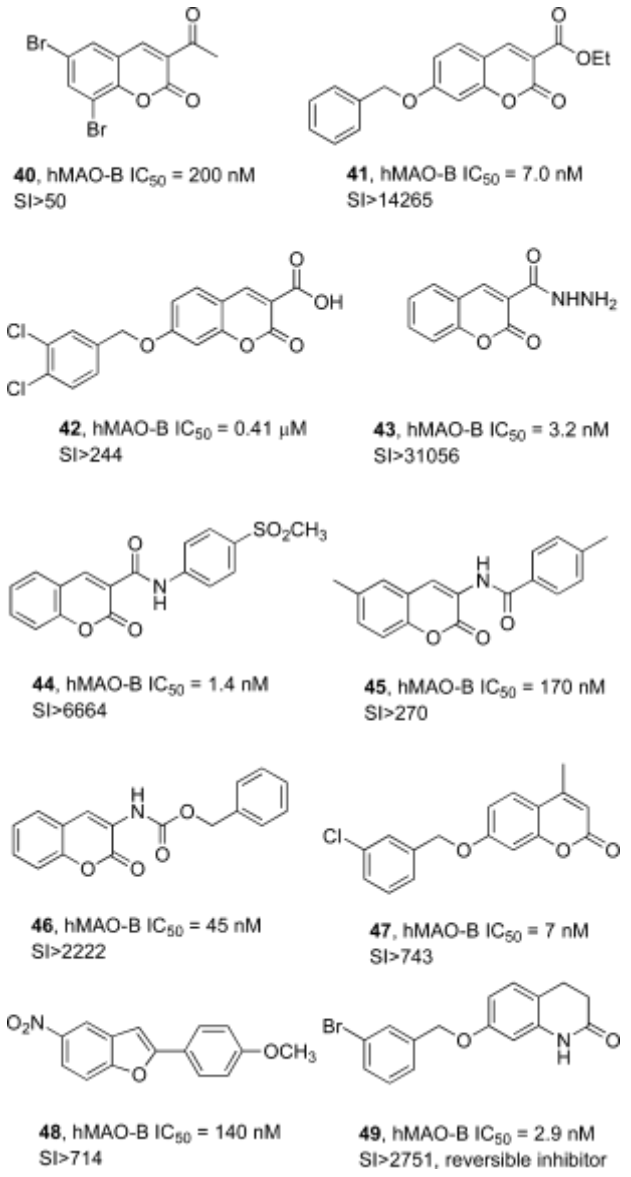

Figure 7. Coumarins as hMAO-B inhibitors.

and were endowed with a good membrane permeability. Administration of compound 46 alone to mice at 10 mg/kg did not alter significantly their motor activity, velocity, time moving and straightening (conversely, 3 decreased these parameters). In mice pretreated with reserpine, compound 46 at 10 and 100 mg/kg (equivalent with 3 at 10 mg/kg) increased motor activity and reduced mortality.

4-Methyl-7-(3-chlorobenzyloxy)coumarin derivatives were synthesized as MAO inhibitors (Figure 7).[71] Among them, compound 47 showed in vitro hMAO-B inhibition of IC_{50} = 7 nM. However, it exhibited unfavorable pharmacokinetic properties due to its high *n*-octanol−water partition coefficient (log *P* = 4.73) and poor aqueous solubility (*S* = 2.63 × 10^{-5} M).

2-Arylbenzofuran/benzofuran-2-one derivatives[72,73] (ring contraction) were generally less active and selective than the corresponding coumarin analogues. However, derivatives such as 48 (Figure 7) that bear a OCH_3 group at para position of the aryl ring proved to be potent hMAO-B inhibitors. 3,4-Dihydro- 2(1*H*)-quinolinone derivatives[74] (bioisosteric replacement) were more potent than the benzofuran-2-ones. Substitution at C7 with a halogenated benzyloxy moiety was preferred. 7-(3- Bromobenzyloxy)-3,4-dihydro-2(1*H*)-quinolinone (49) was the most potent hMAO-B inhibitor within the series.

3.5. Xanthines and Their Analogues. The xanthine scaffold, structurally related to caffeine (50), has been specifically explored to obtain dual A_{2A} antagonists/hMAO-B inhibitors. (*E*)-8-(3-Chlorostyryl)caffeine (CSC) (51) is a potent dual agent endowed with good A_{2A} affinity (K_i = 36 nM in rat brain striatal membranes receptor) and hMAO-B inhibitory activity (K_i = 235 nM in baboon liver mitochondria) (Figure 8). Biochemical and behavioral modifications are

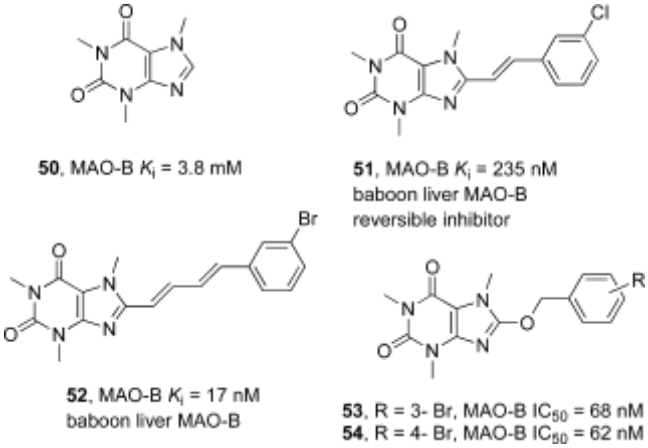

Figure 8. Xanthine derivatives as hMAO-B inhibitors.

reversed in vivo by CSC in 6-hydroxydopamine (6-OHDA)- lesioned rats.[75] 6-OHDA-lesioned rats treated for 14 days with CSC at 1 or 5 mg/kg, ip, alone or in combination with L- DOPA (50 mg/kg) or benserazide (12.5 mg/kg), showed that
(i) the striatal levels of DA, NA, 5-HT, and 5-hydroxyindole- acetic acid (5-HIAA) were significantly enhanced; (ii) the body rotation induced by the 6-OHDA lesion following a successful apomorphine challenge was markedly and dose-dependently reversed; (iii) levels of glutamate and GABA were reduced to contrast excitotoxic neuronal death and to ameliorate move- ments; (iv) nitrite formation and lipid peroxidation were significantly limited; (v) the combination with L-DOPA potentiated these effects. Dual hMAO-B inhibitors/A_{2A} antagonists based on the structure of C8-substituted caffeine analogues were investigated.[76,77]

CSC analogues were synthesized as inhibitors of baboon liver MAO-B by modification of the 3-chlorophenyl group or the unsaturated chain to obtain potent (*E*,*E*)-8-(4-phenylbutadien- 1-yl)caffeine derivatives. All of the CSC analogues inhibited the hMAO-B in the nanomolar/low micromolar range of concentration; derivatives substituted with Cl, F, CH_3, Br, or CF_3 at meta or para position were superior to the unsubstituted counterparts. (*E*,*E*)-8-[4-(3-Bromophenyl)butadien-1-yl]- caffeine, K_i of 17 nM), the most potent hMAO-B inhibitor of all the analogues synthesized in this study, was 3.6-fold more potent than the corresponding (*E*)-8-(3-bromostyryl)caffeine analogue. The presence of a methyl group at position 1, 3, or 7 was optimal for this class of xanthine-based reversible hMAO-B inhibitors. Some compounds were evaluated as potential antagonists of the adenosine A_{2A} receptor. Since caffeine is a weak hMAO-B inhibitor and only a moderate adenosine A_{2A} antagonist, the (*E*)-styryl group at C8 plays a key

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dual action of (*E*)-8-styrylca*ff*eine derivatives. 8-Benzyloxycaf- feine derivatives showed potent binding a*ff*inities for hMAO-B. Similar to 7-(3-chlorobenzyloxy)-4-formylcoumarin and sa*fi*na- mide, the introduction of a halogen at the phenyl ring of C8 a*ff*orded competitive, reversible, and preferentially B-selective inhibitors, depending on the substituent of the phenyl ring (53, R = 3-Br, IC_{50} = 68 nM; 54, R = 4-Br, IC_{50} = 62 nM) (Figure 8). In molecular modeling studies, the 8-benzyloxyca*ff*eine *fi*t into both cavities of hMAO-B, the xanthine moiety pointed toward the FAD, and the benzyloxy group protruded into the entrance cavity. The carbonyl oxygen at C6 formed an H-bond with Tyr435, and the carboxamide of Gln206 formed $\pi-\pi$ interactions with the xanthine ring. The benzyloxy ring is stabilized by van der Waals interactions at the hydrophobic entrance cavity surrounded by Phe103, Trp119, Leu164, Leu167, Phe168, and Ile316 and occupies a space that in the "closed" conformation is hidden by Ile199 side chain.[78,79] 8- Aminoalkyl and 8-aminoaryl derivatives (aminoca*ff*eines) were relatively weak MAO inhibitors, while *S*-aryl-, *S*-benzyl, and *S*- cycloalkylca*ff*eine derivatives displayed hMAO-B inhibition in the micro- or submicromolar range of concentrations.[80,81] 8-Phenoxymethylca*ff*eine derivatives behaved as competitive and reversible hMAO-B inhibitors and showed selectivity for the B isoform.[82,83]

9-Deazaxanthine derivatives were equipotent with xanthines as hMAO-B inhibitors. 8-Styryl-9-deazaxanthines, known as A_{2A} receptor ligands, showed hMAO-B inhibitory activity. Light- induced isomerization to the less potent *Z* isomer remains a major drawback of the styryl substituent of (*E*)-8-styrylxan- thines. Replacement of the 8-styryl double bond by an ethynyl bond led to anti-MAO derivatives endowed with superior potency relative to the corresponding styryl analogues. Insertion of a methylene linker between the phenyl ring and the triple bond caused a drop of hMAO-B inhibition. A series of 1,2,3-triazole bioisosteres of the ethylene linker maintained good anti-hMAO-B activity.[84]

Tetrahydropyrimido[2,1-*f*]purinediones were synthesized as constrained analogues of 8-styrylxanthines by annulation of a tetrahydropyrimidine ring in 7,8-position of ca*ff*eine nucleus.[85] The 1,3-dimethyl derivatives bearing a mono- or dichlor- ophenyl, benzyl or phenethyl ring at position N9 showed potent inhibition of hMAO-B, with no inhibition of hMAO-A at 10 μM, in order of decreasing potency: 3,4-dichloro > 3,5- dichloro > 4-chloro > 3-chloro.

3.6. Isatin Congeners. In the hMAO-B/isatin complex, the dioxoindolyl ring pointed toward the *fl*avin cofactor, the C5 was positioned at the entrance cavity and the C6 deeply in the binding pocket. Introduction of hindered substituents at C5 resulted in structures that were able to cross both cavities and limited tolerance to C6. Molecular modeling studies indicated that in the hMAO-B active site the styryl tail of (*E*)-5- styrylisatin extended beyond Ile199 into the entrance cavity, the dioxoindolyl ring lay in the substrate cavity, similarly to isatin, and the 2-oxo and NH groups formed H-bonds to water molecules. (*E*)-6-Styrylisatin also extended across both cavities with the styryl tail at the entrance cavity, but the dioxoindolyl ring was rotated through ~180° to accommodate the styryl group.[86,87] On the basis of these *fi*ndings, a number of (*E*)-5- and (*E*)-6-styrylisatin derivatives were synthesized (Figure 9). As an hMAO-B inhibitor (*E*)-5-styrylisatin (55) was 68-fold more potent than (*E*)-6-styrylisatin (56). The binding poses of isatin and (*E*)-styrylisatin were investigated using a hMAO-B I199A mutant protein. Isatin and all the (*E*)-styrylisatin

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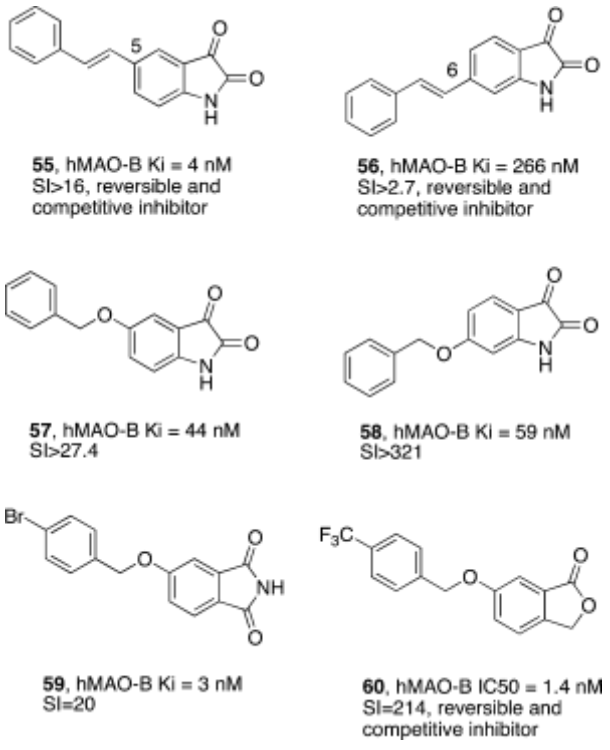

Figure 9. Isatin, phthalimide, and phthalide derivatives as hMAO-B inhibitors.

analogues were weak inhibitors of the hMAO-B I199A mutant enzyme. These findings were consistent with the proposed binding of (*E*)-styrylisatins close to Ile199. C5- and C6- substituted isatin analogues bearing different benzyl, benzyloxy, or phenylalkyloxy tails were synthesized. The 5-benzyloxy- (57) and 6-benzyloxyisatin (58) and their analogues were potent hMAO-B inhibitors, whereas 5-phenoxyisatin, 6-phenoxyisatin, 5-phenylisatin, and 6-phenylisatin were weak hMAO-B inhibitors.

Phthalimide derivatives were superior to isatin and 5- and 6- benzyloxyisatin as hMAO-B inhibitors.[88] Introduction of a benzyloxy, phenylethoxy, phenylpropenyloxy, or phenylpro- poxy tail at C5 yielded highly potent hMAO-B inhibitors; a bromine atom at position para to the 5-benzyloxy group provided the most potent hMAO-B inhibitor within the series (compound 59) (Figure 9). Molecular docking studies with Discovery Studio 1.7 showed that in the hMAO-B active site the phthalimide ring lay close to the flavin ring, while the C5 side chain extended toward the entrance cavity.

A series of phthalide [2-benzofuran-1(3*H*)-one] analogues were synthesized as reversible inhibitors of hMAO-B.[89] The C6-substituted benzyloxy phthalide analogues were highly potent hMAO-B inhibitors, in order of decreasing potency: CF_3 > I > Br > Cl > F > CH_3 > H (e.g., compound 60) (Figure 9). A scaffold simplification strategy led to synthesis of aniline derivatives.[90] These compounds were weak hMAO-B inhib- itors; 4-phenylbutylaniline, the most potent inhibitor within the series, showed an IC_{50} of 5.55 μM. Isatin and aniline derivatives adopted similar binding modes in the active site of hMAO-B. The weak hMAO-B inhibition of the anilines highlighted the key role played by the lactam/dioxoindolyl rings of phthalimide/isatin analogues into the hMAO active site.

3.7. Thiazolidindiones (TDZs) and Their Analogues.

The thiazolidindione class soon followed the discovery of

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neuroprotective effects of pioglitazone (61) and rosiglitazone
(62) in a MPTP mouse model of PD. These drugs, generally known as peroxisome proliferator-activated receptor-γ (PPAR- γ) agonists, show inhibition of hMAO-B. 61 and 62 prevent the conversion of MPTP to its toxic metabolite MPP^+ and reduce inflammation-related events which cause additional neuronal death. As a competitive hMAO-B inhibitor (*R*,*S*)-(61) exhibited submicromolar K_i values (Figure 10) while showing no hMAO-

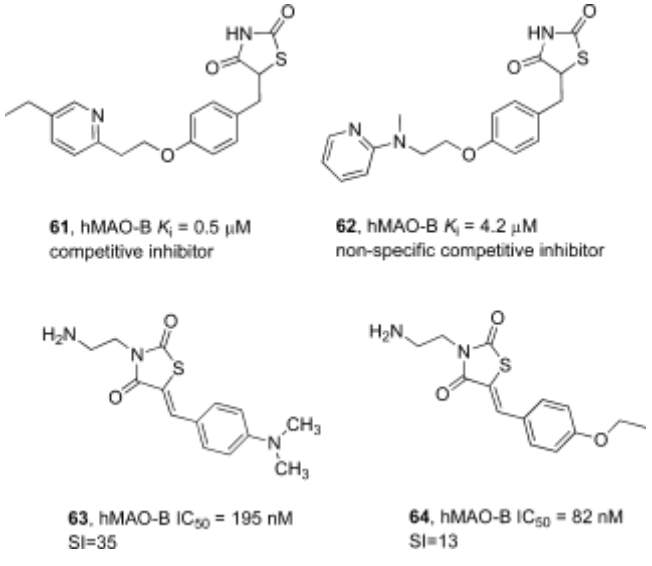

Figure 10. Thiazolidindione derivatives as hMAO-B inhibitors.

A inhibitory effects (>100 μM). On the other hand, (*R*,*S*)-(62) behaved as a nonspecific and competitive inhibitor of the B isoform, and troglitazone showed a noncompetitive and nonselective inhibition of hMAO-B with K_i of ∼10 μM.[91,92]

High-resolution crystal structures of the hMAO-B/61 and hMAO-B/62 complexes did not highlight any covalent interactions (no change in the absorption spectrum) of the thiazolidinedione ring with the active site residues.[92] The benzyl and pyridinyl rings of 61 extended over the substrate cavity of the bipartite active site of hMAO-B, similar to safinamide. The oxygen and nitrogen atoms of the thiazolidinedione ring formed H-bonds with water molecules within a pocket surrounded by Tyr398 and Tyr435. The rapid racemization of the eutomers (*R*)-61 and (*R*)-62 precludes the administration of these drugs as pure enantiomers.

New TDZ derivatives were discovered by virtual screening studies (i.e., 63 and 64) (Figure 10).[93−95] Two key regions of the TDZ scaffold were identified: the thiazolidine ring with the aminoalkyl chain, and the aromatic ring. The most potent hMAO-B inhibitor within this series, 64, showed an IC_{50} value of 82 nM (63, IC_{50} = 195 nM). Docking studies of compounds
63 and 64 show that either the TZD ring or the aromatic group points toward the FAD cofactor, achieving nanomolar or micromolar inhibitory concencentrations, respectively.

3.8. (Thiazol-2-yl)hydrazones and Analogues. The development of hMAO inhibitors started with the discovery of the antidepressant properties of some antitubercular agents, such as isoniazid, iproniazid, and phenelzine. Among them, phenelzine (β-phenylethylhydrazine), an irreversible and non- selective MAO inhibitor (and substrate), has been used over 50 years for the treatment of depression, panic disorder, and social anxiety disorder. Phenelzine is mainly metabolized to β-

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phenylethylidenehydrazine (PEH). Both phenelzine and PEH protect against neuronal loss in a gerbil model of transient global ischemia[96,97] with strong elevation of brain levels of GABA and alanine (inhibition of GABA transaminase and ALA transaminase ascribed to PEH). The hydrazine moiety determines the orientation of the molecule in the catalytic pocket of the enzyme and establishes a strong H-bond with Tyr326 or Cys172. Therefore, various hydrazine derivatives have been developed as hMAO inhibitors.

Several hybrid thiazol-2-ylhydrazones were designed by combining the orientating hydrazine group of the *first* hMAO inhibitors and the thiazole nucleus of the PPAR-γ agonists. The aliphatic, cycloaliphatic, heterocyclic, and bicyclic moieties at the C N group (C2 of the thiazole) modulated the steric and electronic e*ff*ects of the enzyme−inhibitor interaction These derivatives can be viewed as falling into three classes, according to the nature of the hydrazone at C2 of the thiazole. (i) Aliphatic derivatives (C2−C8 atoms, also with rami*fi*cation and/or unsaturation) showed preferential hMAO-A inhibition. The substituents at C4 and C5 positions of the thiazole had little e*ff*ect on inhibition of hMAO-B.[98,99] (ii) The steric hindrance of cycloaliphatic derivatives (substituents at the C4 and C5 of the thiazole nucleus) showed critical e*ff*ect on hMAO-B inhibitory activity and selectivity. Molecular modeling studies showed that the residues Ile335 (hMAO-A) and Tyr326 (hMAO-B) oriented C4 substituent of the inhibitor within the catalytic site. In the B isoform, the steric e*ff*ects of Tyr326 forced the interaction of the inhibitor with FAD. Conversely, in the hMAO-A the smaller Ile335 allowed the ligand to assume multiple poses into the binding cleft with higher enthalpy and entropic penalties. Racemic compounds bearing H, Cl, CH_3, or OCH_3 at position 4 of the phenyl group at C4 of the thiazole ring displayed high hMAO-B inhibitory activity and selectivity. Introduction of F, NO_2, or CN at the phenyl ring led to nanomolar hMAO-B inhibitors. The 2,4-di*fl*uoro derivative 65 showed IC_{50} = 56 nM and B-selectivity >762 (Figure 11). As an hMAO-B inhibitor, the (*R*)-homochiral form (eutomer) was more potent and selective than the corresponding (*S*)- enantiomers (distomer). The hMAO-B selectivity was improved for (*R*)-(+) by the *Z*-C N bond (65 and 66).[100−104] (iii) Introduction of a pyridine/thiophene ring, an α-methyl group as well as a 4-F atom at the 4-phenyl ring resulted in improved anti-hMAO-B activity of 67 (hMAO-B

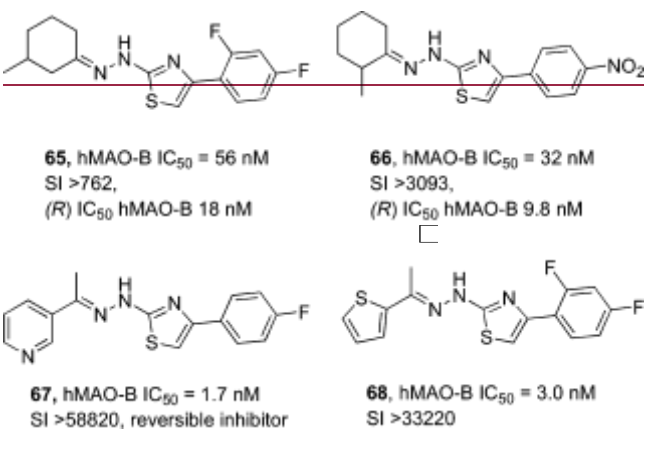

Figure 11. (Thiazol-2-yl)hydrazones derivatives as hMAO-B inhib- itors.

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IC_{50} = 1.7 nM, SI > 58 820) and 68 (hMAO-B IC_{50} = 3.0 nM,
SI > 33 220) of the (hetero)aromatic derivatives.[99,103,105−108]

3.9. Analogues of Marketed Drugs. SAR and X-ray structural studies led to design of new pargyline-based spin- labeled MAO inhibitors endowed with covalent mechanism and specific hMAO-B inhibition.[109,110] These inhibitors were characterized by the spin-labeled 2,2,6,6-tetramethylpiperi- dine-1-oxyl (TEMPO) moiety linked through an amido/ amidomethyl group at the para/meta position of the phenyl of pargyline. The TEMPO-conjugated pargyline derivatives show competitive hMAO-B inhibition with differences in isoform specificity and kinetic properties. The mechanism of pargyline derivatives 69 and 70 (Figure 12) involves a first

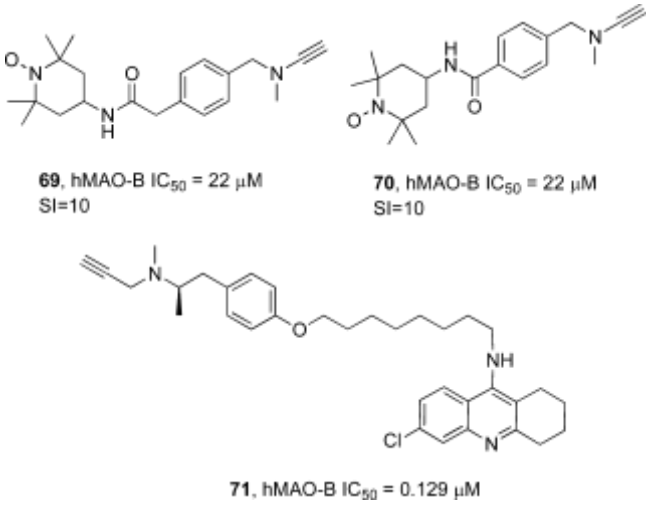

Figure 12. Analogues of marketed drugs as hMAO-B inhibitors.

reversible step with formation of enzyme−inhibitor complex, followed by a second irreversible step whereby the N5 of flavin establishes a covalent bond within the enzyme active site. Compounds 69 and 70 showed 10-fold hMAO-B/hMAO-A selectivity.

Tranylcypromine is an antidepressant drug that has been used since the 1960s. Tranylcypromine is a potent nonselective inhibitor of MAO that can produce adverse effects when combined with certain foods, and it is usually used only to treat cases of resistant depression. Trans-phenylcyclopropylamine (tranylcypromine) is superior to the corresponding cis-isomer as a hMAO-B inhibitor. Tranylcypromine derivatives bearing a fluorine atom on the cyclopropyl ring proved to be potent MAO inhibitors.[111]

Tacrine was the first acetylcholinesterase (AChE) inhibitor
approved by the FDA for the treatment of AD patients. Despite its therapy-limiting liver toxicity, tacrine has been widely used as a scaffold for the development of new multifunctional agents. The identification of both AChE and MAOs as key targets for AD prompted the design of dual AChE/MAO targeting agents. As an example, ladostigil, a bifunctional drug developed from the carbamate of rivastigmine and the indolamine of rasagiline, reached phase IIb clinical trials. Compound 71 bearing an 8C alkyl chain between tacrine and L-deprenyl yielded IC_{50} of
0.129 μM against hMAO-B; a long alkyl chain correlated with a high hMAO-B inhibitory activity. A series of homoisoflavo- noids−tacrine hybrids exhibited selective hMAO-B inhibition in the micromolar range.[112,113] These hybrid derivatives showed potent hMAO-B inhibitory activity with IC_{50} values in the
micromolar range of concentration and behaved as irreversible hMAO-B inhibitors. Some hybrids exhibited good AChE and hMAO-B inhibitory activity and crossed the BBB to target the enzyme in the central nervous system (CNS) in a parallel artificial membrane permeation assay.

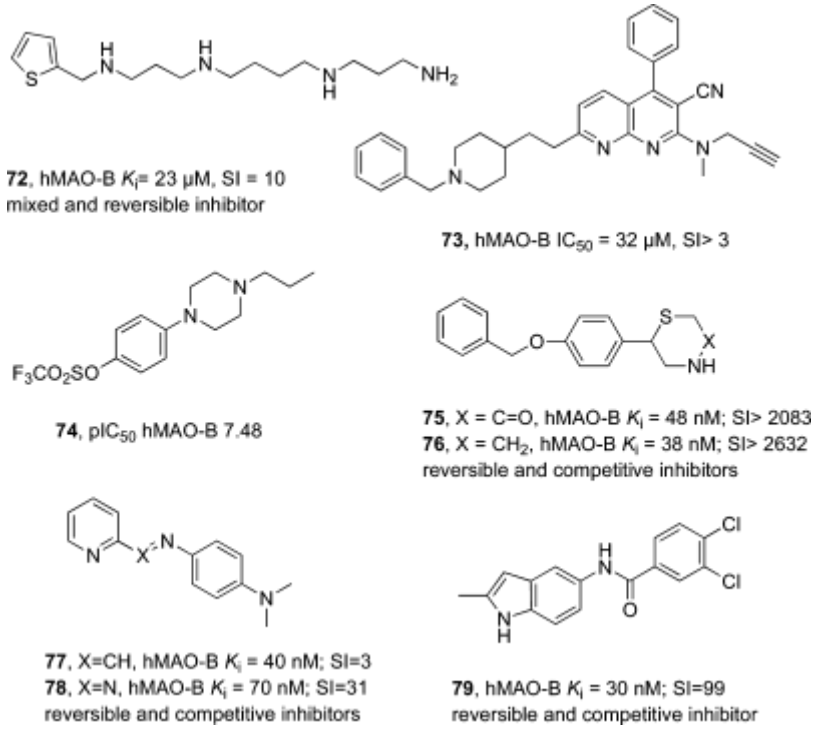

Figure 13. Other hMAO-B inhibitors.

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3.10. Miscellanea. Little information is available about the effect of polyamine derivatives as hMAO inhibitors,[114] Replacement of the benzyl group by different aromatic rings, such as naphthalene, pyridine, or thiophene (73, Figure 13) afforded novel hMAO-B inhibitors. Compound 72 behaved as a reversible and mixed-competitive hMAO-B inhibitor due to a strong interaction of the aliphatic chain with the hydrophobic residues of the MAO binding site.[115] A conjunctive approach combined the *N*-benzylpiperidine and *N*-propargylamine moieties of donepezil and PF9601N (5-(phenylmethoxy)-2- (*N*-(2-propynyl)methylamino)-1*H*-indole), AChE and MAO inhibitor, respectively, through an alkyl linker and a central 1,8- naphthyridine core (i.e., 73).[116] A series of 4-phenylpiperidine/ piperazine para-substituted analogues of the dopaminergic stabilizer pridopidine were investigated.[117] Shifting the triflate group of pridopidine from meta to para position (compound 74) reduced the striatal 3,4-dihydroxyphenylacetic acid (DOPAC) levels while the amounts of 3-methoxytyramine (3-MT) increased significantly in the striatum, limbic regions, and rat prefrontal cortex. Phenylethylamine derivatives with different flexibility (six-membered sulfur containing hetero- cycle) and basic character (secondary amino group or amide functionality) were synthesized as novel hMAO-B inhibitors. Thiomorpholine derivatives (e,g., 75 and 76) selectivity inhibited the hMAO-B with K_i values in the low micromolar and submicromolar range.[118] In docking experiments of the (*S*)-thiomorpholine and thiomorpholin-5-one derivatives, the heterocycle faced the isoalloxazine ring, the aromatic ring established interactions with the Tyr326, and the sulfur atom pointed toward the hydroxyl group of Tyr435. Visual inspection of the best poses suggested that both carboxamide (X is C O) and amine (X is CH_2) series assumed an extended active conformation and occupied both cavities of hMAO-B. Metal chelating stilbene-like derivatives (i.e., 77 and 78) originally designed to interact with β-amyloid selectively inhibited hMAO-B with IC_{50} and K_i values in the nanomolar range of concentration.[119] Docking studies showed that these small molecules occupied both the entrance and substrate cavities of hMAO-B, close to the FAD, and formed hydro- phobic and H-bond interactions. Introduction of a dimethyla- mino group at position para to the stilbene-like scaffold resulted in a significant improvement of the anti-MAO-B activity. A variety of indolylmethylamine derivatives behaved as MAO inhibitors.[120] Bulky substituents at position 5 of the indole generally increased hMAO-B inhibitory activity and selectivity, and the 5-benzyloxy moiety enhanced the B-selectivity. A newer series of indole derivatives bearing chlorine atoms at the 5- aminobenzoyl moiety (compound 79[121]) showed potent hMAO-B inhibition. As discussed above for CSC, A_{2A} antagonists/hMAO-B inhibitors have neuroprotective potential in the treatment of PD. Major drawbacks of xanthines are their low water solubility, light sensitivity, and instability (isomer- ization may occur in solution or dimerization in the solid state). Efforts to overcome this problem led to the design of non- xanthine (4*H*-3,1-benzothiazin-4-one) derivatives bearing a phenoxyacetylamino group at position 2 as dual A_{2A} antagonists/hMAO-B inhibitors.[122] These compounds did not inhibit hMAO-A even at high concentrations. The number and position of halogen atoms at the pendent phenyl ring as well as the presence of an oxygen atom in the spacer chain resulted in an improved hMAO-B inhibitory activity.

4. CONCLUSION AND PERSPECTIVES

A large number of selective hMAO-B inhibitors are now at our disposal for the treatment of several diseases, including neurodegeneration, affective disorders, stroke, and aging-related diseases. Most of them are irreversible inhibitors that form an adduct with N5 flavin (with the only exception being tranylcypromine which forms a flavin C4a adduct). The active site of hMAO-B is a bipartite cavity, where the conformation of flexible Ile199 (gating residue; in human and rat MAO-A is the bulky Phe208) plays a key role to determine an closed/open conformation for the accommodation of the inhibitor. Accordingly, hMAO-B can host either small inhibitors (isatin and tranylcypromine)[123] or cavity-filling ligands (safinamide).[124] Therefore, the former compounds show similar affinity for both isoforms, whereas the latter compounds are highly specific for hMAO-B. A wide variety of chemotypes endowed with hMAO-B inhibitory activities were obtained from natural products, synthetic compounds, and synthetic analogs of the former.[125]

Currently, major interest focuses on selective hMAO-B inhibitors as potential drugs for the treatment of neurological disorders. The multi-target-directed ligands approach provides a complete treatment of some multifactorial diseases, reduces the side effects, and limits the dosage and pill intake, improving patient compliance. However, two problems remain to be overcome in order to extrapolate robust interclass structure−activity relationships: (i) divergences of the test enzyme assays (chemiluminescent, spectrophotometric, radioligand binding);

(ii) different, and sometimes inappropriate, enzyme sources (human recombinant enzyme, rat (brain, liver), or bovine MAO). A strong impact of enzymatic species-dependent differences for several scaffolds has been observed and led to contrasting biological data.[126]

A growing interest in hMAO-B inhibitors is focused on isoform recognition, new potential therapeutic targets correlated with their biological activity in other tissues (cancer, hair loss or damage, muscle dystrophies and fibromyalgia, craving- and addiction-related behaviors, bruxism, virus infection, diabetes symptoms, glaucoma, and inflammation),[127−129] and an innovative role of hMAO as a molecular biomarker or as pharmacological and diagnostic tool. The polypharmacological scenario provides new therapeutic options for hMAO-B inhibitors, not limited to coadjuvant drugs for AD.

Biological and computational data showed that the inactivation of the human B isoform by tranylcypromine induced a substantial increase in affinity for I_2 sites,[130−132] leading to the closure of the Ile199 gate and exposition of the entrance cavity space. These findings should be explored in depth to support the discovery of specific inhibitors of this region of the hMAO-B. New tranylcypromine derivatives may be more selective toward MAO-B/LSD1 enzymes and avoid off-target effects.[133]

The most common polymorphism of the *hMAO-B* gene occurs in the polymorphic repeat region of the intron 13 and includes a single base change (A or G). Studies of the geographical polymorphism of *hMAO-B* gene (intron 13 and exon 14) in neurodegenerative diseases responsible for different levels of biogenic amines and their metabolites could lead to a more rational use of anti-MAO drugs.[134]

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The quest for novel potent and selective hMAO-B inhibitors remains of high interest. Continuous e*ff*orts in understanding binding interactions of the MAO isoforms with their speci*fi*c

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substrates or inhibitors allowed the rational design of new hMAO-B inhibitors. Ligand- and stucture-based drug design studies have been carried out by docking of structurally unrelated substrates or inhibitor analogues to achieve structural information on the MAO-B active site cavity. Further e*ff*orts to design new hMAO-B inhibitors and optimize the currently available agents will be required to obtain drug candidates endowed with high speci*fi*city for the B isoform and an acceptable pharmacological pro*fi*le.

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The authors declare no competing *fi*nancial interest.

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ABBREVIATIONS USED

AO, amine oxidase; MAO, monoamine oxidase; MAO-A, monoamine oxidase type A; MAO-B, monoamine oxidase type B; hMAO-B, human monoamine oxidase type B; CSF, cerebrospinal *fl*uid; SAR, structure−activity relationship; AD, Alzheimer's disease; AChE, acetylcholinesterase; BuChE, butyrylcholinesterase; VS, virtual screening; SI, selectivity index; PD, Parkinson's disease; MPTP, 1-methyl-4-phenyl- 1,2,3,6-tetrahydropyridine; BBB, brain−blood barrier; PSA, polar surface area; CSC, 8-(3-chlorostyryl)ca*ff*eine; 6-OHDA, 6-hydroxydopamine; 5-HIAA, 5-hydroxyindoleacetic acid; PPAR, peroxisome proliferator-activated receptor; TDZ, thiazolidinedione; TEMPO, 2,2,6,6-tetramethypiperidine-1-

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oxyl; AChE, acetylcholinesterase; CNS, central nervous system; DOPAC, 3,4-dihydroxyphenylacetic acid; 3-MT, 3-methoxytyr-amine

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