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Selected furanochalcones as inhibitors of monoamine oxidase

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ABSTRACT

The validity of the chalcone scaffold for the design of inhibitors of monoamine oxidase has previously been illustrated. In a systematic attempt to investigate the effect of heterocyclic substitution on the monoamine oxidase inhibitory properties of this versatile scaffold, a series of furanochalcones were synthesized. The results demonstrate that these furan substituted phenylpropenones exhibited moderate to good inhibitory activities towards MAO-B, but showed weak or no inhibition of the MAO-A enzyme. The most active compound, 2*E*-3-(5-chlorofuran-2-yl)-1-(3-chlorophenyl)prop-2-en-1-one, exhibited an IC_{50} value of 0.174 μM for the inhibition of MAO-B and 28.6 μM for the inhibition of MAO-A. Interestingly, contrary to data previously reported for chalcones, these furan substituted derivatives acted as reversible inhibitors, while kinetic analysis revealed a competitive mode of binding.

Monoaminergic signalling plays an essential role in the modulation of mood and emotion and also in the control of motor and cognitive functions. Correct functioning of synaptic neurotransmission is ensured by the effective degradation of monoamine neurotransmitters, such as dopamine, noradrenaline and serotonin.[1] This degradation includes the oxidative deamination of monoamines to yield the corresponding imine product and hydrogen peroxide and is catalyzed by the monoamine oxidases (MAOs).[2–4] Monoamine oxidase inhibitors have thus found application in the treatment of depression, and also in neurodegenerative conditions such as Alzheimer's and Parkinson's disease.[5] MAOs are flavin adenine dinucleotide (FAD)-containing enzymes which are located on the outer membranes of mitochondria throughout the brain.[6] Two subtypes, namely MAO-A and MAO-B, have been identified based on substrate selectivity and inhibitor sensitivity.[7,8] It is noteworthy that MAO-B is the isoform that is predominant in the human brain.[9] MAO-B inhibitors are clinically used in the treatment of Parkinson's disease and since the activity of both endogenously and exogenously derived dopamine can be prolonged by administering MAO-B selective inhibitors, they can either be used as adjunctive therapy in Parkinson's disease patients treated with levodopa or as monotherapy in early Parkinson's disease.[10]

The by-products of MAO-mediated reactions include several chemical species with neurotoxic potential, such as hydrogen peroxide (which is a source of oxidative stress), ammonia and aldehydes. Since these species may contribute to neuronal degeneration, MAO inhibitors, by reducing the central concentrations of these molecules, are thought to possess neuroprotective properties. This possible neuroprotective role for MAO inhibitors has been extensively reviewed.[11–14] As the concentration of MAO-B is reported to increase in the human brain with age, inhibition of this enzyme is especially relevant in the treatment of age-related neurodegenerative diseases, such as Parkinson's disease.[15]

Chalcones (1,3-diphenyl-2-propen-1-ones) (**1**, Fig. 1) are open chain flavonoids that are ubiquitous in edible plants and have a broad range of reported biological activities,[16,17] which include anti-inflammatory and neuroprotective effects.[18,19] These versatile compounds and their heterocyclic (e.g., furan) counterparts are synthetically easily accessible and are often used as intermediates in the syntheses of inhibitors of MAO.[20–26] The MAO inhibitory activities of chalcones themselves have however, only been determined in a few instances for naturally occurring chalcones (e.g., **2**, Fig. 2) using rat,[27–29] bovine[30] and hamster[31] monoamine oxidases, while some synthetic derivatives, such as **3** (Fig. 2), were screened against human MAO (hMAO).[32] Generally, chalcones show a higher degree of inhibition of MAO-B than of MAO-A,[28,32] as illustrated by the inhibitory activities observed for chalcone **3**, where an IC_{50} of 0.0044 μM was determined for the inhibition of MAO-B and no

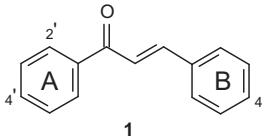

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Figure 1. The structure of 1,3-diphenyl-prop-2-one (chalcone).

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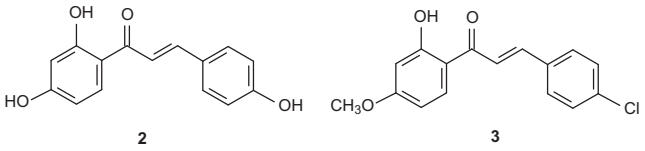
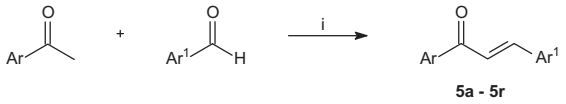


Figure 2. Examples of natural (**2**) and synthetic chalcones (**3**) for which MAO-inhibitory activities have been determined.[27,30,32]



Scheme 1. Synthetic route to furanochalcones **5a**–**r**. Reagents and conditions: (i) NaOH, EtOH, rt, 3 h; Ar = substituted phenyl or furan; Ar^1 = substituted phenyl or furan.

inhibition of MAO-A was observed at 50 μM.[32] However, there are exceptions. For example, isoliquiritigenin (**2**) inhibits MAO-A (13.9 μM) more potently than MAO-B (47.2 μM).[29]

Kinetic analyses of the inhibition of MAO by chalcones have only been carried out in a few instances and the results indicate that chalcones are substrate-competitive inhibitors of rat MAO.[27,28] The issue regarding the reversibility of binding of chalcones to MAO has also not been thoroughly explored. In one study, chalcones have been shown to bind irreversibly to hMAO-B,[32] by a binding mode similar to those of rasagiline and (*R*)-deprenyl, two clinically used MAO-B inhibitors.[10] Since adverse effects, such as psychotoxic and cardiovascular effects, are associated with the irreversible inhibition of particularly MAO-A, obtaining selective MAO-B inhibitors, and preferably reversible inhibitors, are of value.[33]

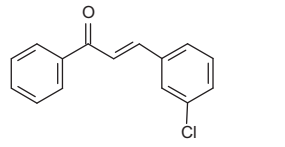
The focus of previous studies were mainly on the MAO inhibitory activities of chalcones substituted with electron donating substituents (e.g., OH groups) on the A-ring,[27,32] while the effect of heteroaromatic substitution on the monoamine oxidase inhibitory potencies of 3-phenylpropenones has not been previously examined. In order to further investigate the monoamine oxidase inhibitory properties of this useful scaffold, and as part of a systematic investigation of the effect of heteroaromatic substitution, a series of furan substituted chalcones (**5a**–**r**), which incorporated mainly electron withdrawing substituents in either the A- or B-rings, were synthesized and screened as monoamine oxidase inhibitors.

The furan moiety was selected as starting point, since this ring quite often appears in other scaffolds associated with MAO inhibitory activity,[21,22,25] although literature regarding variation in the substitution of this ring and its role in the inhibition of MAO are limited. The furan moiety in brofaromine for example, is one of the two regions in this molecule associated with high π electron density which contributes to its interaction with the flavin nucleus of the co-factor.[34]

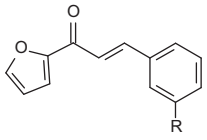
Furanochalcones were obtained by a Claisen–Schmidt condensation between commercially available ketones and aldehydes under basic conditions (Scheme 1).[35] In each instance, the structures of the target compounds were verified by ^{1}H NMR and ^{13}C NMR spectroscopy and mass spectrometry, as cited in the Supplementary material.

To investigate the MAO inhibitory properties of the synthesized chalcones, recombinant hMAO-A and hMAO-B, expressed in microsomes from insect cells, were used. A fluorometric method, measuring the MAO-catalyzed formation of 4-hydroxyquinoline (λ_{ex} 310 nm; λ_{em} 400 nm) from the MAO-A/B mixed substrate, kynuramine, was used to measure the enzyme activities.[36,37] The inhibitory potencies (IC_{50} values) of the chalcones were determined from sigmoidal dose–response curves, which were constructed by measuring the MAO catalytic activities in the presence of various concentrations of the test inhibitors. The IC_{50} values for the inhibition of MAO-A and MAO-B by compounds **5a**–**r** (Fig. 3) are given inTable 1.

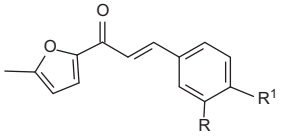
The results show that the synthesized furanochalcones are moderate to good inhibitors of MAO-B, but exhibited weak or no inhibition of MAO-A. These results are thus in agreement with pre-



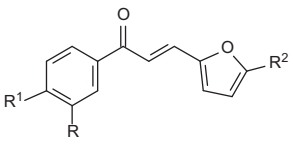
5a



5b R = Cl
5c R = OCH_3



5d	R = Cl	R^1 = H
5e	R = H	R^1 = Cl
5f	R = Br	R^1 = H
5g	R = H	R^1 = Br
5h	R = F	R^1 = H
5i	R = H	R^1 = F
5j	R = Br	R^1 = F
5k	R = CF_3	R^1 = H
5l	R = H	R^1 = CF_3
5m	R = OCH_3	R^1 = H



5n	R = Cl	R^1 = H	R^2 = CH_3
5o	R = Cl	R^1 = H	R^2 = Cl
5p	R = Cl	R^1 = H	R^2 = Br
5q	R = H	R^1 = F	R^2 = H
5r	R = H	R^1 = F	R^2 = Br

Figure 3. The structures of the target furanochalcone derivatives **5a**–**r**.