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2-Benzylidene-1-indanone derivatives as inhibitors of monoamine oxidase

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ABSTRACT

In the present study, a series of twenty-two 2-benzylidene-1-indanone derivatives were synthesised and evaluated as inhibitors of recombinant human monoamine oxidase (MAO) A and B. The 2-benzylidene-1-indanone derivatives are structurally related to a series of benzylideneindanone derivatives which has previously been found to be MAO-B inhibitors. This study finds that the 2-benzylidene-1-indanones are MAO-B specific inhibitors with IC_{50} values <2.74 μM. Among the compounds evaluated, twelve compounds exhibited IC_{50} < 0.1 μM and may be considered as high potency inhibitors. The 2-benzylidene-1-indanone derivatives also inhibited MAO-A with the most potent inhibition exhibited by **5g** (IC_{50} = 0.131 μM). An analysis of the structure–activity relationships for MAO-B inhibition show that substitution on the A-ring with a 5-hydroxy group and on the B-ring with halogens and the methyl group yield high potency inhibition. It may therefore be concluded that 2-benzylidene-1-indanone analogues are promising leads for design of therapies for disorders such as Parkinson's disease.

The monoamine oxidases (MAOs) are mitochondrial bound enzymes which regulate the levels of amine-containing compounds in the brain and peripheral tissues.[1,2] The MAOs consist of two isoforms, MAO-A and MAO-B. Both are widely expressed in mammalian tissues, but at different levels. In humans MAO-A is the principal isoform in the intestines, placenta and heart while MAO-B is the major isoform in platelets, glial cells in the brain and liver.[1] The clinical importance of the MAOs arises from their role in the oxidative deamination of neurotransmitter monoamines; MAO-A catalyses the oxidation of 5-hydroxytryptamine (5-HT, serotonin) while the false neurotransmitter, β-phenylethylamine, is a MAO-B specific substrate. The catecholamines, dopamine, noradrenaline and adrenaline, as well as the dietary amines, tryptamine and tyramine, are oxidised by both MAO-A and MAO-B.[3] Inhibitors of MAO-A and MAO-B have thus been used for the treatment of diseases that result from deficient neurotransmitter levels. For example, MAO-A inhibitors increase central serotonin levels and are used for the treatment of major depression.[4,5] MAO-B inhibitors are used in the treatment of Parkinson's disease where they reduce the MAO-catalysed breakdown of dopamine.[3] This is expected to enhance striatal dopaminergic activity leading to the improvement of motor symptoms.[6] MAO-B inhibitors are often combined with L-Dopa, the metabolic precursor of dopamine, in Parkinson's disease therapy.[7–9] Selective MAO-B inhibitors may also possess disease modifying properties by protecting against neurodegeneration in Parkinson's disease.[10,11] The neuroprotective effect of MAO-B inhibitors may, at least in part, be attributed to the reduction of the central formation of toxic metabolic by-products (hydrogen peroxide and aldehydes) of the MAO catalytic cycle.[11]

Although both MAO isoforms oxidise dopamine in the human brain, MAO-B specific inhibitors are used for the treatment of Parkinson's disease, principally because MAO-A inhibitors are used with caution in the clinic. MAO-A inhibitors may lead to a potentially fatal hypertensive event when combined with tyramine-containing food such as cheeses and fermented drinks (e.g., wine and beer).[12,13] Normally dietary tyramine (and other sympathomimetic amines) are extensively metabolised by MAO-A in the intestinal wall and in the liver, thus preventing their entry into the systemic circulation. When MAO-A is inhibited, tyramine and other sympathomimetic amines present in food cannot be metabolised and thus reaches systemic levels high enough to induce a significant release of noradrenaline from peripheral adrenergic neurons. This may lead to a potentially lethal hypertensive crisis with cerebral haemorrhages.[11,14] Selective MAO-B inhibitors do not have this effect because there is little MAO-B in the intestine. The development of reversible MAO-A inhibitors, however, avoids this problem because, with increasing substrate concentrations, the reversible inhibitor is displaced from MAO-A, allowing metabolism to occur.[15,16] As a result, the focus now falls on the discovery and

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development of reversible MAO inhibitors for the treatment of disorders such as depression and Parkinson's disease.[17,18]

As early as 1987, chalcones (1,3-diphenyl-2-propen-1-ones) have been explored as potential MAO inhibitors. Researchers have isolated isoliquiritigenin (**1**) from the roots of *Glycyrrhiza uralensis* and carried out kinetic studies to determine the MAO inhibitory activity (Fig. 1).[19] This compound exhibited an IC_{50} value of 17.3 μM, but no distinction was made between MAO-A and MAO-B inhibition.[19] A number of studies have since shown that synthetic chalcones and chalcones from natural sources are inhibitors of MAO.[20–23] This is exemplified by synthetic chalcone **2** which inhibits human MAO-B with an IC_{50} value of 0.0051 μM.[20] This compound is a MAO-B specific inhibitor since relatively weak inhibition of MAO-A was observed (IC_{50} = 4.95 μM).

In a recent study, Morales-Camilo et al. evaluated sixteen compounds, 8 chalcones and 8 aurones.[24] Both the chalcones and aurones proved to be MAO-B specific inhibitors with compound **3** (IC_{50} = 11.6 μM) being the most potent inhibitor among the aurones. This was the first report that the aurone class of compounds inhibits MAO. 2-Benzylidene-1-indanone may be considered to be the cyclic analogue of chalcone. It may thus be postulated that 2-benzylidene-1-indanone derivatives may, similar to chalcones, also possess MAO inhibition properties. Support for this viewpoint is the observation that 2-benzylidene-1-indanone are structurally similar to aurones which, as mentioned above, are compounds known to inhibit MAO. 2-Benzylidene-1-indanones have not been extensively investigated as MAO inhibitors. In 2012, Huang et al. reported the MAO activities of a series of seven 2-benzylidene-1-indanone derivatives.[25] These compounds also are MAO-B specific and exhibited IC_{50} values for the inhibition of MAO-B in the micromalor range (7.50–40.5 μM). The most potent inhibitor, compound **4**, exhibited an IC_{50} value of 7.5 μM for the inhibition of MAO-B.[25] In this reported study ring A was disubstituted with hydroxy and methoxy substituents while the benzylidene ring B was monosubstituted on the C4′ position with a dialkylamine. Based on the study done by Huang et al., the present study aims to expand on the structure–activity relationships of MAO inhibition by 2-benzylidene-1-indanone derivatives. As secondary objective, high potency MAO inhibitors may thus be discovered. For the purpose of this study, ring A will be substituted on C5 and C6 with either a hydroxy or methoxy group, and ring B will be substituted on C3′ and C4′ with halogens (F, Cl, Br), alkyl groups [CH_3, CN, OCH_3, $CH(CH_3)_2$], an amine containing group [$N(CH_3)_2$] and the hydroxy group. For comparison, some 2-benzylidene-1-indanone derivatives will not be substituted on the A- and/or B-rings (e.g. **5a**, **5b**, **6a**–**c**). It is anticipated that the halogen substituted derivatives may display potent MAO-B inhibition since the reported halogen substituted chalcones (e.g., **2**) possess high potency inhibition. In this respect, the halogen enhances Van der Waals interactions with the entrance cavity of MAO-B, while the polar hydroxy group (and possibly methoxy) establish polar contacts such as hydrogen bonding with residues and water molecules in the MAO-B substrate cavity.[20]

In the present study twenty-two 2-benzylidene-1-indanone derivatives (**5a**–**r** and **6a**–**d**) were synthesised with the aim of examining their MAO inhibitory properties. The target 2-benzylidene-1-indanone derivatives were synthesised employing either acidic (HCl) or basic (KOH) conditions.[24] For the synthesis of **5a**–**r**, 5-hydroxy- or 6-hydroxy-1-indanone was reacted with an appropriate benzaldehyde in a reaction solvent consisting of a mixture of methanol and 32% HCl (1:1.5) (Fig. 2). Compounds **6a**–**d**, in turn, were synthesised by reaction of 1-indanone or 5-methoxy-1-indanone with an appropriate benzaldehyde in methanol containing 4.7% KOH. These reactions gave the target 2-benzylidene-1-indanone derivatives in yields of 8–83%. The structures of the target compounds were verified by ^1H NMR, ^{13}C NMR and mass spectrometry as cited in the experimental section.

The MAO inhibitory properties of the 2-benzylidene-1-indanone derivatives were examined using the recombinant human MAO-A and MAO-B enzymes.[26] The mixed MAO-A/B substrate, kynuramine, was used as substrate for both enzyme isoforms. The enzyme reactions contained the enzyme, substrate and test inhibitor and control reactions conducted in the absence of inhibitor were always included. After incubation for 20 min at 37 °C, the reactions were terminated with the addition of sodium hydroxide (2 N). The rate of oxidation of kynuramine by the MAOs was determined by measuring (at endpoint) the concentration of 4-hydroxyquinoline, the metabolite of kynuramine oxidation. Since 4-hydroxyquinoline fluoresces in alkaline media, concentration measurements were carried out by fluorescence spectrophotometry. By thus measuring rates of oxidation of kynuramine by the MAOs in the presence of various concentrations of the 2-benzylidene-1-indanones, sigmoidal dose–response plots were constructed from which IC_{50} values were estimated. Examples of such sigmoidal dose–response plots are shown in Figure 3.

The IC_{50} values for the inhibition of the human MAOs by the 2-benzylidene-1-indanone derivatives are given in Table 1. The IC_{50} values for the inhibition of MAO-B ranges from 0.0052 to 2.74 μM while those for the inhibition of MAO-A ranges from 0.131 to >100 μM. From the selectivity index (SI) values, it is clear that the 2-benzylidene-1-indanone derivatives are specific inhibitors of the MAO-B isoform. Only **5b** and **5o** exhibit higher inhibition potencies for MAO-A compared to MAO-B. The finding that the 2-benzylidene-1-indanones are mostly MAO-B specific, is similar to the MAO isoform specificities of the 2-benzylidene-1-indanone derivatives previously reported.[25] In general, substitution on the A-ring with a 5-hydroxy group and on the B-ring with halogens and the methyl group (**5c**–**5j**, **5m**) yielded high potency MAO-B inhibition with IC_{50} values <0.084 μM. 5-Hydroxy substitution (**5a**, IC_{50} = 0.376 μM) appears to be more favourable than 6-hydroxy substitution (**5b**, IC_{50} = 2.42 μM) for MAO-B inhibition. With 5-hydroxy substitution on the A-ring, polar (OH and OCH_3) and larger [$N(CH_3)_2$, $CH(CH_3)_2$] substituents on the B-ring yields

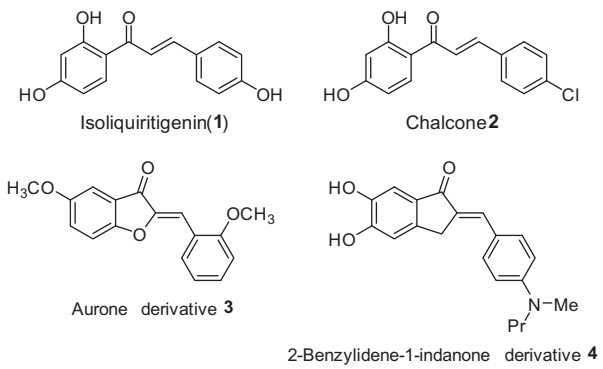

Figure 1. The structures of isoliquiritigenin (**1**), chalcone **2**, aurone **3** and 2-benzylidene-1-indanone **4**.

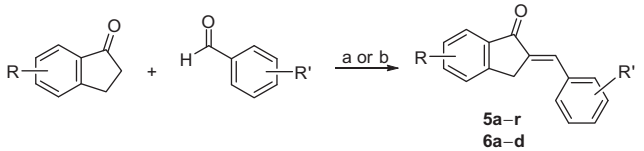

Figure 2. Synthetic pathway to 2-benzylidene-1-indanone derivatives (**5a**–**r** and **6a**–**d**). Reagents and conditions: (a) methanol/32% HCl (1:1.5), reflux; (b) KOH, methanol, rt.