An evaluation of synthetic indole derivatives as inhibitors of monoamine oxidase

Zhanna V. Chirkova, Mariya V. Kabanova, Sergey I. Filimonov, Igor G. Abramov, Anél Petzer, Jacobus P. Petzer, Kyrill Yu. Suponitsky

PII: S0960-894X(16)30280-3
DOI: http://dx.doi.org/10.1016/j.bmcl.2016.03.060
Reference: BMCL 23703

To appear in: *Bioorganic & Medicinal Chemistry Letters*

Received Date: 25 January 2016
Revised Date: 14 March 2016
Accepted Date: 15 March 2016

Please cite this article as: Chirkova, Z.V., Kabanova, M.V., Filimonov, S.I., Abramov, I.G., Petzer, A., Petzer, J.P., Suponitsky, K.Y., An evaluation of synthetic indole derivatives as inhibitors of monoamine oxidase, *Bioorganic & Medicinal Chemistry Letters* (2016), doi: http://dx.doi.org/10.1016/j.bmcl.2016.03.060

An evaluation of synthetic indole derivatives as inhibitors of monoamine oxidase

Zhanna V. Chirkova [a], Mariya V. Kabanova [a], Sergey I. Filimonov [a], Igor G. Abramov [a], Anél Petzer [b], Jacobus P. Petzer [b], Kyrill Yu. Suponitsky [c]

[a] *Yaroslavl State Technical University, 150023 Yaroslavl, Russian Federation*

[b] *Pharmaceutical Chemistry and Centre of Excellence for Pharmaceutical Sciences, North-West University, Potchefstroom 2520, South Africa*

[c] *A.N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, 28 Vavilov St., 119991 Moscow, Russian Federation*

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.

Keywords: monoamine oxidase; MAO; inhibition; selective; indole; dicarbonitrile.

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]

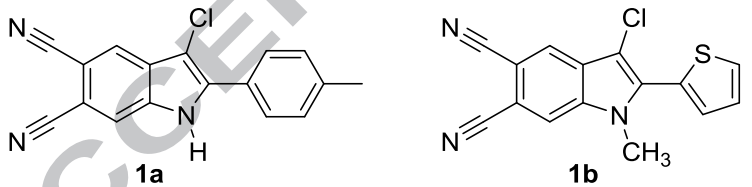
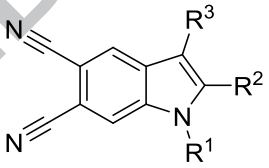


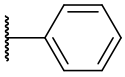
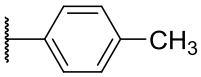
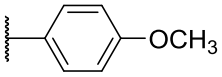
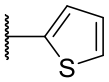
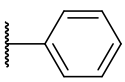
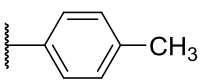
Fig. 1. The structure of indole-5,6-dicarbonitrile derivatives **1a** and **1b**.

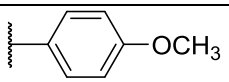
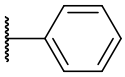
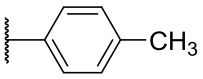
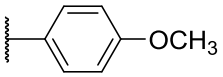
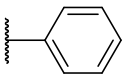
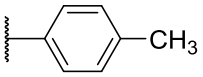
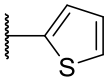
Based on the therapeutic significance of MAO inhibitors the discovery of new classes of chemical compounds that exhibit MAO inhibition properties are pursued by several research groups. We have recently shown that several indole-5,6-dicarbonitrile derivatives are potent inhibitors of the human MAOs.[11] 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 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]

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



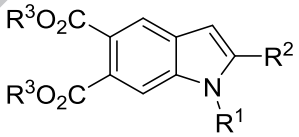
	R^1	R^2	R^3	IC_{50} (μM)[a]		SI[b]
				MAO-A	MAO-B	
2a	OH		H	6.92 ± 0.955	10.3 ± 1.83	1.5
2b	OH		H	1.14 ± 0.097	0.821 ± 0.035	0.72
2c	OH		H	1.84 ± 0.121	1.79 ± 0.473	0.97
2d	OH		H	11.1 ± 0.865	>100	>9
2e	OCH_3		CHO	0.522 ± 0.067	>100	>192
2f	OCH_3		CHO	0.405 ± 0.049	74.8 ± 12.0	185

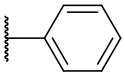
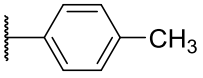
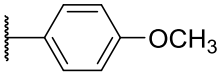
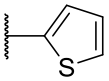
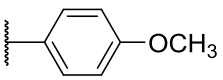
2g	OCH_3		CHO	0.147 ± 0.033	>100	>680
2h	OCH_3		CH_2OH	4.99 ± 0.468	>100	>20
2i	OCH_3		CH_2OH	5.12 ± 0.525	>100	>20
2j	OCH_3		CH_2OH	1.13 ± 0.248	>100	>88
2k	OCH_3		Br	>100	>100	–
2l	OCH_3		Br	>100	7.46 ± 2.08	<0.075
2m	OAc		H	2.08 ± 0.269	1.94 ± 0.401	0.93

[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).

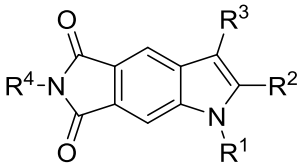
Table 2. The human MAO inhibition potencies of indole-5,6-dicarboxylic acid derivatives **3**.

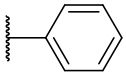
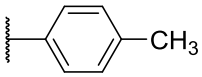
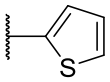
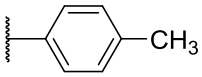
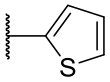
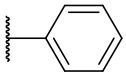
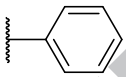


				IC_{50} (μM)[a]		
	R^1	**R^2**	**R^3**	MAO-A	MAO-B	SI[b]
3a	OH		H	23.3 ± 4.14	56.2 ± 3.06	2.4
3b	OH		H	>100	>100	–
3c	OH		H	>100	>100	
3d	OH		H	>100	>100	–
3e	OCH_3		CH_3	19.0 ± 5.63	>100	>5. 3

See table 1 for footnotes.

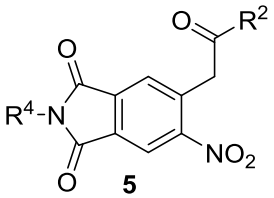
Table 3. The human MAO inhibition potencies of pyrrolo[3,4-*f*]indole-5,7-dione derivatives **4**.



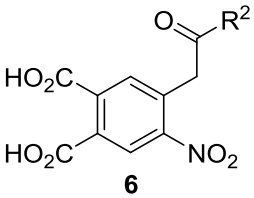
					IC_{50} (μM)[a]		
	R^1	**R^2**	**R^3**	**R^4**	MAO-A	MAO-B	SI[b]
4a	OH		H	H	>100	83.1 ± 4.62	<0.83
4b	OH		H	H	1.16 ± 0.121	8.09 ± 0.240	7
4c	OH		H	H	6.35 ± 0.317	>100	16
4d	OCH_3		H	H	1.75 ± 0.106	0.581 ± 0.066	0.33
4e	OCH_3		H	H	6.70 ± 0.606	3.75 ± 0.532	0.56
4f	OCH_3		H	CH_3	1.24 ± 0.030	>100	>81
4g	H		Cl	H	0.250 ± 0.099	>100	>400

See table 1 for footnotes.

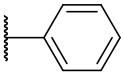
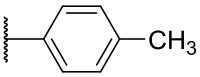
Table 4. The human MAO inhibition potencies **5** and **6**.

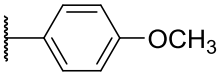
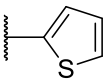
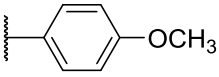
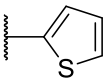
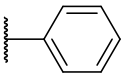
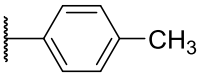
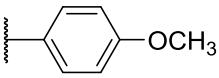
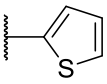


5



6

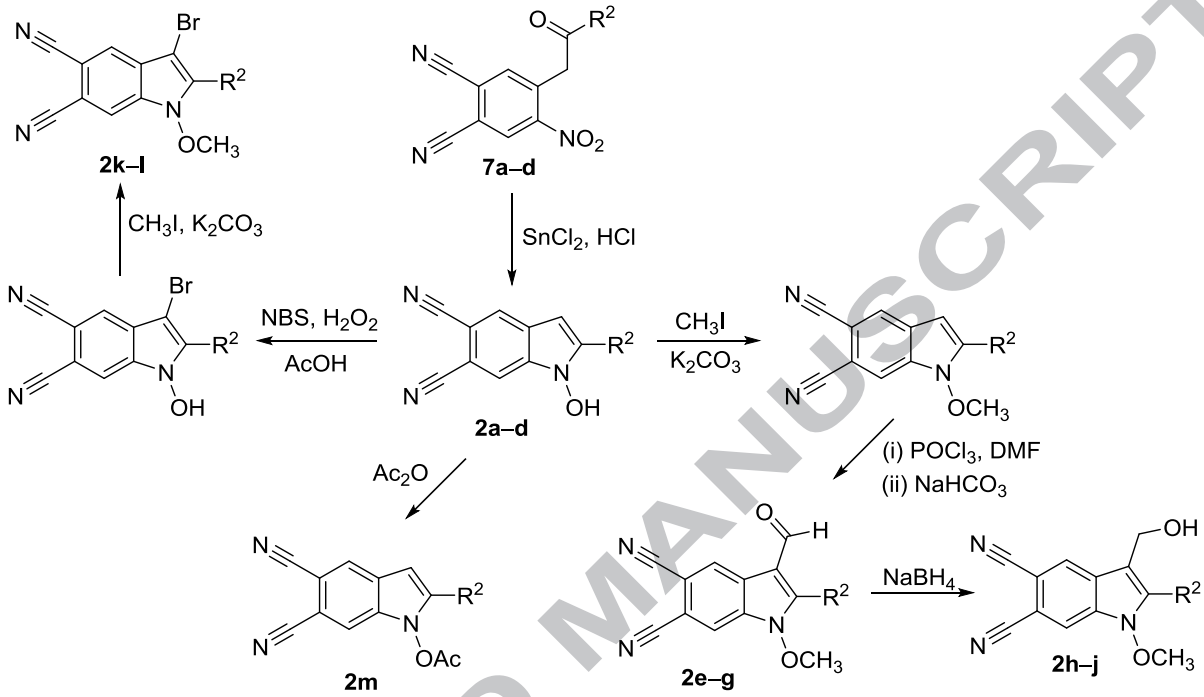
			IC_{50} (μM)[a]		
	R^2	**R^4**	MAO-A	MAO-B	SI[b]
5a		H	5.38 ± 0.357	6.79 ± 1.07	1.3
5b		H	2.11 ± 0.492	0.923 ± 0.122	0.44

5c		H	0.661 ± 0.024	1.21 ± 0.080	1.8
5d		H	6.12 ± 0.042	>100	>16
5e		CH_2Ph	5.51 ± 1.39	>100	>18
5f		CH_2Ph	>100	>100	–
6a		–	>100	>100	–
6b		–	>100	>100	–
6c		–	>100	>100	–
6d		–	>100	>100	–

See table 1 for footnotes.

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 with various functional groups. The preparation of 2-aryl-1-hydroxy-1*H*-indole-5,6-dicarbonitriles **2a**–**d**,[20] 2-aryl-3-formyl-1-methoxy-1*H*-indole-5,6-dicarbonitriles **2e**–**g**[21] and 2-aryl-3-bromo-1-methoxy-1*H*-indole-5,6-dicarbonitriles **2k**–**l**[11] have been reported previously (Scheme 1). The formyl groups of compounds **2e**–**g** were found to be relatively inert in chemical reactions, and practically unreactive towards hydrazine. It was therefore not possible to carry out simple chemical transformations with the formyl groups of **2e**–**g**, or hydrazides that may have been prepared from these. However, substituted 3-(hydroxymethyl)-1-methoxy-1*H*-indole-5,6-dicarbonitriles **2h**–**j** were prepared by reduction of formylindoles **2e**–**g** with $NaBH_4$ in alcohol to give the desired products with yields of 37–57%. The structures of these compounds were confirmed by IR

and NMR spectroscopy, as well as by mass spectrometry and in certain instances X-ray diffraction (**2i**) (Fig. 2).



Scheme 1. Synthetic route to derivatives **2a**–**m**.

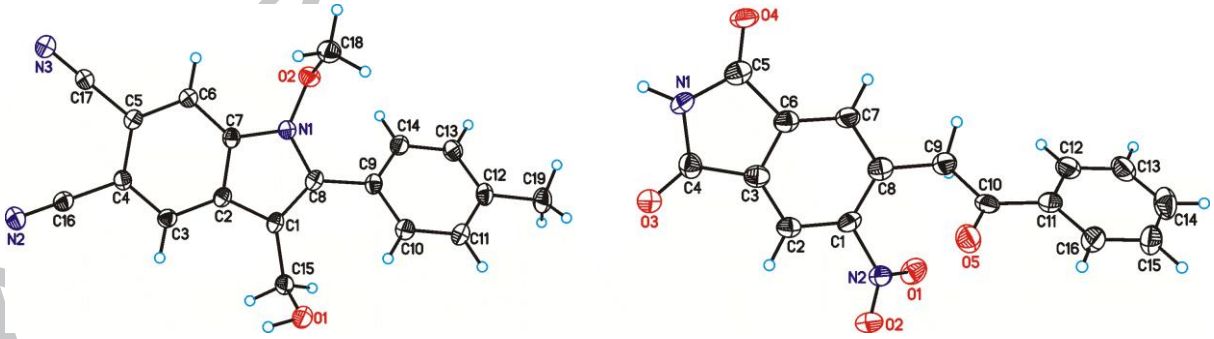
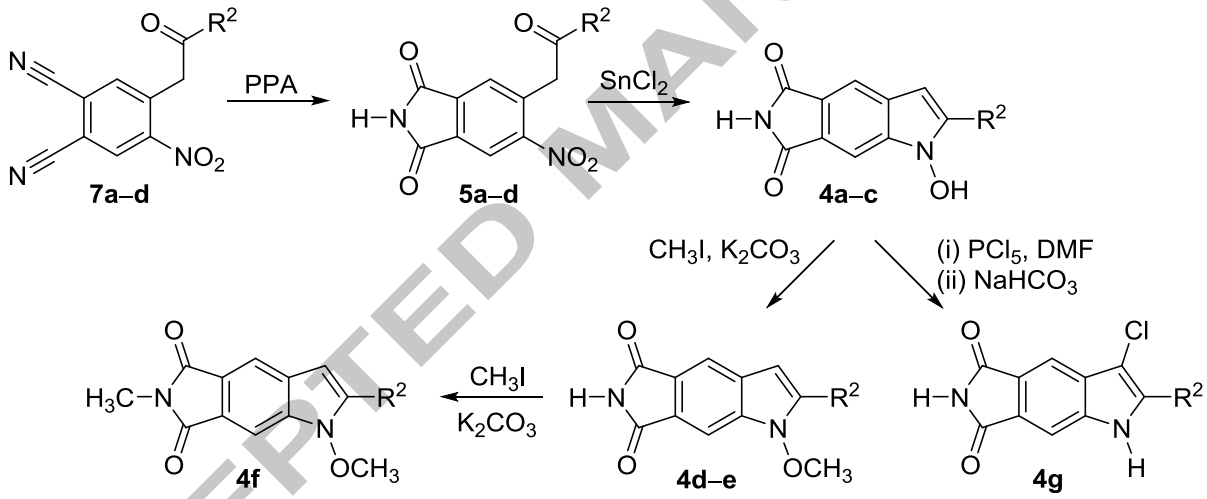


Fig. 2. The X-ray structures of **2i** (left) and **5a** (right) with the atoms represented by thermal displacements ellipsoids with 50% probability.

Substituted indoles containing the imide moiety (**4**) and indole-5,6-dicarboxylic acids (**3**) have not been studied extensively and convenient methods for their syntheses are not available. Previously described synthetic pathways for the syntheses of these compounds are complex multi-step processes

using metal-catalysis (Heck reaction).[22–24] Since substituted indole-5,6-dicarbonitriles **2a**–**d** are highly resistant to acid and alkaline hydrolysis, imide derivatives **5a**–**d** were synthesised by firstly hydrolysing 4-nitro-5-(2-oxo-2-arylethyl)benzene-1,2-dicarbonitriles **7a**–**d** (Scheme 2). Alkaline hydrolysis of **7a**–**d** is not suitable since these compounds readily undergoes nitro-nitrite rearrangement to yield 1,2-benzoxazoles.[20] For this purpose, acid hydrolysis proved to be more successful. To carry out acid hydrolysis polyphosphoric acid (PPA) was employed. Hydrolysis of **7a**–**d** in PPA at 80–110 °C for 2–4 h gave the 5-(2-aryl-2-oxoethyl)-6-nitro-1*H*-isoindol-1,3(2*H*)-diones **5a**–**d** as the major products in yields of 40–87%. The structures of the synthesised compounds **5a**–**d** were confirmed by IR and NMR spectroscopy.

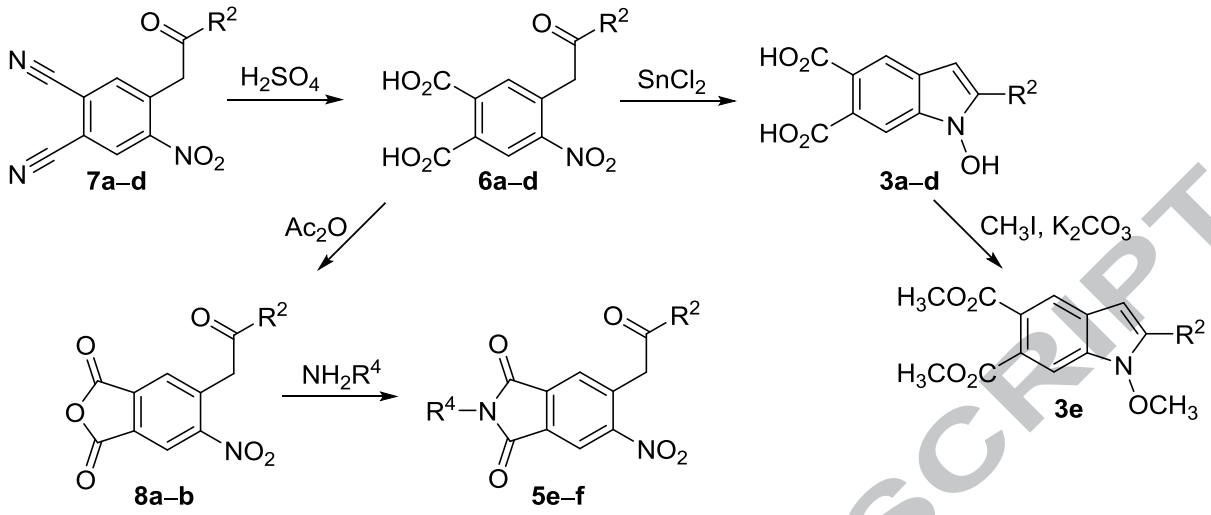


Scheme 2. Synthetic route to derivatives **4a**–**g** and **5a**–**d**.

Reduction of the nitro groups of **5a**–**b** and **5d** were carried out using $SnCl_2$ in HCl.[25] This resulted in cyclisation to give 1-hydroxy-2-arylpyrrolo[3,4-*f*]indole-5,7(1*H*,6*H*)-diones **4a**–**c** in yields of 50–85%. Formation of *N*-hydroxyindole moiety was confirmed after methylation of **4b**–**c** with methyl iodide in DMF with potassium carbonate serving as a deprotonation agent. Methylation proceeded firstly at the OH-group followed by reaction at the NH-group. The mono-O-methyl products **4d**–**e** could thus selectively be obtained and only after employing threefold excess of methyl iodide and increasing the reaction time was the fully methylated product **4f** obtained. Proof for the formation of

the mono-O-methyl products were a characteristic downfield signal of the OCH_3-group (3.89–4.11 ppm) and the signal of the NH-proton at 11.12–11.13 ppm on the ^{1}H NMR spectrum, as well as a carbon signal of the OCH_3-group (65.31 ppm) on the ^{13}C NMR spectrum. The structures of all the newly synthesised compounds (**5a**–**d**, **4a**–**c**, **4d**–**e**, **4f**) were confirmed by IR and NMR spectroscopy as well as by mass spectrometry and X-ray diffraction analysis (compound **5a**).

For the synthesis of 2-aryl-1-hydroxy-1*H*-indole-5,6-dicarboxylic acids **3a**–**d**, the nitrile groups of compounds **7a**–**d** were hydrolysed under acidic conditions (to yield **6a**–**d**) followed by reduction and subsequent cyclisation to yield **3a**–**d** (Scheme 3). Thus, 4-nitro-5-(2-oxo-2-arylethyl)benzene-1,2-dicarboxylic acids **6a**–**d** were prepared in yields of 82–91% by heating the 4-nitro-5-(2-oxo-2-arylethyl)benzene-1,2-dicarbonitriles **7a**–**d** in 85% sulphuric acid at 80–110 °C for 20–36 h. The dicarboxylic acids **6a**–**d** were transformed into the corresponding indoles **3a**–**d** by reduction with $SnCl_2$. The yields of the target indoles were 71–83%. The structures of the dicarboxylic acids **6a**–**d** and **3a**–**d** were confirmed by IR and NMR spectroscopy, mass spectrometry and chemically by complete methylation of the carboxylic acid and hydroxyl groups of **3c** with methyl iodide to give **3e**. The mass spectra of **3a**–**d** did not show an intense molecular ion peak, but rather a prominent fragment ion of $[M^+\text{-}H_2O]$. On the ^{1}H NMR spectra the signals of the carboxylic acid protons were not observed due to exchange with the deuterated solvent. On the ^{13}C NMR spectra the pair of carbon signals of the carboxylic acid groups (in the region of 168–169 ppm) were, however, observed although the chemical shifts are similar to that of imides.[26]



Scheme 3. Synthetic route to derivatives **3a**–**e**, **5e**–**f** and **6a**–**d**.

The synthesis of 2-substituted 5-(2-oxoethyl)-6-nitro-1*H*-isoindol-1,3(*2H*)-diones **5e**–**f** was carried out in two steps starting from dicarboxylic acids **6c**–**d**. Firstly anhydrides **8a**–**b** were obtained by heating compounds **6c**–**d** in acetic anhydride for to 2 h at 120–140 °C. The anhydrides **8a**–**b** were converted to the imides **5e**–**f** by heating with benzylamine in glacial acetic acid at 100–120 °C for 2–3 h. Yields of 62–64% were obtained. The structures of compounds **8a**–**b** and **5e**–**f** were confirmed by NMR spectroscopy. It should be noted that we were unable to obtain mass spectra for these compounds with electron impact ionisation. To determine the mass of the molecular ions of **5e**–**f**, the softer electrospray ionisation (LCMS) was employed.

The MAO inhibition potencies of the test compounds were measured using the recombinant human MAO-A and MAO-B enzymes and kynuramine as substrate for both enzymes. Kynyramine is oxidised by the MAOs to yield 4-hydroxyquinoline, a fluorescent metabolite which was quantified by fluorescence spectrophotometry.[27] After measuring the rates of kynuramine oxidation in the absence and presence of the test inhibitor (0.003–100 μM), sigmoidal dose-response curves were constructed in triplicate from which IC_{50} values were estimated. An example of such a sigmoidal dose-response curve is given in Fig. 3. Since the IC_{50} values of previously reported indole-5,6-dicarbonitrile

derivatives were recorded under identical conditions as this study, direct comparison of the inhibition data is possible.[11]

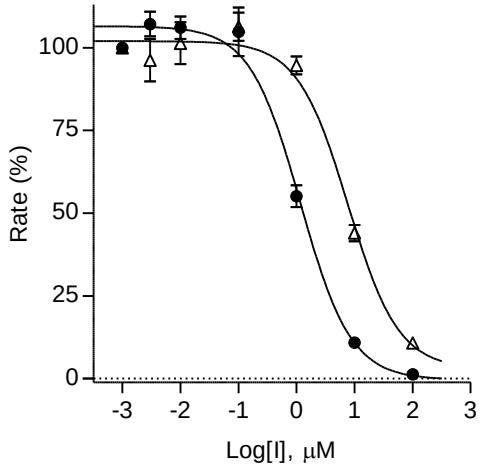


Fig. 3. Sigmoidal dose-response curves for the inhibition of MAO-A (circles) and MAO-B (triangles) by **4b**.

The results of the MAO inhibition studies are provided in tables 1–4. With the exception of **2l**, the indole-5,6-dicarbonitrile derivatives **2** are specific inhibitors of MAO-A with 7 of 13 homologues displaying MAO-B inhibition potencies >100 µM. Compounds **2b**, **2c** and **2m** may be viewed as nonspecific MAO-A/B inhibitors. The most potent MAO inhibitors among the indole-5,6-dicarbonitriles are **2e**–**g** with IC_{50} values for the inhibition of MAO-A in the submicromolar range. In fact **2g** (IC_{50} = 0.147 µM) is the most potent MAO inhibitor of the present study and also the most selective with an IC_{50} >100 µM for the inhibition of MAO-B. To place this inhibition potency in perspective, the clinically used inhibitor, toloxatone, inhibits MAO-A with an IC_{50} value of 3.92 µM under identical conditions.[28] The reference MAO-B inhibitors, lazabemide and safinamide, in turn display IC_{50} values of 0.091 µM and 0.048 µM under identical experimental conditions to this study.[28] It is noteworthy the **2e**–**g** are the formyl-substituted derivatives, which suggests that among the indole-5,6-dicarbonitriles examined here, the 3-formyl-1-methoxy substitution pattern is most suitable for MAO-A inhibition. It should be noted that reaction between

the formyl groups and kynuramine may occur leading to low IC_{50} values for MAO-A. This, however, seems unlikely since weak MAO-B inhibition was recorded for these compounds although the MAO-A and MAO-B inhibition studies were conducted under the same conditions. 3-Chloro-1*H*-indole-5,6-dicarbonitriles (e.g. **1a**) previously reported are significantly more potent MAO-A (IC_{50} = 0.004–0.121 µM) and MAO-B (IC_{50} = 0.017–1.27 µM) inhibitors.[11] Interestingly, similar to the formyl substituted compounds the C3 hydroxymethyl substituted derivatives **2h**–**j** all are weak MAO-B inhibitors (IC_{50} >100 µM).

As shown in table 2 indole-5,6-dicarboxylic acid derivatives **3** including ester **3e** are weak MAO inhibitors. Since **3a**–**d** are weaker MAO inhibitors than their dicarbonitrile homologues **2a**–**d**, it may be concluded that for indoles, dicarbonitrile substitution yields higher potency MAO inhibitors than dicarboxylic acid substitution. Among the pyrrolo[3,4-*f*]indole-5,7-dione derivatives (table 3) compounds **4d** and **4g** are noteworthy MAO inhibitors. These compounds inhibit MAO-A (**4g**) and MAO-B (**4d**) with IC_{50} values of 0.250 and 0.581 µM, respectively. Compound **4d** is thus the most potent MAO-B inhibitor of the present study while **4g** is the second most potent MAO-A inhibitor. The finding that these imides are relatively good MAO inhibitors are to be expected since related phthalimides have previously been reported to inhibit the MAOs, with selectivity for the MAO-B isoform.[29] Thus imide derivatives **5** also exhibit MAO inhibition with **5c** (IC_{50} = 0.661 µM) being the most noteworthy inhibitor (table 4). As with **3a**–**d**, dicarboxylic acids **6** also proved to be weak MAO inhibitors, and in fact did not inhibit the MAOs at 100 µM.

In conclusion, nitrile containing compounds, particularly dicarbonitriles have recently emerged as privileged structures for the design of MAO inhibitors.[30,31] A recent study have shown that indole-5,6-dicarbonitrile derivatives, such as **1a**, are potent inhibitors of both human MAOs.[11] In the present manuscript we have expanded on the structure-activity relationships (SARs) of MAO inhibition by indole-5,6-dicarbonitriles. The importance of the nitrile group was demonstrated by the observation that dicarboxylic acid homologues possess weak MAO inhibition properties and in most instances exhibit IC_{50} >100 µM. Even esterification does not lead to improved inhibition. It is clear

that, with the appropriate substitution indole-5,6-dicarbonitriles can be obtained with good potency MAO inhibition and isoform selectivity. This is exemplified by **2g** (SI >680), a compound displaying potent MAO-A inhibition and weak MAO-B inhibition. Since other homologues (e.g. **2e**, **2f**) also possess good MAO-A inhibition potencies and isoform selectivities (SI = 185 and >192) it may be concluded that the 3-formyl-1-methoxy substitution pattern of indole-5,6-dicarbonitriles is a viable strategy for the design of MAO-A selective inhibitors. Although previously reported 3-chloro-1*H*-indole-5,6-dicarbonitriles (e.g. **1a**) are significantly more potent MAO-A and MAO-B inhibitors they display little isoform selectivity (SI = 1.2–10.8).[11] It should, however, be noted that in the reported study, methylated indole-5,6-dicarbonitriles (e.g. **1b**) also represent a class of compounds with potent and selective MAO-A inhibition properties.[11] These compounds inhibit MAO-A with IC_{50} values of 0.035–19.4 μM and MAO-B with IC_{50} values > 100 μM. Another interesting finding is that imides such as **4d**, **4g** and **5c** also display good potency MAO inhibition. This is in accordance with literature reports that numerous members of the phthalimide class of compounds are high potency MAO-B selective inhibitors. Good potency and isoform selective MAO inhibitors such as **2g** and **4g** may thus represent leads for the design of drugs for the treatment of a variety of disease states such as depression, prostate cancer and certain cardiomyopathies.

Acknowledgements

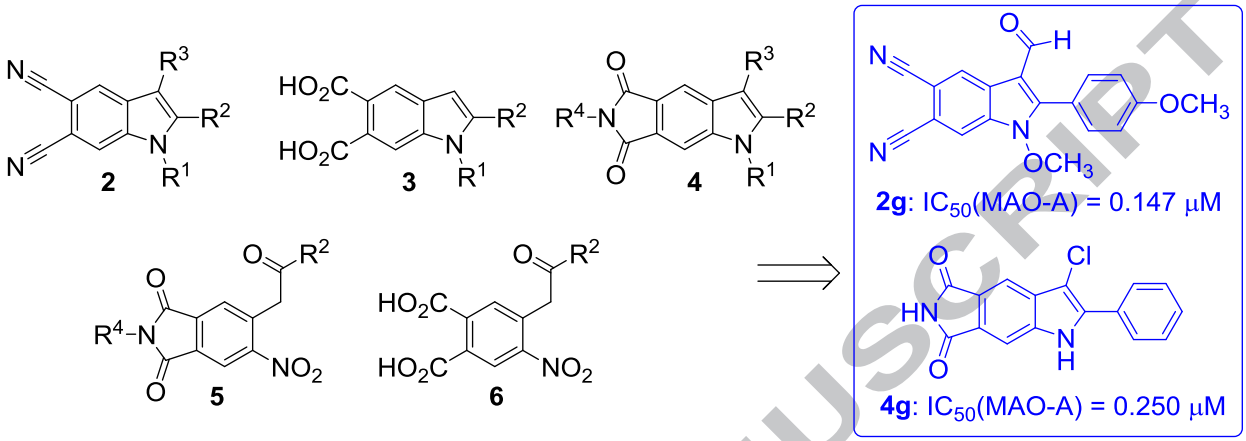
This work is based on the research supported in part by the Medical Research Council and National Research Foundation of South Africa (Grant specific unique reference numbers (UID) 85642 and 96180). The Grantholders acknowledge that opinions, findings and conclusions or recommendations expressed in any publication generated by the NRF supported research are that of the authors, and that the NRF accepts no liability whatsoever in this regard.

References

1. Ramsay, R. R. *Curr. Top. Med. Chem.* **2012**, *12*, 2189.
2. Ramsay, R. R. *Curr. Pharm. Des*. **2013**, *19*, 2529.
3. Lum, C. T.; Stahl, S. M. *CNS Spectr*. **2012**, *17*, 107.
4. Shulman, K. I.; Herrmann, N.; Walker, S. E. *CNS Drugs.* **2013**, *27*, 789.
5. Dexter, D. T.; Jenner, P. *Free Radic. Biol. Med.* **2013**, *62*, 132.
6. Umbarkar, P.; Singh, S.; Arkat, S.; Bodhankar, S. L.; Lohidasan, S.; Sitasawad, S. L. *Free Radic. Biol. Med.* **2015**, *87*, 263.
7. Kaludercic, N.; Mialet-Perez, J.; Paolocci, N.; Parini, A.; Di Lisa, F. *J. Mol. Cell Cardiol*. **2014**, *73*, 34.
8. Youdim, M. B.; Bakhle, Y. S. *Br. J. Pharmacol*. **2006**, *147*, S287.
9. Naoi, M.; Maruyama, W. *Curr. Pharm. Des*. **2010**, *16*, 2799.
10. Flamand, V.; Zhao, H.; Peehl, D. M. *J. Cancer Res. Clin. Oncol*. **2010**, *136*, 1761.
11. Chirkova, Z. V.; Kabanova, M. V.; Filimonov, S. I.; Abramov, I. G.; Petzer, A.; Petzer, J. P.; Firgang, S. I.; Suponitsky, K. Y. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 1206.
12. Cseke, L. J.; Kirakosyan, A.; Kaufman, P. B.; Warber, S.; Duke, J. A.; Brielmann H. L. Natural Products from Plants, Second Edition; CRC Press: Boca Raton, 2006.
13. Kaushik, N. K.; Kaushik, N.; Attri, P.; Kumar, N.; Kim, C. H.; Verma, A. K.; Choi, E. H. *Molecules.* **2013**, *18*, 6620.
14. Hibino, S.; Choshi, T. *Nat. Prod. Rep*. **2002**, *19*, 148.
15. Szántay, C. *Pure Appl. Chem*. **1990**, *62*, 1299.
16. Hopkins, C. R.; O'Neil, S. V.; Laufersweiler, M. C.; Wang, Y.; Pokross, M.; Mekel, M.; Evdokimov, A.; Walter, R.; Kontoyianni, M.; Petrey, M. E.; Sabatakos, G.; Roesgen, J. T.; Richardson, E.; Demuth, T. P., Jr. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5659.
17. Dhondge, R.; Chaturvedi, S. C. *Med. Chem. Res*. **2009**, *18*, 167.
18. Samsoniya, Sh. A.; Trapaidze, M. V.; Kuprashvili, N. A. *Pharm. Chem. J*. **2009**, *43*, 92.
19. Stolc, S.; Snirc, V.; Májeková, M.; Gáspárová, Z.; Gajdosíková, A.; Stvrtina, S. *Cell Mol. Neurobiol*. **2006**, *26*, 1495.
20. Filimonov, S. I.; Chirkova, Z. V.; Abramov, I. G.; Firgang, S. I.; Stashina, G. A.; Strelenko, Y. A.; Khakimov, D. V.; Pivina, T. S.; Samet, A. V.; Suponitsky, K. Y. *Tetrahedron.* **2012**, *68*, 5991.

21. Chirkova, Z. V.; Kabanova, M. V.; Sergeev, S. S.; Filimonov, S. I.; Abramov, I. G.; Samet, A. V.; Suponitsky, K. Y. *Mendeleev Commun*. **2015**, *25*, 315.
22. Hussain, M.; Toguem, S. -M. T.; Ahmad, R.; Tùng, D. T.; Knepper, I.; Villinger, A.; Langer, P. *Tetrahedron*. **2011**, *67*, 5304.
23. Toguem, S. -M. T.; Langer, P. *Synlett*. **2011**, *4*, 513.
24. Duflos, J.; Dupas, G.; Quéguiner, G. *J. Heterocyclic Chem.* **1983**, *20*, 1191.
25. Attar, K.; Camara, H. D.; Benchidmi, M.; Essassi, E. M.; Pierrot, M. *Heterocycl. Commun*. **2003**, *9*, 373.
26. Pretsch, E.; Bühlmann, P.; Badertscher, M. Structure Determination of Organic Compounds. Tables of Spectral Data, Fourth, Revised and Enlarged Edition; Springer-Verlag: Berlin Heidelberg, 2009, pp 200.
27. Mostert, S.; Petzer, A.; Petzer, J. P. *ChemMedChem.* **2015**, *10*, 862.
28. Petzer, A.; Pienaar, A.; Petzer, J. P. *Arzneimittel-Forsch*. **2013**, *63*, 462.
29. Manley-King, C. I.; Berghm J. J.; Petzer, J. P. *Bioorg. Med. Chem*. **2011**, *19*, 4829.
30. Manley-King, C. I.; Bergh, J. J.; Petzer, J. P. *Bioorg. Chem*. **2012**, *40*, 114.
31. Juárez-Jiménez, J.; Mendes, E.; Galdeano, C.; Martins, C.; Silva, D. B.; Marco-Contelles, J.; do Carmo Carreiras, M.; Luque, F. J.; Ramsay, R. R. *Biochim. Biophys. Acta*. **2014**, *1844*, 389.

Graphical abstract:



Indole derivatives and related compounds were evaluated as inhibitors of the human monoamine oxidases