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

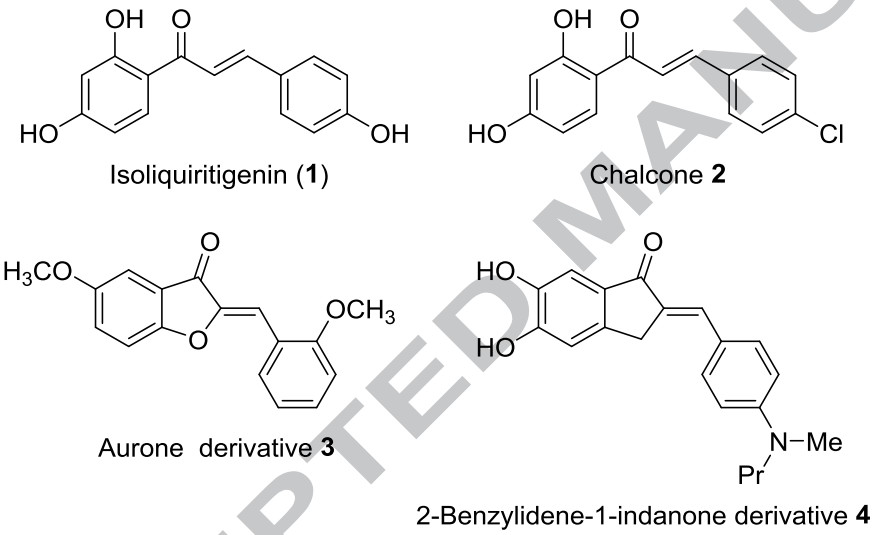



**Figure 1**. The structures of isoliquiritigenin (**1**), chalcone **2**, aurone **3** and 2-benzylidene-1-indanone **4**.

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 and co-workers 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 and co-workers 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 and co-workers, 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 $^{1}$H NMR, $^{13}$C NMR and mass spectrometry as cited in the experimental section.

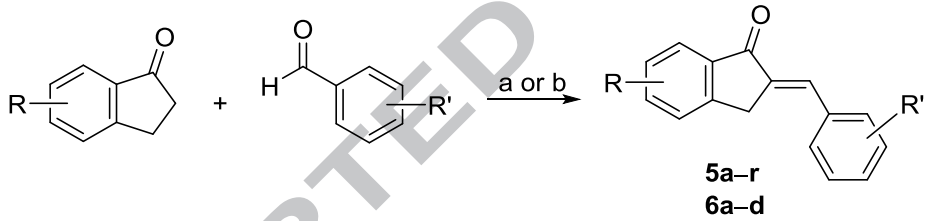



**Figure 2**. Synthetic pathway to 2-benzylidene-1-indanone derivatives (**5a**–**r** and **6a**–**d**). Reagents and conditions: (a) methanol/32% HCl (1:1.5), reflux; (b) KOH, methanol, rt.

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 Fig. 3.

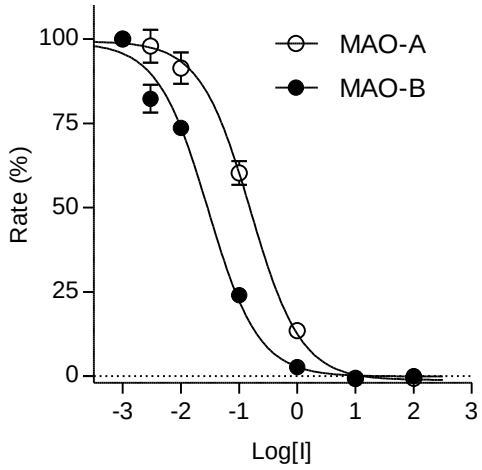
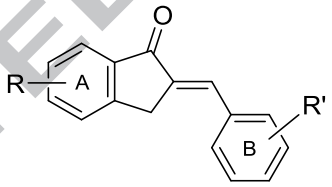



**Figure 3**. Sigmoidal dose-response plots for the inhibition of MAO-A (open circles) and MAO-B (filled circles) by **5e**. The enzyme activities are given as mean ± SD.

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 0.0052–2.74 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 comparatively lower MAO-B inhibition (**5n**–**r**, $IC_{50}$ = 0.215–2.74 µM). Interestingly, with either no substituent or a methoxy on the A-ring, $N(CH_3)_2$ substitution on the B-ring yields good potency MAO-B inhibitors as shown with **6b** ($IC_{50}$ = 0.031 µM) and **6d** ($IC_{50}$ = 0.060 µM). An appropriate substitution pattern is, however, required for potent MAO-B inhibition as evidenced by the finding that the unsubstituted derivative **6a** ($IC_{50}$ = 2.57 µM) is a relatively weaker MAO-B inhibitor. Finally, **6c** ($IC_{50}$ = 0.0092 µM), substituted with a methoxy on the A-ring is noteworthy as a very specific MAO-B inhibitor since it displays an $IC_{50}$ for MAO-A inhibition of > 100 µM. Derivative **6d**, also substituted with a methoxy on the A-ring, similarly displays weak MAO-A inhibition ($IC_{50}$ = 11.5 µM) compared to the other 2-benzylidene-1-indanones, which indicates that this structural feature reduces MAO-A inhibition, thus enhancing specificity for MAO-B.

**Table 1**. The $IC_{50}$ values for the inhibition of recombinant human MAO-A and MAO-B by 2-benzylidene-1-indanone derivatives.




| | R | R' | $IC_{50}$ (µM)[a] | | SI[b] |
|---|---|---|---|---|---|
| | | | MAO-A | MAO-B | |
| **5a** | 5-OH | H | 1.94 ± 0.201 | 0.376 ± 0.101 | 5.2 |
| **5b** | 6-OH | H | 0.440 ± 0.062 | 2.42 ± 0.443 | 0.2 |
| **5c** | 5-OH | 3'-F | 0.458 ± 0.049 | 0.084 ± 0.018 | 5.5 |
| **5d** | 5-OH | 4'-F | 0.679 ± 0.020 | 0.047 ± 0.009 | 14 |
| **5e** | 5-OH | 3'-Cl | 0.157 ± 0.015 | 0.030 ± 0.002 | 5.2 |
| **5f** | 5-OH | 4'-Cl | 0.741 ± 0.048 | 0.013 ± 0.002 | 57 |
| **5g** | 5-OH | 3'-Br | 0.131 ± 0.008 | 0.013 ± 0.002 | 10 |
| **5h** | 5-OH | 4'-Br | 1.05 ± 0.053 | 0.0053 ± 0.0004 | 198 |

| | | | | | |
|---|---|---|---|---|---|
| **5i** | 5-OH | 3'-$CH_3$ | 0.860 ± 0.076 | 0.052 ± 0.013 | 17 |
| **5j** | 5-OH | 4'-$CH_3$ | 3.22 ± 0.171 | 0.0052 ± 0.001 | 619 |
| **5k** | 5-OH | 3'-CN | 0.444 ± 0.043 | 0.130 ± 0.029 | 3.4 |
| **5l** | 5-OH | 4'-CN | 2.08 ± 0.158 | 0.316 ± 0.091 | 6.6 |
| **5m** | 5-OH | 3',4'-Cl | 0.235 ± 0.010 | 0.014 ± 0.007 | 17 |
| **5n** | 5-OH | 3'-OH | 1.20 ± 0.127 | 0.966 ± 0.125 | 1.2 |
| **5o** | 5-OH | 4'-OH | 1.67 ± 0.033 | 2.74 ± 0.668 | 0.6 |
| **5p** | 5-OH | 3'-$OCH_3$ | 1.19 ± 0.056 | 0.471 ± 0.071 | 2.5 |
| **5q** | 5-OH | 4'-$N(CH_3)_2$ | 1.72 ± 0.114 | 0.768 ± 0.044 | 2.2 |
| **5r** | 5-OH | 4'-$CH(CH_3)_2$ | 0.961 ± 0.126 | 0.215 ± 0.034 | 4.5 |
| **6a** | H | H | 5.43 ± 0.754 | 2.57 ± 0.972 | 2.1 |
| **6b** | H | 4'-$N(CH_3)_2$ | 1.52 ± 0.134 | 0.031 ± 0.004 | 49 |
| **6c** | 5-$OCH_3$ | H | No inh[c] | 0.0092 ± 0.001 | >10870 |
| **6d** | 5-$OCH_3$ | 4'-$N(CH_3)_2$ | 11.5 ± 0.798 | 0.060 ± 0.007 | 192 |

[a] All values are expressed as the mean ± standard deviation (SD) of triplicate determinations.

[b] Selectivity index (SI) = $IC_{50}$(MAO-A)/$IC_{50}$(MAO-B).

[c] No inhibition observed at a maximal tested concentration of 100 μM.

While the 2-benzylidene-1-indanone derivatives are MAO-B specific inhibitors, good potency MAO-A inhibitors also exist among the series. Derivative **5g** ($IC_{50}$ = 0.131 μM) possesses the highest potency MAO-A inhibition among the series. Few clear structure-activity relationships for MAO-A inhibition are apparent. As mentioned above, substitution with the methoxy group on the A-ring reduces MAO-A inhibition. It is also noteworthy that the three most potent MAO-A inhibitors (**5e**, **5g**, **5m**) bear halogens on ring B. As for MAO-B, an appropriate substitution pattern is, however, required for potent MAO-A inhibition since the unsubstituted derivative **6a** ($IC_{50}$ = 5.43 μM) is the third weakest MAO-A inhibitor of the series. In contrast to MAO-B inhibition, 5-hydroxy substitution (**5a**, $IC_{50}$ = 1.94 μM) is less favourable than 6-hydroxy substitution (**5b**, $IC_{50}$ = 0.440 μM) for MAO-A inhibition. Interestingly, with an enhancement of MAO-A inhibition with 6-hydroxy substitution, reversal of isoform selectivity occurs, and **5b** is thus MAO-A specific (SI = 0.2).

As mentioned in the introduction, irreversible MAO-A inhibition may lead to a potentially fatal hypertensive event when combined with certain food.[12,13] Reversible MAO-A inhibitors, however, are considered safer in this regard. We have therefore set out to investigate the reversibility of MAO-A inhibition by 2-benzylidene-1-indanone derivative **5g**, a compound that displays the highest potency MAO-A inhibition of the present series. It is expected that this compound would act as a reversible inhibitor since it does not possess functional groups associated with irreversible MAO inhibition.[27] To investigate the reversibility of inhibition dialysis was used. MAO-A and **5g** (at a concentration of 4 × $IC_{50}$) were combined and pre-incubated for 15 min and afterwards dialysed for 24 h. After the addition of the substrate, kynuramine, the pre-incubations were diluted twofold to yield an inhibitor concentration of 2 × $IC_{50}$. The residual MAO-A activity was subsequently measured as described above for the determination of $IC_{50}$ values. As controls, this dialysis experiment was carried out in the presence of the irreversible MAO-A inhibitor, pargyline, as well as in the absence of inhibitor. The activities recorded in the absence of the inhibitor served as negative control and designate 100% residual activity (Fig. 4). Also the residual MAO activities of undialysed mixtures of MAO-A and the test inhibitor were measured for comparison. As evident form the results, **5g** is a reversible MAO-A inhibitor. Dialysis restores MAO-A activity to 99% of the negative control. For reversible inhibition it is expected that dialysis of enzyme–inhibitor mixtures would restore activity to 100%. Inhibition, however persists in undialysed mixtures of MAO-A and **5g** with the residual activity at 50%. As expected for the irreversible inhibitor, pargyline, dialysis does not restore activity with the residual activity at 1.7%.

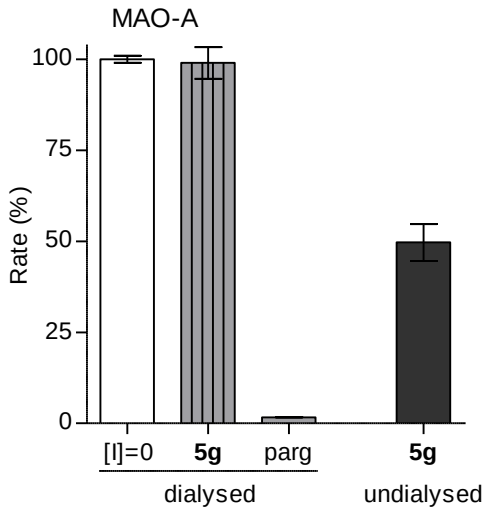
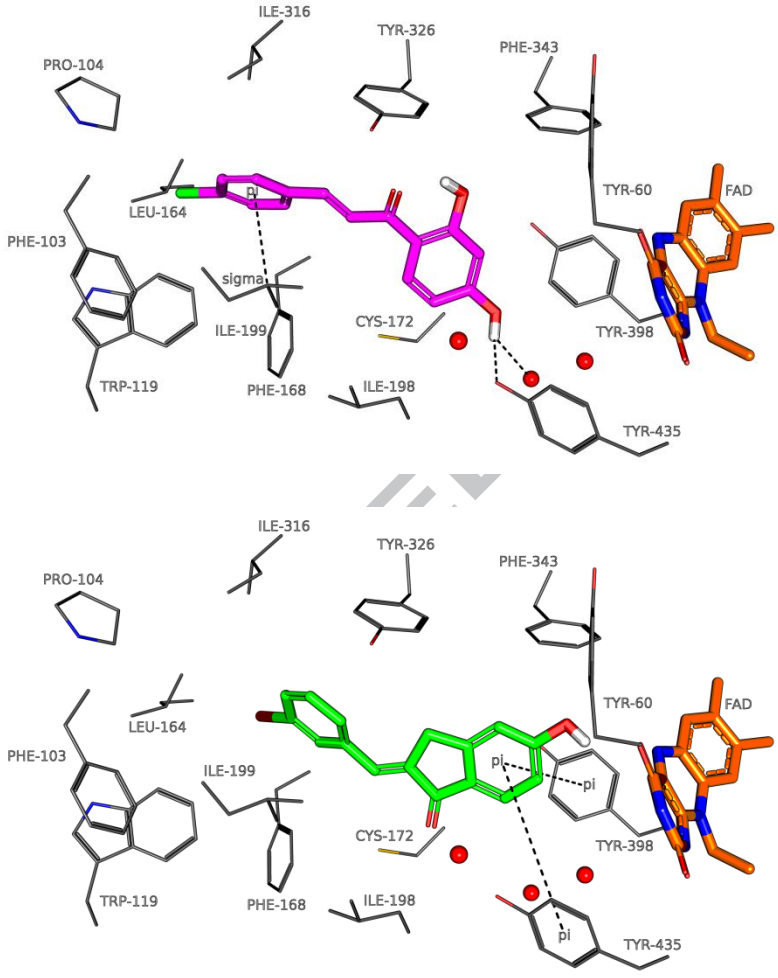



**Figure 4**. A selected 2-benzylidene-1-indanone is a reversible MAO-A inhibitor. The test inhibitor **5g** (at 4 × $IC_{50}$) was preincubated with MAO-A for 15 min, dialysed for 24 h and the residual enzyme activity was measured (**5g** dialysed). Similar incubation and dialysis of MAO-A in the absence inhibitor ([I] = 0, dialysed) and presence of the irreversible inhibitor, pargyline (parg, dialysed), were also carried out. The residual activities of undialysed mixtures of MAO-A and the test inhibitor were also recorded (**5g** undialysed).

Employing molecular docking studies, the binding modes and key interactions of chalcones to the human MAOs have been proposed.[20] For comparison with the chalcone class of compounds, the present study docked selected 2-benzylidene-1-indanone derivatives, **5g** (most potent MAO-A inhibitor) and **5j** (most potent MAO-B inhibitor) as well as chalcone **2** into the MAO active sites using the CDOCKER docking algorithm of Discovery Studio 3.1 (Accelrys). A docking protocol previously reported by us was followed for this purpose.[26] As enzyme models, the crystal structures of human MAO-A (PDB code: 2Z5X) and MAO-B (PDB code: 2V5Z) were employed.[28,29] The binding orientations and selected interactions of the inhibitors with the MAOs are given in Fig. 5 and 6. In the MAO-B active site, chalcone **2** as well as **5g** and **5j** bind with ring A in the substrate cavity in proximity to the FAD while ring B extends into the entrance cavity. The orientation of **2** is similar to that reported in literature.[20] In the substrate cavity, the polar functional groups of **2** establish hydrogen bonding with Tyr-435 and a water molecule, while **5g** and **5j** forms π–π interactions with Tyr-398 and

Tyr-435. In the entrance cavity, which is reported to be a hydrophobic space, the B-rings of the inhibitors are most likely stabilised by Van der Waals interactions. Interestingly, the B-ring of **2** may undergo a π–σ interaction with Ile-199. It is also noteworthy that compared to **2**, the carbonyl groups of **5g** and **5j** are directed in the opposite direction, an orientation required for placement of the B-ring in the entrance cavity. Since the carbonyl carbon of **2** is exocyclic and free to rotate, it may adopt the observed orientation while still allowing for the side chain to extend into the entrance cavity.



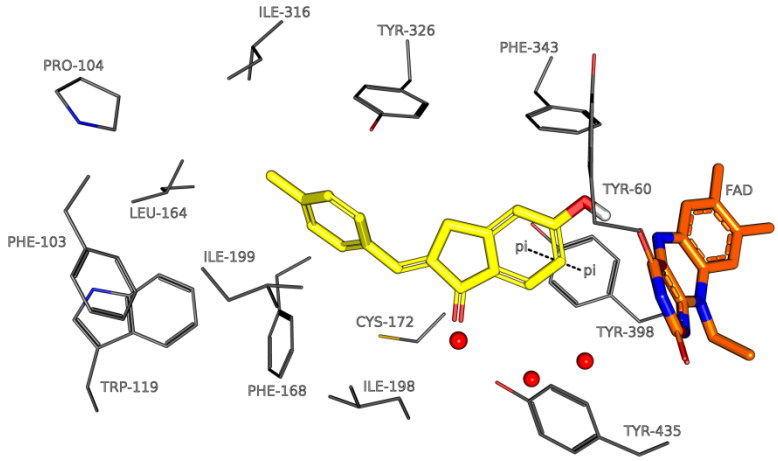



**Figure 5**. The docked binding orientations of **2** (magenta), **5g** (green) and **5j** (yellow) in MAO-B.

In MAO-A, chalcone **2** also binds with ring A directed towards the rear of the active site where the FAD is located. Here the polar functional groups establish hydrogen bonding with a water molecule while π–π interaction occurs with Tyr-444. This orientation is also similar to that reported in literature.[20] Compound **5j** binds with a similar orientation to **2** and forms π–π interactions with both tyrosine residues. As seen with **5g**, the reversed orientation is also a possibility for 2-benzylidene-1-indanone derivatives. In this instance hydrogen bonding may occur with the main chain carbonyl oxygen of Phe-208. Unfortunately, the docking studies do not provide an explanation for the observed MAO-B specificities of chalcones and 2-benzylidene-1-indanones. From literature it is however clear that, in MAO-A, the side chain of Phe-208 may restrict the binding of larger inhibitors. In MAO-B, the residue that corresponds to Phe-208 is Ile-199. In contrast to Phe-208, the side chain of Ile-199 may rotate from the active site cavity, allowing for larger inhibitors to traverse both entrance and substrate cavities. Some larger inhibitors are thus better accommodated in MAO-B than MAO-A leading to specific inhibition of the MAO-B isoform. This analysis may explain the MAO-B specificities of chalcones and 2-benzylidene-1-indanones.

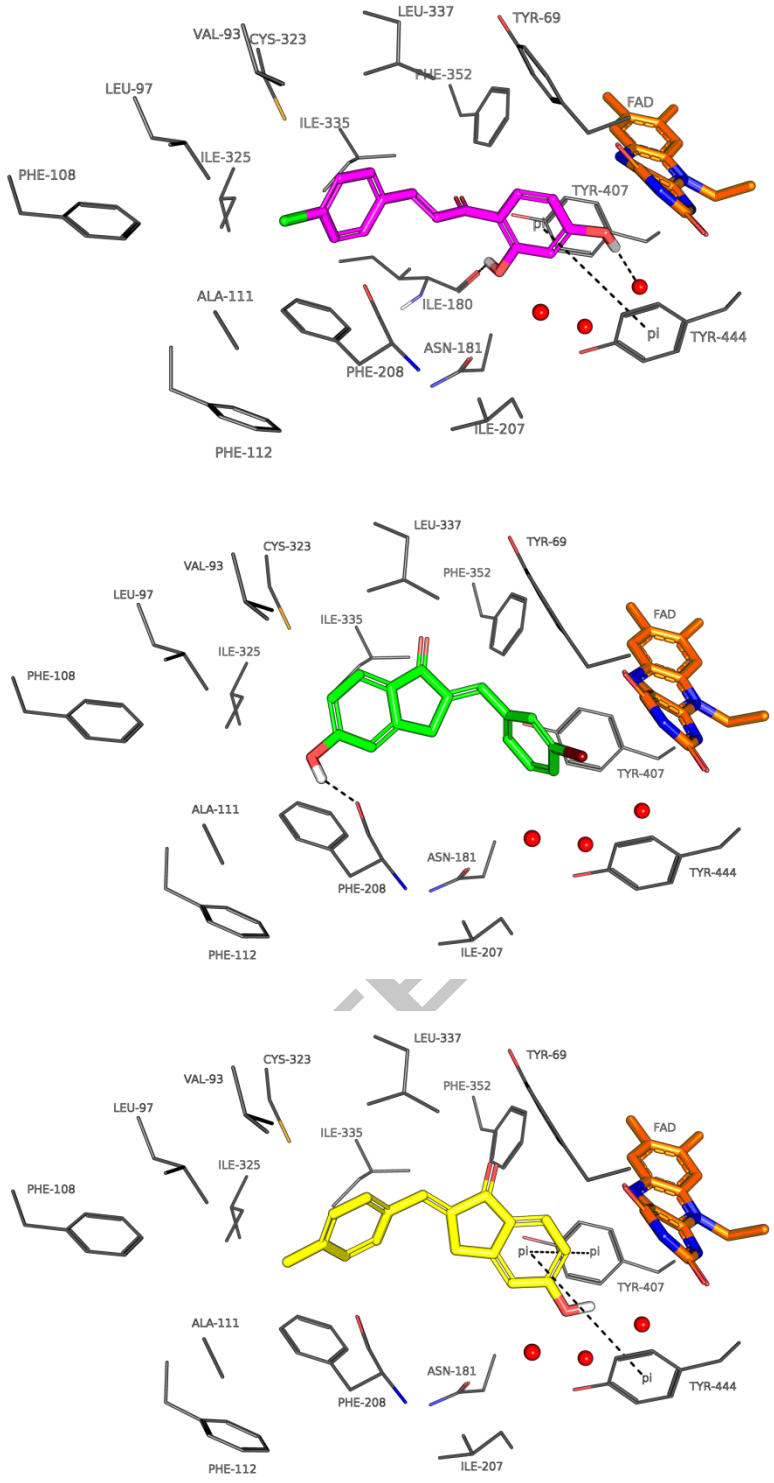



**Figure 6**. The docked binding orientations of **2** (magenta), **5g** (green) and **5j** (yellow) in MAO-A.

In conclusion, based on a literature report that 2-benzylidene-1-indanone derivatives possess MAO inhibitory properties, the present study synthesises a series twenty-two derivatives and evaluated their human MAO inhibition potencies. The 2-benzylidene-1-indanone derivatives proved to be MAO-B

specific inhibitors with good potencies recorded for a number of compounds. Among the series, twelve compounds exhibited $IC_{50}$ < 0.1 μM and may be considered as high potency inhibitors. These potencies are comparable to reference inhibitors such as lazabemide, which is reported to inhibit MAO-B with an $IC_{50}$ value of 0.091 μM under identical conditions.[30] The most noteworthy structure-activity relationship for MAO-B inhibition is 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. The 2-benzylidene-1-indanone derivatives also inhibited MAO-A with **5g** in particular displaying an $IC_{50}$ of 0.131 μM. This is significantly more potent than the clinically used antidepressant, toloxatone, which is reported to inhibit MAO-A reversibly with an $IC_{50}$ value of 3.92 μM under identical conditions.[30] The present study also confirms that a selected 2-benzylidene-1-indanone is a reversible MAO-A inhibitor, a property which reduces the probability of adverse events arising from interaction with certain food. The calculated logP values (ChemSketch) for the 2-benzylidene-1-indanone derivatives ranges from 3.05 (**5k**, **5n**)–4.97 (**5r**), indicating that these compounds are highly lipophilic. It may thus be expected that the 2-benzylidene-1-indanone derivatives would exhibit limited aqueous solubility and oral absorption. The ligand-lipophilicity efficiency (LLE) of the series ranges from 0.90 (**6a**)–3.3 (**5k**) for MAO-A and 1.22 (**6a**)–4.2 (**5j**) for MAO-B. Since the LLE for **5j** is relatively large, this compound may be suitable as a lead for MAO-B inhibitor design. In general a LLE >3 is acceptable for a lead and indicates an acceptable pharmacological activity at the expense of higher lipophilicity. It is, however, recommended that further structural modification should focus on reducing lipophilicity, which represents a potential liability for bioavailability.

Based on this study, it may be concluded that 2-benzylidene-1-indanone derivatives are promising MAO-B inhibitors for the treatment disorders such as Parkinson's disease. Nonspecific MAO inhibitors may also find application in the treatment of depression, particularly where depression is a comorbidity of Parkinson's disease.

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**Conflict of Interest**

The authors have no conflicts of interest to declare.

**References**

1. Ramsay, R. R. *Curr. Top. Med. Chem.* **2012**, *12*, 2189.
2. Ramsay, R R. *Curr. Pharm. Des.* **2013**, *19*, 2529.
3. Youdim, M. B.; Edmondson, D.; Tipton, K. F. *Nat. Rev. Neurosci*. **2006**, *7*, 295.
4. Schwartz, T. L. *CNS Spectr*. **2013**, *18*(Suppl 1), 25.
5. Lum, C. T.; Stahl, S. M. *CNS Spectr*. **2012**, *17*, 107.
6. Gershanik, O. S. *Mov. Disord*. **2015**, *30*, 103.
7. Shoulson, I.; Oakes, D.; Fahn, S.; Lang, A.; Langston, J. W.; LeWitt, P.; Olanow, C. W.; Penney, J. B.; Tanner, C.; Kieburtz, K.; Rudolph, A. *Ann. Neurol.* **2002**, *51*, 604.
8. Fernandez, H. H.; Chen, J. J. *Pharmacotherapy*. **2007**, *27*, 174S.
9. Finberg, J. P.; Wang, J.; Bankiewicz, K.; Harvey-White, J.; Kopin, I. J.; Goldstein, D. S. *J. Neural Transm. Suppl.* **1998**, *52*, 279.
10. LeWitt, P. A.; Taylor, D. C. *Neurotherapeutics*. **2008**, *5*, 210.
11. Youdim, M. B.; Bakhle, Y. S. *Br. J. Pharmacol*. **2006**, *147*(Suppl 1), S287.
12. Da Prada, M.; Zürcher, G.; Wüthrich, I.; Haefely, W. E. *J. Neural Transm. Suppl*. **1988**, *26*, 31.
13. Flockhart, D. A. *J. Clin. Psychiatry*. **2012**, *73*(Suppl 1), 17.
14. Bortolato, M.; Chen, K.; Shih, J. C. *Adv. Drug Deliv. Rev*. **2008**, *60*, 1527.
15. Bonnet, U. *CNS Drug Rev*. **2003**, *9*, 97.

16. Provost, J. C.; Funck-Brentano, C.; Rovei, V.; D'Estanque, J.; Ego, D.; Jaillon, P. *Clin. Pharmacol. Ther*. **1992**, *52*, 384.
17. Carradori, S.; Silvestri, R. *J. Med. Chem.* **2015**, *58*, 6717.
18. Carradori, S.; Petzer, J. P. *Expert Opin. Ther. Pat*. **2015**, *25*, 91.
19. Tanaka, S.; Kuwai, Y.; Tabata, M. *Planta Med*. **1987**, *53*, 5.
20. Chimenti, F.; Fioravanti, R.; Bolasco, A.; Chimenti, P.; Secci, D.; Rossi, F.; Yáñez, M.; Orallo, F.; Ortuso, F.; Alcaro, S. *J. Med. Chem*. **2009**, *52*, 2818.
21. Haraguchi, H.; Tanaka, Y.; Kabbash, A.; Fujioka, T.; Ishizu, T.; Yagi, A. *Phytochemistry*. **2004**, *65*, 2255.
22. Pan, X.; Kong, L. D.; Zhang, Y.; Cheng, C. H.; Tan, R. X. *Acta Pharmacol. Sin*. **2000**, *21*, 949.
23. Gao, G. Y.; Li, D. J.; Keungm W. M. *J. Med. Chem*. **2001**, *44*, 3320.
24. Morales-Camilo, N.; Salas, C. O.; Sanhueza, C.; Espinosa-Bustos, C.; Sepúlveda-Boza, S.; Reyes-Parada, M.; Gonzalez-Nilo, F.; Caroli-Rezende, M.; Fierro, A. *Chem. Biol. Drug Des*. **2015**, *85*, 685.
25. Huang, L.; Lu, C.; Sun, Y.; Mao, F.; Luo, Z.; Su, T.; Jiang, H.; Shan, W.; Li, X. *J. Med. Chem*. **2012**, *55*, 8483.
26. Mostert, S.; Petzer, A.; Petzer, J. P. *ChemMedChem*. **2015**, *10*, 862.
27. Edmondson, D. E.; Mattevi, A.; Binda, C.; Li, M.; Hubálek, F. *Curr. Med. Chem*. **2004**, *11*, 1983.
28. Son, S. Y.; Ma, J.; Kondou, Y.; Yoshimura, M.; Yamashita, E.; Tsukihara, T. *Proc. Natl. Acad. Sci. USA*. **2008**, *105*, 5739.
29. Binda, C.; Wang, J.; Pisani, L.; Caccia, C.; Carotti, A.; Salvati, P.; Edmondson, D. E.; Mattevi, A. *J. Med. Chem*. **2007**, *50*, 5848.
30. Petzer, A.; Pienaar, A.; Petzer, J. P. *Drug Res (Stuttg)*. **2013**, *63*, 462.

**Graphical abstract:**