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Sulfanylphthalonitrile analogues as selective and potent inhibitors of monoamine oxidase B

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ABSTRACT

It has recently been reported that nitrile containing compounds frequently act as potent monoamine oxidase B (MAO-B) inhibitors. Modelling studies suggest that this high potency inhibition may rely, at least in part, on polar interactions between nitrile functional groups and polar moieties within the MAO-B substrate cavity. In an attempt to identify potent and selective inhibitors of MAO-B and to contribute to the known structure–activity relationships of MAO inhibition by nitrile containing compounds, the present study examined the MAO inhibitory properties of series of novel sulfanylphthalonitriles and sulfanylbenzonitriles. The results document that the evaluated compounds are potent and selective MAO-B inhibitors with most homologues possessing IC_{50} values in the nanomolar range. In general, the sulfanylphthalonitriles exhibited higher binding affinities for MAO-B than the corresponding sulfanylbenzonitrile homologues. Among the compounds evaluated, 4-[(4-bromobenzyl)sulfanyl]phthalonitrile is a particularly promising inhibitor since it displayed a high degree of selectivity (8720-fold) for MAO-B over MAO-A, and potent MAO-B inhibition (IC_{50} = 0.025 μM). Based on these observations, this structure may serve as a lead for the development of therapies for neurodegenerative disorders such as Parkinson's disease.

The enzyme monoamine oxidase B (MAO-B) is considered to be a major dopamine metabolizing enzyme in the human brain and, as such, a target for the treatment of Parkinson's disease.[1–3] Inhibitors of MAO-B are thought to reduce the metabolic degradation of central dopamine and as a result increase dopaminergic neurotransmission.[4,5] MAO-B inhibitors are frequently combined with levodopa in the therapy of Parkinson's disease since this may enhance the dopamine levels derived from levodopa and allow for a reduction of the effective levodopa dose.[6] In the initial stages of the disease, MAO-B inhibitors may also delay the emergence of disabilities that require the initiation of levodopa therapy. The inhibition of MAO-B has also been associated with a neuroprotective effect. This effect may, at least in part, depend on blocking the formation of H_2O_2 and aldehyde species, metabolic by-products of substrate metabolism by MAO-B.[7] These metabolites may be harmful if not rapidly cleared from the central nervous system. Considering that central MAO-B activity increases with age,[8–10] inhibition of the MAO-B-catalyzed formation of toxic by-products in the aged parkinsonian brain is of particular relevance. Interestingly, dopamine is also oxidized by the MAO-A isoform in the human brain, and MAO-A inhibitors have been shown to enhance central dopamine levels in primates.[4,5] MAO-A inhibitors may, however, lead to serious adverse effects when combined with certain drugs and food. Most notably, when MAO-A inhibitors are used with indirectly acting sympathomimetic amines such as tyramine, which is present is certain foods, a potentially fatal hypertensive response may occur.[7,11] MAO-A inhibitors should also be used with caution in combination with levodopa since this may elicit a hypertensive crisis.[12] For these reasons, inhibitors that are selective for the MAO-B isoform are more desirable as antiparkinsonian agents.

Based on these considerations, the present study aims to discover novel compounds that bind selectively and with high binding affinities to MAO-B. Among the various types of structures that have been reported to inhibit the MAO enzymes are nitrile containing compounds. Both phthalonitriles and benzonitriles have been found to act as potent and selective MAO-B inhibitors.[13,14] For example, 4-benzyloxyphthalonitrile (**1**) and 4-benzyloxybenzonitrile (**2**) inhibit human MAO-B reversibly with IC_{50} values of 0.0079 and 0.785 μM, respectively (Fig. 1).[13] These homologues display 227- and 41-fold selectivities, respectively, for the MAO-B isoform. Based on its good selectivity and high potency, compound **1** may be viewed as a particularly promising inhibitor. The high binding affinities of nitrile containing compounds to MAO-B may be explained by the highly polar nature of this functional group. Modelling studies predict that the nitrile group interacts with the polar regions in the substrate cavity of the MAO-B enzyme.[13] This seems

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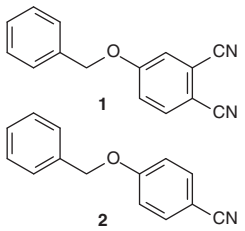


Figure 1. The structures of 4-benzyloxyphthalonitrile (**1**) and 4-benzyloxybenzonitrile (**2**).

to be a prerequisite for potent inhibition since elimination of the nitrile results in a loss of MAO-B inhibitory activity. Literature also documents that phthalonitriles are in general more potent MAO-B inhibitors than benzonitriles, which suggests that the productive interactions between nitrile groups and the MAO-B enzyme are additive. The active site cavity of MAO-B is, however, bipartite and besides the substrate cavity where the phthalonitrile and benzonitrile moieties are predicted to bind, the active site also possesses an entrance cavity.[15] The benzyloxy side chains of compounds **1** and **2** are predicted to bind within the entrance cavity of MAO-B, where they are most likely stabilized via Van der Waals interactions. The interactions between the benzyloxy side chain and the entrance cavity are thought to also contribute significantly to the binding affinities of these inhibitors, since modification (e.g. replacement with a phenoxy) leads to a two orders of magnitude loss in MAO-B inhibition activity. In addition, several other potent MAO-B inhibitors possess the benzyloxy side chain. These include safinamide (**3**) and 8-benzyloxycaffeine (**4**) (Fig. 2). Crystallographic as well as modelling studies have shown that the benzyloxy side chains of these inhibitors bind within the MAO-B entrance cavity.[16,17] Of note is a recent report that the benzylsulfanyl side chain exhibit similar properties to that of the benzyloxy moiety, since a series of 8-(benzylsulfanyl)caffeines (**5**) possesses similar MAO-B inhibition potencies to those of the 8-benzyloxycaffeines (**4**).[18] In addition, modelling suggests that the binding modes of the benzylsulfanyl and benzyloxy side chains within the entrance cavity of MAO-B are highly comparable. Based on these observations, the present study examines the possibility that benzylsulfanyl substitution on the phthalonitrile and benzonitrile moieties, to yield compounds **6a** and **7a**, would also lead to highly potent and selective MAO-B inhibition (Fig. 3). To explore the structure–activity relationships (SARs) of MAO inhibition by

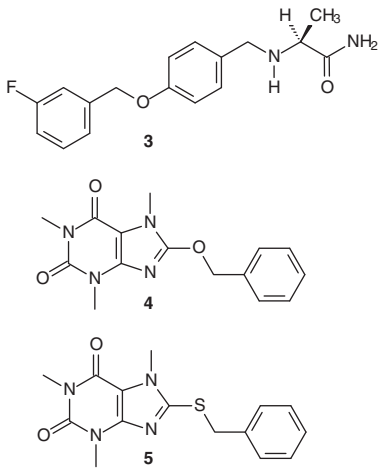


Figure 2. The structures of safinamide (**3**), 8-benzyloxycaffeine (**4**) and 8-(benzylsulfanyl)caffeine (**5**).

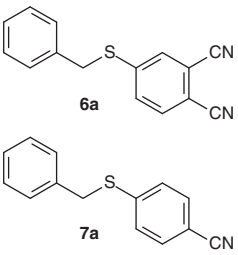


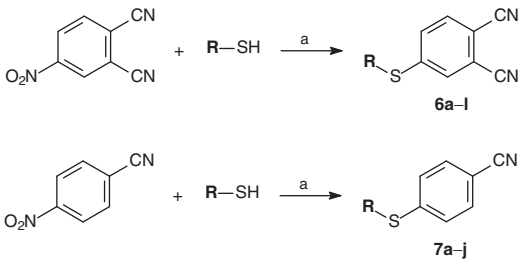
Figure 3. The general structures of 4–(benzylsulfanyl)phthalonitrile (**6a**) and 4–(benzylsulfanyl)benzonitrile (**7a**).

these compounds, the effects that substitution (Cl, Br, F and OCH_3) on the benzylsulfanyl ring have on MAO inhibition were considered. Halogen substitution on the benzylsulfanyl ring of **5** has been shown to be beneficial for MAO-B inhibition.[18] In addition, substitution on the phthalonitrile and benzonitrile moieties with phenylsulfanyl, (2-phenylethyl)sulfanyl, cyclohexylsulfanyl, cyclopentylsulfanyl and (3-methylbutyl)sulfanyl substituents were also considered.

The target sulfanylphthalonitriles (**6a–l**) and sulfanylbenzonitriles (**7a–j**) were synthesized according to the procedures described in literature.[13,19] The sulfanylphthalonitriles were synthesized in fair to good yields (16–83%) by reacting an appropriate thiol with 4-nitrophthalonitrile in the presence of K_2CO_3 in dimethyl sulfoxide (DMSO) (Scheme 1). The crude products were purified by recrystallization from an appropriate solvent as indicated in the Supplementary data. The sulfanylbenzonitriles were synthesized in an analogous manner by reacting 4-nitrobenzonitrile with an appropriate thiol (2–72%). The structures of the target nitrile derivatives were verified by ^1H NMR, ^{13}C NMR and mass spectrometry, while their purities were estimated by HPLC analysis as cited in the Supplementary data.

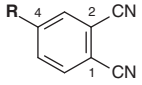
The MAO inhibitory activities of the sulfanylphthalonitriles and sulfanylbenzonitriles were evaluated by employing recombinant human MAO-A and -B as enzyme sources.[20] Kynuramine, a mixed MAO-A/B substrate, served as enzyme substrate for these inhibition studies. Kynuramine undergoes MAO-catalyzed oxidation to yield the fluorescent metabolite, 4–hydroxyquinoline, which may be conveniently measured by fluorescence spectrophotometry without interference from the substrate and inhibitors evaluated in this study.[21] The inhibitory potencies of the nitriles are expressed as the corresponding IC_{50} values, and their selectivities for the MAO-B isoform are expressed as the selectivity index (SI) value $[IC_{50}(MAO–A)]/[(IC_{50}(MAO–B)]$.

The results document that the sulfanylphthalonitriles (**6**) are potent MAO-B inhibitors with all homologues, except **6f**, possessing IC_{50} values in the submicromolar range (Table 1). In accordance to expectation, benzylsulfanyl substitution on the phthalonitrile moiety, to yield **6a** (IC_{50} = 0.167 μM), resulted in potent MAO-B inhibition. Substitution (Cl, Br, F and OCH_3) on the benzylsulfanyl



Scheme 1. Synthetic pathway to sulfanylphthalonitriles (**6a–l**) and sulfanylbenzonitriles (**7a–j**). Reagents and conditions: (a) K_2CO_3, DMSO, argon.

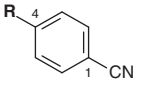
Table 1
The IC_{50} values for the inhibition of recombinant human MAO-A and –B by sulfanylphthalonitriles **6a–l**



	R	IC_{50} (μM)[a]			
		MAO-A	MAO-B	SI[b]	SI[c,d]
6a	–S–(CH_2)-C_6H_5	9.02 ± 0.896	0.167 ± 0.016	54	33
6b	–S–(CH_2)-(4-Cl-C_6H_4)	0.623 ± 0.053	0.014 ± 0.004	45	27
6c	–S–(CH_2)-(4-Br-C_6H_4)	218 ± 23.9	0.025 ± 0.003	8720	5334
6d	–S–(CH_2)-(4-F-C_6H_4)	2.10 ± 0.218	0.034 ± 0.006	62	38
6e	–S–(CH_2)-(4-OCH_3-C_6H_4)	129 ± 78.1	0.067 ± 0.021	1925	1178
6f	–S–C_6H_5	3.58 ± 0.592	2.13 ± 0.067	1.7	1.0
6g	–S–(4-Cl-C_6H_4)	11.1 ± 1.17	0.114 ± 0.002	97	59.6
6h	–S–(4-Br-C_6H_4)	19.0 ± 8.27	0.079 ± 0.017	240	147.1
6i	–S–$(CH_2)_2$-C_6H_5	7.19 ± 1.35	0.124 ± 0.009	58	35.5
6j	–S–C_6H_{11}	5.96 ± 0.382	0.223 ± 0.039	27	16.3
6k	–S–C_5H_9	2.78 ± 0.936	0.887 ± 0.072	3.1	1.9
6l	–S–$(CH_2)_2$-$CH(CH_3)_2$	1.45 ± 0.203	0.242 ± 0.035	6.0	3.7

[a] All values are expressed as the mean ± SD of triplicate determinations.
[b] The selectivity index is the selectivity for the MAO-B isoform and is given as the ratio of [IC_{50} (MAO-A)]/[IC_{50}(MAO-B)].
[c] The selectivity index is the selectivity for the MAO-B isoform and is given as the ratio of K_i (MAO-A)/K_i(MAO-B).
[d] The K_i values were calculated from the experimental IC_{50} values according to the equation by Cheng and Prusoff: $K_i = IC_{50}/(1 + [S]/K_m)$. For human MAO-A, [S] = 45 μM and K_m (kynuramine) = 16.1 μM, while for human MAO-B, [S] = 30 μM and K_m (kynuramine) = 22.7 μM.[17,23]

Table 2
The IC_{50} values for the inhibition of recombinant human MAO-A and –B by sulfanylbenzonitriles **7a–j**



	R	IC_{50} (μM)[a]			
		MAO-A	MAO-B	SI[b]	SI[c,d]
7a	–S–(CH_2)-C_6H_5	42.4 ± 3.10	1.58 ± 0.327	27	16
7b	– S–(CH_2)-(4-Cl-C_6H_4)	20.3 ± 6.62	0.531 ± 0.114	38	23
7c	– S–(CH_2)-(4-Br-C_6H_4)	129 ± 18.5	0.484 ± 0.052	267	163
7d	– S–(CH_2)-(4-F-C_6H_4)	54.7 ± 22.8	0.449 ± 0.128	122	75
7e	–S–(CH_2)-(4-OCH_3-C_6H_4)	5.59 ± 0.744	0.861 ± 0.165	6.5	4.0
7f	–S–C_6H_5	36.9 ± 1.02	11.2 ± 0.584	3.3	2.0
7g	–S–(4-Cl-C_6H_4)	18.2 ± 2.17	4.28 ± 2.09	4.3	2.6
7h	– S–(4-Br-C_6H_4)	8.52 ± 0.869	0.637 ± 0.162	13	8.2
7i	–S–$(CH_2)_2$-C_6H_5	54.3 ± 11.9	1.81 ± 0.130	30	18
7j	–S–C_6H_{11}	9.87 ± 3.03	4.77 ± 0.383	2.1	1.3

[a] All values are expressed as the mean ± SD of triplicate determinations.
[b] The selectivity index is the selectivity for the MAO-B isoform and is given as the ratio of [IC_{50}(MAO-A)]/[IC_{50}(MAO-B)].
[c] The selectivity index is the selectivity for the MAO-B isoform and is given as the ratio of K_i(MAO-A)/K_i(MAO-B).
[d] The K_i values were calculated from the experimental IC_{50} values according to the equation by Cheng and Prusoff: $K_i = IC_{50}/(1 + [S]/K_m)$. For human MAO-A, [S] = 45 μM and K_m (kynuramine) = 16.1 μM, while for human MAO-B, [S] = 30 μM and K_m (kynuramine) = 22.7 μM.[17,23]

ring further enhanced MAO-B inhibition potency with compounds **6b–e** exhibiting IC_{50} values of 0.014–0.067 μM. In fact, **6b** proved to be the most potent MAO-B inhibitor of the present series. In contrast to the effect of the benzylsulfanyl moiety, phenylsulfanyl substitution on the phthalonitrile moiety, to yield **6f** (IC_{50} = 2.13 μM), resulted in only moderate MAO-B inhibition. Interestingly, halogen substitution on the phenyl ring of **6f** improved MAO-B inhibition with **6g–h** exhibiting IC_{50} values of 0.079–0.114 μM. Substitution on the phthalonitrile moiety with (2-phenylethyl)sulfanyl, cyclohexylsulfanyl, cyclopentylsulfanyl and (3-methylbutyl)sulfanyl side chains also resulted in potent MAO-B inhibition. These homologues (**6i–l**) displayed IC_{50} values of 0.124–0.887 μM. It is noteworthy that the (2-phenylethyl)sulfanyl substituted homologue **6i** (IC_{50} = 0.124 μM) is slightly more potent than the benzylsulfanyl substituted phthalonitrile **6a**. This suggests that extension of the benzylsulfanyl side chain result in slightly improved MAO-B inhibition. Reduction of the length of the benzylsulfanyl side chain of **6a** to yield **6f**, however, markedly lowers MAO-B inhibition potency.

The MAO inhibitory properties of the sulfanylbenzonitriles are given in Table 2. The results show that, although several compounds exhibit IC_{50} values in the submicromolar range, the sulfanylbenzonitriles exhibited lower binding affinities for MAO-B than the corresponding sulfanylphthalonitrile homologues. The MAO-B inhibitor potencies of the sulfanylbenzonitriles ranged from 0.449–11.2 μM with the most potent inhibitor being compound **7d**. As observed for the sulfanylphthalonitriles, substitution (Cl, Br, F and OCH_3) on the benzylsulfanyl ring enhanced MAO-B inhibition potency compared to the unsubstituted homologue **7a** (IC_{50} = 1.58 μM). These substituted homologues, compounds **7b–e**, possessed IC_{50} values of 0.449–0.861 μM. Similarly, halogen substitution on the phenyl ring of **7f** (IC_{50} = 11.2 μM) improved MAO-B inhibition with **7g–h** exhibiting IC_{50} values of 0.637–4.28 μM. Among the sulfanylbenzonitriles, phenylsulfanyl substitution (to yield **7f**) resulted in the weakest MAO-B inhibition. This result is similar to that obtained with the sulfanylphthalonitriles. Based on these results it may be concluded that sulfanylphthalonitriles are more favourable for MAO-B inhibition compared to sulfanylbenzonitriles.

The results given in Tables 1 and 2 show that the sulfanylphthalonitriles and sulfanylbenzonitriles also are inhibitors of MAO-A. In all instances, these compounds are, however, selective for MAO-B with SI values ranging from 1.7–8720. Only one compound, **6b** (IC_{50} = 0.623 μM), exhibited an IC_{50} value in the submicromolar range for the inhibition of MAO-A. Based on IC_{50} values of 0.623–218 μM, it may therefore be concluded that sulfanylphthalonitriles and sulfanylbenzonitriles are in general weak to moderate inhibitors of MAO-A. It is noteworthy that two compounds, **6c** and **6e**, exhibited SI values in excess of 1000. These compounds, particularly **6c** (SI = 8720), may therefore be considered as highly selective for MAO-B. Compounds **6c** and **6e** are also highly potent MAO-B inhibitors. As mentioned, selective and potent MAO-B inhibitors represent good candidates for antiparkinsonian therapy.

It has been reported that phthalonitriles act as reversible MAO-B inhibitors.[13] To verify that the sulfanylphthalonitrile class of compounds also interacts reversibly with MAO-B, the reversibility of MAO-B inhibition by **6c** was examined. For this purpose **6c**, at concentrations of 10 × IC_{50} and 100 × IC_{50}, was preincubated with MAO-B for 30 min and the extent of enzyme recovery after dilution of the enzyme–inhibitor complex was measured.[22] The results show that, after dilution of the enzyme-inhibitor complexes to concentrations of **6c** equal to 0.1 × IC_{50} and 1 × IC_{50}, the MAO-B catalytic activities are recovered to levels of approximately 76% and 48%, respectively, of the control value (Fig. 4). This recovery of MAO-B activity is consistent with a reversible interaction between **6c** and MAO-B. For comparison, MAO-B was treated in a similar manner with the irreversible inhibitor, (*R*)-deprenyl, at a concentration of 10 × IC_{50}. After 100-fold dilution, MAO-B activity was, however, not recovered (0.8% of control).

In conclusion, the present study shows that the sulfanylphthalonitrile and to a lesser extent the sulfanylbenzonitrile classes of compounds are in general highly potent inhibitors of MAO-B. A particularly promising compound among those examined is the *para* bromo substituted derivative of 4-(benzylsulfanyl)phthalonitrile, compound **6c**. This compound displays potent MAO-B

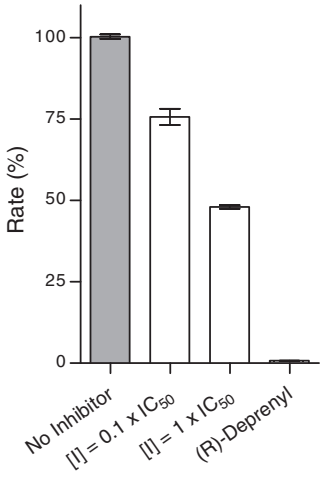


Figure 4. The reversibility of the interaction between MAO-B by **6c**. Compound **6c** at concentrations of $10 \times IC_{50}$ and $100 \times IC_{50}$ was preincubated with MAO-B for 30 min. The resulting reactions were diluted 100-fold to yield inhibitor concentrations of $0.1 \times IC_{50}$ and $1 \times IC_{50}$, respectively. The control reactions were conducted in the absence of inhibitor. For comparison, reactions containing (*R*)-deprenyl, at $10 \times IC_{50}$, was also preincubated with MAO-B and diluted to $0.1 \times IC_{50}$. After dilution of all reactions, the residual enzyme activities were subsequently measured.

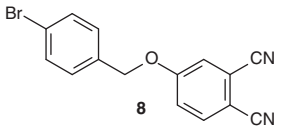


Figure 5. The structure of 4-(4-bromobenzyloxy)phthalonitrile (**8**).

inhibition (IC_{50} = 0.025 μM) and a high degree of selectivity (8720-fold) for MAO-B over MAO-A. For comparison, (R)-deprenyl exhibits an IC_{50} value for the inhibition of MAO-B of 0.079 μM under identical experimental conditions.[22] Compared to (*R*)-deprenyl, compound **6c** is a threefold more potent MAO-B inhibitor. The MAO-A inhibitor, clorgyline, exhibits an IC_{50} value for the inhibition of MAO-A of 0.0026 μM under identical experimental conditions.[22] The most potent MAO-A inhibitor of the present series, compound **6b** (IC_{50} = 0.623) is therefore 240-fold less potent as a MAO-A inhibitor than clorgyline. Compared to the lead compounds of this study, the 4-benzyloxyphthalonitrile (**1**) class of compounds, the sulfanylphthalonitriles are, however, less potent MAO-B inhibitors. For example, the *para* bromo substituted homologue of 4-benzyloxyphthalonitrile, compound **8**, inhibits human MAO-B with an IC_{50} value of 0.0048 μM, approximately fivefold more potent than **6c** (Fig. 5).[13] Compound **6c** is, however, a considerably (66-fold) more selective MAO-B inhibitor than **8** (SI = 134). From this analysis it may be concluded that among the phthalonitrile and benzonitrile derivatives examined to date, **6c** is the most appropriate candidate for Parkinson's disease therapy.[13,14]

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2012.10.070.

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