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An evaluation of synthetic indole derivatives as inhibitors of monoamine oxidase

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ABSTRACT

In a recent study we have shown that several indole-5,6-dicarbonitrile derivatives are potent inhibitors of human monoamine oxidase (MAO) A and B. To expand on these results and to further determine structure–activity relationships (SARs) for MAO inhibition by this chemical class, the present study investigates the MAO inhibition properties of additional indole-5,6-dicarbonitriles and related indole-5,6-dicarboxylic acid and pyrrolo[3,4-*f*]indole-5,7-dione derivatives. Among the active compounds two pyrrolo[3,4-*f*]indole-5,7-dione derivatives inhibited MAO-A (**4g**) and MAO-B (**4d**) with IC_{50} values of 0.250 and 0.581 μM, respectively. In general indole-5,6-dicarbonitriles, however, exhibit higher MAO inhibition potencies while indole-5,6-dicarboxylic acids are weak MAO inhibitors. Active MAO inhibitors such as **4g** and **4d** may be used as leads for the development of drugs for the treatment of disease states such as Parkinson's disease and depression. MAO inhibitors are also under investigation as potential agents for the treatment of prostate cancer, certain types of cardiomyopathies and Alzheimer's disease.

The monoamine oxidase (MAO) enzymes consist of two isoforms, MAO-A and MAO-B, which are expressed in most human tissues including the brain, liver and heart. These enzymes play key roles in the metabolism of neurotransmitter amines and are therefore important drug targets for disease states arising from deficient levels of particular neurotransmitters.[1,2] Reduced central serotonin levels are linked to depressive illness and since serotonin is a specific substrate of MAO-A, inhibitors of this isoform are used in the clinic as antidepressants.[3,4] In Parkinson's disease, central dopamine is depleted and inhibitors of the MAO-B isoform is thus used to inhibit dopamine metabolism, a strategy often combined with therapy with L-Dopa, the metabolic precursor of dopamine.[5] MAO inhibitors may also decrease oxidative stress by reducing the tissue levels of hydrogen peroxide formed as by-product in the MAO catalytic cycle. In this respect, MAO-A is an important source of hydrogen peroxide in the heart and MAO-A inhibitors may find future use in certain types of cardiomyopathies.[6,7] Hydrogen peroxide production by MAO in the brain has been implicated in the neurodegenerative process of Parkinson's disease, thus providing a rationale for MAO inhibitors as potential neuroprotectants.[8] Recently, MAO inhibitors have also been investigated as potential therapy for Alzheimer's disease, acting via various molecular mechanisms.[9] Interestingly, laboratory evidence suggests that MAO-A inhibitors may represent potential therapy for advanced prostate cancer.[10]

Based on the therapeutic significance of MAO inhibitors the discovery of new classes of chemical compounds that exhibit MAO inhibition properties are pursued by several research groups. We have recently shown that several indole-5,6-dicarbonitrile derivatives are potent inhibitors of the human MAOs.[11] For example derivative **1a** was shown to inhibit MAO-A and MAO-B with IC_{50} values of 0.014 and 0.017 μM, respectively (Fig. 1). This compound also is a reversible and competitive inhibitor of both MAOs. Based on the potent activities of **1a** and other derivatives in this class, the present study investigates the MAO inhibition properties of additional indole-5,6-dicarbonitrile derivatives (**2**) and related indole-5,6-dicarboxylic acid (**3**) and pyrrolo[3,4-*f*]indole-5,7-dione derivatives (**4**). In addition, several related compounds (**5**) and intermediates (**6**) in the synthetic pathway of these compounds were also evaluated in an attempt to discover new chemical classes that may be used as leads for MAO inhibitor design. The derivatives examined in this study are given in Tables 1–4. The importance of indole derivatives are illustrated by the fact that they are found in many natural compounds[12] and pharmaceuticals.[13] Indole derivatives influence the neurotransmitter

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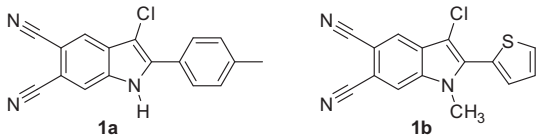
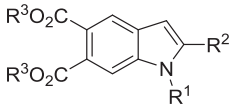


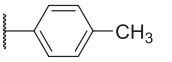
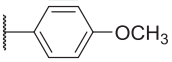
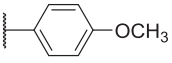
Figure 1. The structure of indole-5,6-dicarbonitrile derivatives **1a** and **1b**.

serotonin[14,15] and are potent PPAR-c binding agents with potential application for the treatment of osteoporosis.[16] Indoles also are reported to be potent anti-inflammatory[17] and antimicrobial agents,[18] and may possess neuroprotective properties by modulating oxidative stress.[19]

4-Nitro-5-(2-oxo-2-arylethyl)benzene-1,2-dicarbonitriles **7a–d** are convenient building-blocks for the synthesis of substituted indoles.[20] These dicarbonitriles with multiple reactive centres can be used in reactions such as intramolecular cyclisation followed by the introduction of various substituents on a number of positions. Using these compounds as starting materials it is possible to develop general methods for the synthesis of new indoles

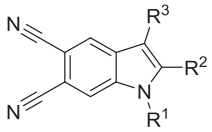
Table 2
The human MAO inhibition potencies of indole-5,6-dicarboxylic acid derivatives **3**

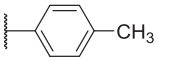
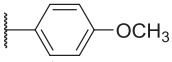
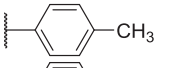
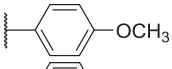
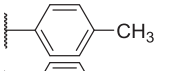
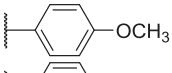
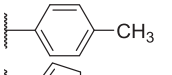


	R^1	R^2	R^3	IC_{50} (μM)[a]		SI[b]
				MAO-A	MAO-B	
3a	OH		H	23.3 ± 4.14	56.2 ± 3.06	2.4
3b	OH		H	>100	>100	–
3c	OH		H	>100	>100	
3d	OH		H	>100	>100	–
3e	OCH_3		CH_3	19.0 ± 5.63	>100	>5.3

See Table 1 for footnotes.

Table 1
The human MAO inhibition potencies of indole-5,6-dicarbonitrile derivatives **2**



	R^1	R^2	R^3	IC_{50} (μM)[a]		SI[b]
				MAO-A	MAO-B	
2a	OH		H	6.92 ± 0.955	10.3 ± 1.83	1.5
2b	OH		H	1.14 ± 0.097	0.821 ± 0.035	0.72
2c	OH		H	1.84 ± 0.121	1.79 ± 0.473	0.97
2d	OH		H	11.1 ± 0.865	>100	>9
2e	OCH_3		CHO	0.522 ± 0.067	>100	>192
2f	OCH_3		CHO	0.405 ± 0.049	74.8 ± 12.0	185
2g	OCH_3		CHO	0.147 ± 0.033	>100	>680
2h	OCH_3		CH_2OH	4.99 ± 0.468	>100	>20
2i	OCH_3		CH_2OH	5.12 ± 0.525	>100	>20
2j	OCH_3		CH_2OH	1.13 ± 0.248	>100	>88
2k	OCH_3		Br	>100	>100	–
2l	OCH_3		Br	>100	7.46 ± 2.08	<0.075
2m	OAc		H	2.08 ± 0.269	1.94 ± 0.401	0.93

[a] All values are expressed as the mean ± standard deviation (SD) of triplicate determinations.
[b] The selectivity index is the selectivity for the MAO-A isoform and is given as the ratio of IC_{50}(MAO-B)/IC_{50}(MAO-A).