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1,3,4-Oxadiazol-2-ylbenzenesulfonamides as privileged structures for the inhibition of monoamine oxidase B

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ABSTRACT

The present study investigates the monoamine oxidase (MAO) inhibition properties of a series of ten 5-aryl-1,3,4-oxadiazol-2-ylbenzenesulfonamides. The target compounds were synthesized by dehydration of the corresponding N,N′-diacylhydrazines with phosphorus oxychloride to yield the 1,3,4-oxadiazole cycle with concomitant transformation of the sulfonamide to the sulfonyl chloride group. Treatment with aqueous ammonia in acetonitrile regenerated the target sulfonamides. The results of the enzymology document that these compounds are potent and specific MAO-B inhibitors with the most potent compound exhibiting an IC_{50} value of 0.0027 μM. An analysis of the structure-activity relationships shows that the 4-benzenesulfonamides are significantly more potent MAO-B inhibitors than the corresponding 3-benzenesulfonamides, and that the corresponding N,N′-diacylhydrazine synthetic precursors are weak MAO inhibitors. Although MAO inhibition by oxadiazole compounds are known, this is the first report of nanomolar MAO inhibition potencies recorded for sulfonamide derivatives. MAO-B specific inhibitors such as those discovered here may be of interest in the treatment of neurodegenerative disorders such as Parkinson's disease.

Introduction

Monoamine oxidase (MAO) exists as two isoforms, MAO-A and MAO-B, that are products of distinct genes.[1,2] The MAOs are bound to the outer membrane of mitochondria and are found in most mammalian tissues including brain, liver, intestine, heart, placenta and platelets. The MAO-A isoform predominates in the intestinal and placental tissues while platelets express exclusively MAO-B. The MAOs are approximately 70% similar on the amino acid sequence level and also have similar three-dimensional structures with the active sites being highly conserved.[3,4] In spite of this, MAO-A and MAO-B exhibit different substrate specificities. Serotonin is a specific substrate for MAO-A while 2-phenylethylamine and benzylamine are specific substrates for the MAO-B isoform.[5,6] Dopamine, adrenaline, noradrenaline and tyramine are substrates for both isoforms. The MAOs also exhibit differing inhibitor specificities with clorgyline and selegiline being the classical MAO-A and MAO-B specific inhibitors, respectively.[5] Numerous experimental MAO inhibitors have been described, many of which exhibit isoform specificity, while others are non-specific inhibitors.

The MAOs are key enzymes in the degradation of neurotransmitter amines and are thus important targets for the treatment of neuropsychiatric and neurodegenerative disorders.[5] Inhibitors of the MAO-A isoform are established therapy for depressive illness and social phobia, and act by increasing the levels of serotonin and noradrenaline in the central nervous system.[7] MAO-B inhibitors reduce the metabolism of dopamine in the brain and are used for the treatment of Parkinson's disease, particularly in combination with L-dopa, the metabolic precursor of dopamine.[8,9] By blocking the metabolism of amine substrates, MAO inhibitors also reduce the formation of hydrogen peroxide and aldehyde species, by-products of MAO catalysis.[10] Since these by-products may lead to neuronal cell damage, they have been implicated in the pathogenesis of Parkinson's disease, and MAO inhibitors have been advocated as potential neuroprotective agents. MAO-B inhibitors may be particularly relevant to neuroprotection in aged-related neurodegenerative disorders since the density of the MAO-B isoform increases in the brain with age while that of MAO-A remains unchanged.[11] MAO-A inhibitors may have a similar protective function in the heart since MAO-A has been associated with hydrogen peroxide formation in cardiac tissue.[12] MAO-A inhibitors may thus have a potential role in the treatment of cardiovascular diseases such as

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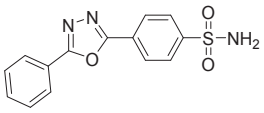
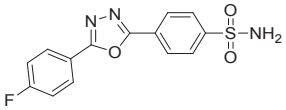
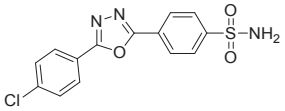
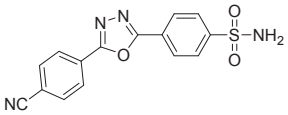
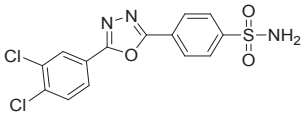
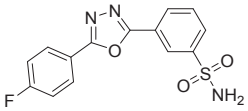
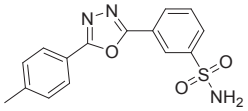
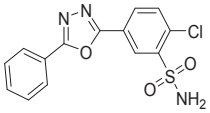
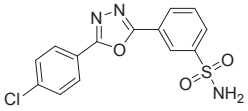
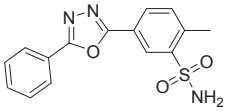
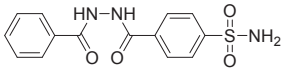
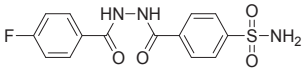
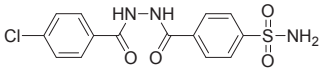
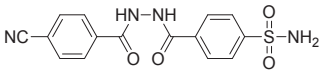
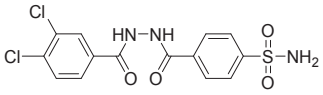
Table 1
IC_{50} values for the inhibition of MAO by 1,3,4-oxadiazol-2-ylbenzenesulfonamides **1a–e** and **2a–e**, and N,N'-diacylhydrazines synthetic precursors **8a–e**. The values for reference inhibitors are also given for comparison.

№	Structure	IC_{50} (μM ± SD)[a]		SI[b]
		MAO-A	MAO-B	
1a		63.9 ± 23.1	0.168 ± 0.019	380
1b		83.8 ± 11.8	0.079 ± 0.010	1061
1c		68.0 ± 6.20	0.048 ± 0.0043	1417
1d		24.3 ± 3.97	0.318 ± 0.0087	76
1e		46.2 ± 11.2	0.0027 ± 0.00064	17,111
2a		34.4 ± 6.02	0.975 ± 0.014	35
2b		61.4 ± 5.03	0.571 ± 0.083	108
2c		> 100[c]	0.439 ± 0.027	> 228
2d		> 100[c]	0.210 ± 0.023	> 476
2e		> 100[c]	0.767 ± 0.016	> 130
8a		62.8 ± 6.71	> 100[c]	< 0.6
8b		39.6 ± 0.354	> 100[c]	< 0.4
8c		55.9 ± 7.20	11.7 ± 2.24	4.8
8d		16.1 ± 1.97	1.17 ± 0.388	14

(*continued on next page*)

Table 1 (*continued*)

№	Structure	IC_{50} (μM ± SD)[a]		SI[b]
		MAO-A	MAO-B	
8e		13.6 ± 2.33	10.1 ± 0.643	1.3
Toloxatone		3.92[d]	–	–
Lazabemide		–	0.091[d]	–

[a] All values are expressed as the mean ± SD of triplicate determinations.
[b] Selectivity index (SI) = IC_{50}(MAO-A)/IC_{50}(MAO-B).
[c] No inhibition observed at maximum tested concentration of 100 μM.
[d] Value obtained from reference.[33]

congestive heart failure.[13–15] Interestingly, MAO-A activity has been found to be increased in certain types of cancer, and MAO-A inhibitors have thus been investigated as potential treatment of prostate cancer.[16]

Based on the therapeutic applications of MAO inhibitors and the academic interest in the discovery of new classes of compounds that may inhibit the MAOs, the present study investigates the MAO inhibition properties of a series of ten 5-aryl-1,3,4-oxadiazol-2-ylbenzenesulfonamides (**1a–e**; **2a–e**) (Table 1). Oxadiazole derivatives are well known to inhibit the MAOs, and numerous examples of high potency inhibitors exist in literature. This is demonstrated by a recent report of 1,2,4-oxadiazole compounds with good potency MAO inhibition with, for example, compound **3** exhibiting an IC_{50} value of 0.012 μM for the inhibition of MAO-B (Fig. 1).[17] In an earlier study, both 1,2,4-oxadiazole and 1,3,4-oxadiazole compounds were found to be potent and specific MAO-A inhibitors as shown by example with compounds **4** and **5**.[18] As exemplified by zonisamide, sulfonamide compounds have also been reported to inhibit the MAOs. This drug inhibits MAO-B with an IC_{50} value of 24.8 μM.[19] No sulfonamide compound has, however, been reported to possess nanomolar MAO inhibition potency, and the sulfonamide functional group is not considered privileged for MAO inhibition. The present study will show that 5-aryl-1,3,4-oxadiazol-2-ylbenzenesulfonamides are potent and specific inhibitors of MAO-B. In this regard, molecular docking suggests that the sulfonamide functional group forms key productive interactions in the substrate cavity, and thus should be considered for the future design of MAO inhibitors. Many clinical drugs are sulfonamide compounds and are used for the treatment of a wide variety of disease states.[20] Examples of such sulfonamide drugs are antimicrobial agents, diuretics, anticonvulsants and antidiabetic agents.

A significant number of works are devoted to the synthesis of 1,3,4-oxadiazoles containing the 1,3- and 1,4-arylidene sulfonamide moiety.[21–24] It was shown that the direct chlorosulfonation of 3,5-diaryl-1,3,4-oxadiazoles leads to the introduction of the sulfonyl chloride moiety in position 3 of the selected aromatic ring.[21] Therefore, for the selective synthesis of 2-(4-sulfonylamidophenyl)-5-aryl-1,3,4-oxadiazoles, a convergent approach is required. For this purpose, using

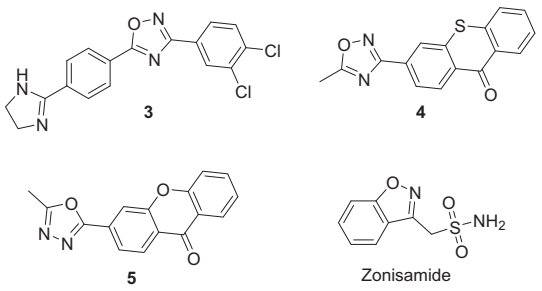
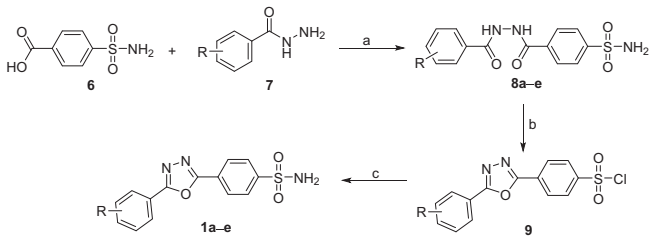


Fig. 1. Examples of known oxadiazole-based MAO inhibitors and the structure of zonisamide.

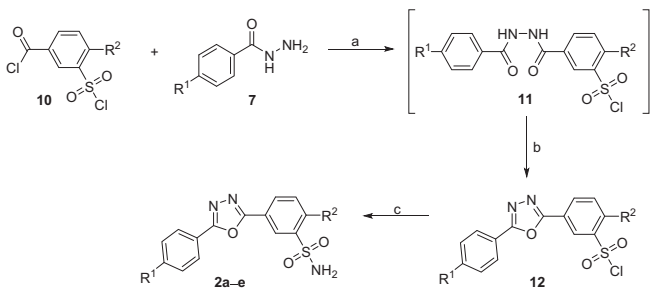


Scheme 1. The synthesis of compounds **8a–e** and **1a–e**. Key: (a) EDC, DMF, 12 h, rt; (b) $POCl_3$, 24 h, reflux; (c) NH_3 (aq), CH_3CN, 2 h, 50 °C.

the commercially available 3- and 4-sulfamoylbenzoic acids and arylhydrazide derivatives as building blocks represents a promising strategy, and allows for the selective introduction of the sulfamoyl moiety on position 4 of the aromatic ring of the intermediate N,N'-diacylhydrazine. These compounds, under the action of acid catalysis in the presence of dehydrating agents, can be converted to the corresponding 1,3,4-oxadiazoles in a good yield. It should be noted that the presence of the primary sulfonamide moiety makes it difficult to form a 1,3,4-oxadiazole ring because of the low solubility of the corresponding N,N'-diacylhydrazine in most common solvents (THF, toluene, acetonitrile). Also, the reaction is complicated by the lability of the sulfamoyl moiety when heated in an acidic medium. However, the problem of synthesizing such structures was successfully solved and is reported in literature,[22] where the practical and transition metal-free one-pot synthesis of (1,3,4-oxadiazol-2-yl)anilines have been developed via reaction of isatins with hydrazides in the presence of molecular iodine.

Scientists at *Novartis* company, as well as others followed an approach that was based on the use of Burgess reagent.[23] Researchers have used thionyl chloride as a dehydrating agent for a N,N'-diacylhydrazines containing a sulfonamide moiety, which generally resulted in relatively low yields (40–50%) of the desired 1,3,4-oxadiazoles.[24]

In this work, we used the classical and effective approach for the



Scheme 2. "One pot" synthesis of compounds **2a–e**. Key: (a) Pyridine, CH_3CN, 1 h, 25 °C; (b) $POCl_3$, toluene, 6 h, reflux; (c) NH_3 (aq), CH_3CN, 2 h, 50 °C.

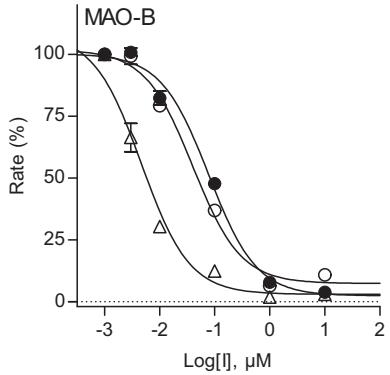


Fig. 2. Sigmoidal plots for the inhibition of MAO-B by compounds **1c** (open circles), **1b** (filled circles) and **1e** (triangles). Each data point represents the mean ± SD of triplicate measurements.

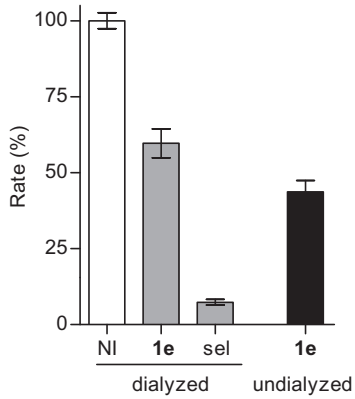


Fig. 3. Reversibility of MAO-B inhibition by **1e**. MAO-B and the test inhibitor (at a concentration of 4 × IC_{50}) were incubated for 15 min, dialyzed for 24 h and the residual enzyme activity was measured (**1e** – dialyzed). Similar incubation and dialysis of the enzyme in the absence of inhibitor (NI – dialyzed) and presence of the irreversible inhibitor, selegiline (sel – dialyzed), were also carried out. The residual activity of undialysed mixtures of MAO-B and the test inhibitor was also recorded (**1e** – undialyzed).

cyclization of N,N'-diacylhydrazines, which consists of in situ dehydration of the corresponding N,N'-diacylhydrazines **8a–e** with an excess of phosphorus oxychloride for 24 h under reflux (Scheme 1). Together with the formation of the 1,3,4-oxadiazole cycle, we observed the transformation of the sulfamoyl group to the sulfonyl chloride group; therefore, after the dehydration of N,N'-diacylhydrazines, the reaction mass was treated with aqueous ammonia in acetonitrile to regenerate the target sulfonamides **1a–e**. Synthesis of the key reagents **8** was carried out according to literature by reaction of commercially available hydrazides with carboxylic acids in DMF using EDC as a dehydrating agent.[25]

To obtain isomeric 1,3,4-oxadiazoles **2a–e**, an alternative one-pot synthetic approach was developed (Scheme 2). In our previous works,[26,27] it was shown that reactions of equimolar amounts of 3-chlorosulfonylbenzoyl chlorides **10** with amidoximes and aromatic amines lead to the corresponding *O*-acylated amidoximes and benzamides, with the SO_2Cl moiety remaining unmodified. In the present work, it is shown that compounds **10** can successfully be reacted in a similar manner with equimolar amounts of hydrazides **7**, yielding corresponding compounds **11**. The sulfonyl chlorides **11** thus obtained were subjected without isolation to cyclocondensation in a mixture of $POCl_3$-toluene to yield the corresponding oxadiazoles **12**. After the solvent was replaced with acetonitrile, **12** was treated, without isolation, with an aqueous solution of ammonia to form the 1,3,4-oxadiazoles **2a–e** in good yields (69–78%).

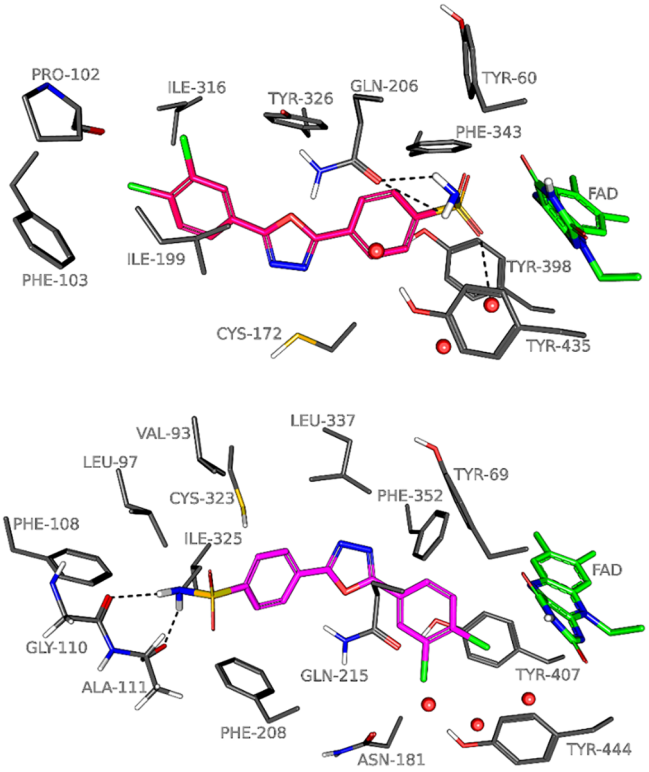


Fig. 4. Predicted binding orientation of **1e** in the active sites of MAO-B (top) and MAO-A (bottom).

Fig. 5. The predicted binding orientation of **1e** in the active site of MAO-B compared to the orientation of zonisamide in the crystal structure (PDB entry: 3PO7).

To determine the inhibition potencies of the synthesized compounds, the recombinant human MAO enzymes were used as enzyme sources, and kynuramine served as the non-selective substrate.[28] Kynuramine is oxidized by MAO to ultimately yield 4-hydroxyquinoline, a metabolite which may conveniently be measured by fluorescence spectrophotometry. By thus measuring MAO activity in the presence of various test inhibitor concentrations, sigmoidal curves of enzyme catalytic rate versus the logarithm of inhibitor concentration may be constructed, from which IC_{50} values are estimated. Examples of sigmoidal curves for the inhibition of MAO-B are given in Fig. 2.

The IC_{50} values are given in Table 1, and show that the 5-aryl-1,3,4-oxadiazol-2-ylbenzenesulfonamides (**1a–e**; **2a–e**) are specific inhibitors of MAO-B with SI values > 35. In this regard, **1a–e** and **2a–e** are weak MAO-A inhibitors with IC_{50} > 24.3 μM. In contrast, these compounds are good potency MAO-B inhibitors with all compounds exhibiting IC_{50} < 1 μM. The most potent MAO-B inhibition was observed for **1e** which exhibit an IC_{50} of 0.0027 μM. This compound is therefore approximately 33-fold more potent than the reference MAO-B inhibitor, lazabemide. Substitution of the sulfonamides on position 4 of the

phenyl yielded significantly higher MAO-B inhibition compared to substitution on position 3 (e.g. **1b** vs. **2a**; **1c** vs. **2d**). Furthermore, halogen substitution as observed with **1b–c** and **1e** further enhanced MAO-B inhibition (compare with **1a** and **1d**). Compared to the 1,3,4-oxadiazole compounds, the N,N'-diacylhydrazines synthetic precursors are weak MAO inhibitors, which demonstrates the requirement for the oxadiazole functionality for MAO-B inhibition. Finally, *ortho* substitution to the 3-benzenesulfonamides reduced MAO-B inhibition (e.g. **2c** and **2e** vs. **2d**).

The reversibility of MAO-B inhibition was investigated for the most potent inhibitor of this study, **1e**. For this purpose, dialysis experiments were carried out. MAO-B and **1e** were pre-incubated (at a concentration of 4 × IC_{50}) and subsequently dialyzed. The incubation mixtures were diluted twofold to yield an inhibitor concentration of 2 × IC_{50}, and the residual MAO-B activity was recorded. For comparison, a similar experiment was carried out with the exception that the pre-incubations were not dialyzed. As negative and positive controls, respectively, dialysis experiments were carried out in the absence of test inhibitor and presence of the irreversible MAO-B inhibitor, selegiline. The results of the dialysis experiments show that **1e** is a reversible MAO-B inhibitor since, after dialysis, MAO-B activity is recovered to 60% of the negative control value (100%) (Fig. 3). As expected, inhibition of MAO-B persists in non-dialysed pre-incubations with the residual activity at 44%. For the positive control selegiline, dialysis does not restore catalytic activity with the residual activity at 7%. It may thus be concluded that **1e** is a reversible inhibitor of MAO-B, but may exhibit tight-binding to the MAO-B active site since dialysis does not completely (100%) restore catalytic activity.

Possible binding orientations and interactions of **1e**, the most potent inhibitor of this study, in the MAO-B active site were predicted using molecular docking experiments. For comparison, this inhibitor was also docked into the MAO-A active site. For this purpose, the Discovery Studio 3.1 modelling software (Accelrys) was used, and the X-ray crystal structures of human MAO-A co-crystallised with harmine (PDB entry: 2Z5X) and human MAO-B co-crystallised with safinamide (PDB entry: 2V5Z) served as protein models.[3,29] The docking experiments were carried out as described previously with the CDOCKER application of Discovery Studio.[30] In the first step, the pKa values and protonation states of the amino acid residues were calculated for the protein models, and an energy minimization, with the protein backbone constrained, was carried out. The structure of **1e** was drawn in Discovery Studio, and after docking with CDOCKER, the docked orientations (ten solutions generated) were refined using in situ ligand minimization.

The results of the docking study show that **1e** binds to the MAO-B active site with the sulfonamide group in proximity to the FAD, the polar region of the MAO-B active site (Fig. 4). The sulfonamide group of **1e** binds in the same region as that of zonisamide as reported in the crystal structure of this compound in complex with MAO-B (Fig. 5).[31] The inhibitor extends towards the entrance of the active site with the dichlorophenyl bound in the entrance cavity, the space beyond the Ile-199 gating residue. Hydrogen bonding occurs between the sulfonamide functional group and an active site water and Gln-206. Pi-pi stacking interactions occurs between the oxadiazole ring and Tyr-326, and between Tyr-398 and the benzenesulfonamide phenyl ring. Pi-sulfur interactions are present between the sulfonamide and Tyr-60, and between Cys-172 and the oxadiazole and benzenesulfonamide rings. In the entrance cavity, the dichlorophenyl undergoes hydrophobic interactions. The finding that the dichlorophenyl binds within the entrance cavity may explain the 17-fold difference in the MAO-B inhibition activities of **1e** (IC_{50} = 0.0027 μM) versus **1c** (IC_{50} = 0.048 μM). The substitution of **1e** with an additional chloro group would increase the hydrophobic interaction between the inhibitor and the entrance cavity leading to the observed increase in inhibition potency. No unfavorable interactions have been recorded.

For binding to MAO-A, **1e** exhibit a reversed orientation with the dichlorophenyl bound in proximity to the FAD, while the sulfonamide moiety is placed towards to the entrance of the active site. The sulfonamide undergoes hydrogen bonding with the backbone carbonyl groups of Gly-110 and Ala-111, while pi-pi interactions are established between the benzenesulfonamide ring and Phe-208, and between Tyr-407 and the dichlorophenyl ring. Pi-sulfur interactions are present between the oxadiazole ring and Cys-323 and Met-350. Of significance is a steric conflict between Leu-97 and the sulfonamide group, which indicates that **1e** does not fit well in the MAO-A active site. The orientation of binding in MAO-A also may be less favorable since it would be expected that the polar sulfonamide will bind in the polar region of the active site, in front of the FAD.

This study shows that 5-aryl-1,3,4-oxadiazol-2-ylbenzenesulfonamides are potent and specific inhibitors of MAO-B, with IC_{50} values as low as 0.0027 μM for the most potent inhibitor. Although MAO inhibition by oxadiazole compounds is known, this is the first report of nanomolar MAO inhibition potencies recorded for sulfonamide derivatives. Molecular docking studies show that the sulfonamide of the most potent inhibitor, **1e**, undergoes hydrogen bonding in the MAO-B substrate cavity, while the oxadiazole and benzenesulfonamide phenyl rings forms pi-pi stacking interactions. The dichlorophenyl binds in the entrance cavity where interactions are mostly hydrophobic in nature. This large inhibitor thus fills the MAO-B active site and forms numerous productive interactions, which may explain its highly potent inhibition of this enzyme. In this regard, the sulfonamide moiety undergoes extensive hydrogen bonding, and is likely a key contributor to inhibitor stabilization. In contrast, the MAO-A active site is more restricted and does not accommodate larger inhibitors as well as MAO-B. In particular, Phe-208 prevents larger inhibitors from binding to MAO-A, while the side chain of the analogous residue in MAO-B, Ile-199, is able to rotate from the active site cavity, thus increasing the space available for inhibitors to bind.[32] This may, at least in part, explain the specificity of these compounds. In conclusion, MAO-B specific inhibitors such as those discovered here may be of interest in the treatment of neurodegenerative disorders such as Parkinson's disease.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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