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# Inhibition of Rat Brain Monoamine Oxidase Activities by Psoralen and Isopsoralen: Implications for the Treatment of Affective Disorders

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*Abstract:* Psoralen and isopsoralen, furocoumarins isolated from the plant *Psoralea corylifolia* L., were demonstrated to exhibit *in vitro* inhibitory actions on monoamine oxidase (MAO) activities in rat brain mitochondria, preferentially inhibiting MAO-A activity over MAO-B activity. This inhibition of enzyme activities was found to be dose-dependent and reversible. For MAO-A, the $IC_{50}$ values are 15.2±1.3 μM psoralen and 9.0±0.6 μM isopsoralen. For MAO-B, the $IC_{50}$ values are 61.8±4.3 μM psoralen and 12.8±0.5 μM isopsoralen. Lineweaver-Burk transformation of the inhibition data indicates that inhibition by both psoralen and isopsoralen is non-competitive for MAO-A. The $K_i$ values were calculated to be 14.0 μM for psoralen and 6.5 μM for isopsoralen. On the other hand, inhibition by both psoralen and isopsoralen is competitive for MAO-B. The $K_i$ values were calculated to be 58.1 μM for psoralen and 10.8 μM for isopsoralen. These inhibitory actions of psoralen and isopsoralen on rat brain mitochondrial MAO activities are discussed in relation to their toxicities and their potential applications to treat affective disorders.

Furocoumarins have been reported to be present in various plants such as celery, parsley, figs, parsnips, and grapefruit (Edwards *et al.* 1996; Fukuda *et al.* 1997; Koenigs & Trager 1998). These natural products have been reported to possess diverse biological activities. Psoralen and isopsoralen (fig. 1), furocoumarins isolated from the plant *Psoralea corylifolia* L. (Leguminosae), are believed to be the active components of the herb (Wang *et al.* 1999), which is used traditionally in China to treat symptoms of ageing.

Monoamine oxidase (MAO; EC 1.4.3.4) is a flavin-containing enzyme that catalyses the oxidation of a variety of amine-containing neurotransmitters such as serotonin and dopamine to yield the corresponding aldehydes. MAO exists in two isoforms, namely MAO-A and MAO-B, which are the products of two distinct genes (Bach *et al.* 1988). These two forms of MAO exhibit different substrate specificities and inhibitor selectivities (Johnston 1968; Suzuki *et al.* 1976; Fowler & Callingham 1978; Tipton 1986; Youdim & Tenne 1987). MAO-A acts preferentially on serotonin and norepinephrine, and is inhibited by clorgyline. MAO-B acts preferentially on 2-phenylethylamine and benzylamine, and is inhibited by R(−)deprenyl.

Biogenic amines occupy a significant role in controlling CNS function. MAO is important in regulating the level of biogenic amines in the brain. For example, the ageing brain is characterised by a decrease in its dopamine content and a progressive decline of dopaminergic control in the striatum. This has been demonstrated both in human subjects and in animal models (Volkow *et al.* 1998a & b; Yurek *et al.* 1998). The activity of tyrosine hydroxylase, the enzyme catalysing the rate-limiting step in catecholamine biosynthesis, is decreased in the human brain with advanced age (McGeer *et al.* 1971). It has also been demonstrated that MAO activity progressively increases in the ageing brain (Robinson *et al.* 1971; Benedetti & Keane 1980), explaining, in part at least, the decreased level of dopamine in the brain associated with senescence. Thus, inhibition of MAO constitutes a feasible control point in regulating the pool size of biogenic amines in the CNS.

Here we report that rat brain mitochondrial MAO-A and MAO-B are inhibited by psoralen and isopsoralen. Thus, these natural products might benefit the population where perturbation of the level of biogenic amines in the brain is desirable.

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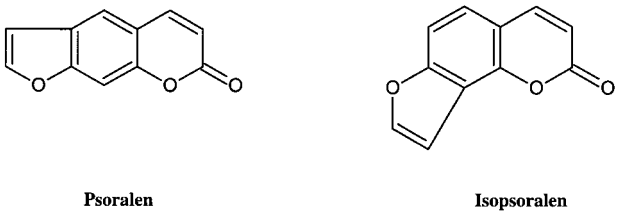
## Materials and Methods

*Materials.* Two known compounds, psoralen and isopsoralen, were isolated from the seeds of *P. corylifolia* by repeated column chromatography on silica gel (Wall *et al.* 1988; Wang *et al.* 1999). The purity of the compounds was checked by TLC and HPLC to be at least 97% pure (Wisneski 1976; Edwards *et al.* 1996). The chemical structures of the two compounds were confirmed by $^{1}H$- and $^{13}C$-NMR (fig. 1). [$^{14}C$]5-Hydroxytryptamine and [$^{14}C$]β-phenylethylamine were purchased from DuPont NEN. All other reagents were of analytical grade purchased from Sigma.

*Enzyme preparation.* The rat brain mitochondrial fraction was used as a source of MAO activities (Walther *et al.* 1987). Male Sprague-



Psoralen Isopsoralen

Fig. 1. Structures of psoralen and isopsoralen.

Dawley rats, 250~300 g, were decapitated and their brains rapidly removed and homogenised in 10 volumes of 10 mM phosphate buffer pH 7.4 containing 0.25 M sucrose. The mitochondrial fraction was prepared by differential centrifugation (Sandri *et al.* 1990). Protein concentration was determined by a modified method of Lowry (Hatzoglou *et al.* 1992) using bovine serum albumin as the standard. Aliquots of the enzyme preparation were frozen in liquid nitrogen, stored at −80°, and thawed before use.

*Assays for MAO-A and MAO-B.* MAO activities were assayed radiochemically using a modification of the method described by Pizzinat *et al.* (1999). Briefly, the assay mixture contained 50 μM [$^{14}$C] 5-hydroxytryptamine or 10 μM [$^{14}$C] β-phenylethylamine, as specific substrate for MAO-A and MAO-B, respectively, in a final volume of 200 μl of 100 mM phosphate buffer pH 7.4. The tested compounds were added into the reaction mixture in a 10 μl DMSO solution. The same amount of DMSO was also added in the control tubes. Preliminary experiments indicated that this amount of DMSO did not affect the MAO assays. The reaction mixture was preincubated for 10 min. at 37° and the reaction was started by adding 50 μg protein of the enzyme preparation, and terminated by adding 1 ml 2 M HCl. In the standard assays, the reaction was allowed to proceed at 37° for 10 min. Two ml of toluene/ethylacetate (1:1, v/v) was then added to extract the radioactive product. The reversible nature of the inhibitors was assessed by the method of dilution (Dostert *et al.* 1992). Prior to the enzyme assays, the enzyme preparation was preincubated with the inhibitors at 5 times the $IC_{50}$ concentrations for 30 min., followed by a dilution 5 times before commencement of the assay procedures as described in Materials and Methods. Preincubation of the enzyme in the absence of inhibitors was also carried out in parallel, followed by the dilution 5 times and addition of the inhibitors at the $IC_{50}$ concentrations. Thus, the final concentrations of the inhibitors were the same irrespective of whether the preincubations were carried out in the absence or presence of inhibitors. The radioactivity contained in the organic phase was counted in a liquid scintillation spectrometer at 98% efficiency. Enzyme activity was expressed as nmol product formed per mg protein per min. The assays were validated by known inhibitors of MAO, namely clorgyline (a specific MAO-A inhibitor, $IC_{50}$=4 nM), R(-)deprenyl (a specific MAO-B inhibitor, $IC_{50}$=60 nM), and harmane (an inhibitor for both MAO-A, with $IC_{50}$=0.7 μM, and MAO-B, with $IC_{50}$=100 μM). In the kinetic analyses, the reaction mixture consisted of five different concentrations of [$^{14}$C] 5-hydroxytryptamine (30 to 100 μM) or [$^{14}$C] β-phenylethylamine (1 to 50 μM) as substrate, in the absence or presence of inhibitors. In the kinetic studies, the concentrations of the inhibitors were chosen such that approximately 40% and 60% of the enzyme activities were inhibited.

## Results

It was found that psoralen and isopsoralen, when incorporated into the enzyme assays in micromolar concentrations, could elicit a dose-dependent inhibitory action on both MAO-A (fig. 2) and MAO-B (fig. 3) activities. The inhibition curves for both compounds on MAO-A are parallel

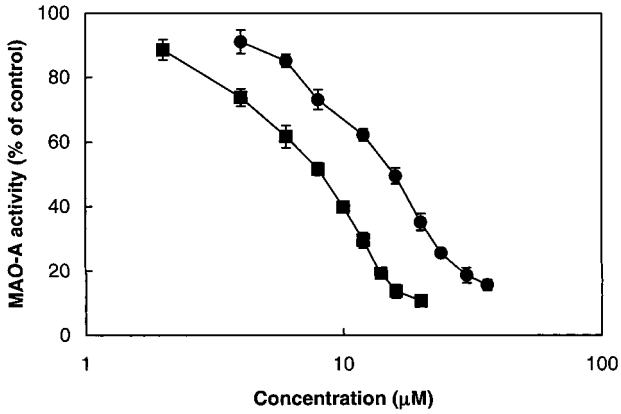



Fig. 2. Dose-dependent inhibitory actions of psoralen and isopsoralen on rat brain mitochondrial MAO-A activity. MAO-A assays were performed as described under Materials and Methods. Different concentrations of psoralen (●) and isopsoralen (■) were incorporated in the assays. Results were expressed as percentage of control where no inhibitor was added. Data are the average of 4 independent experiments and error bars indicate S.D.

to each other (fig. 2), with isopsoralen ($IC_{50}$=9.0±0.6 μM) more potent than psoralen ($IC_{50}$=15.2±1.3 μM). It was observed that the inhibition curves for both compounds on MAO-B are also essentially parallel to each other (fig. 3). However, the difference in potency between the two compounds appears to be larger in this case, with isopsoralen ($IC_{50}$=12.8±0.5 μM) again more potent than that of psoralen ($IC_{50}$=61.8±4.3 μM).

The same inhibitory effects (i.e. about 50% reduction in enzyme activities) were found in both methods of preincubation, indicating the reversible nature of the inhibitors. Also, it was found that the duration of preincubation of the inhibitors with the enzyme, from 10 min. up to 40 min., did not affect the inhibitory effects (results not shown).

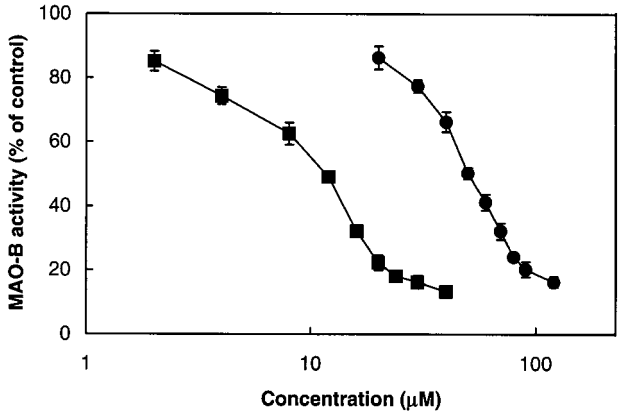



Fig. 3. Dose-dependent inhibitory actions of psoralen and isopsoralen on rat brain mitochondrial MAO-B activity. MAO-B assays were performed as described under Materials and Methods. Different concentrations of psoralen (●) and isopsoralen (■) were incorporated in the assays. Results were expressed as percentage of control where no inhibitor was added. Data are the average of 4 independent experiments and error bars indicate S.D.

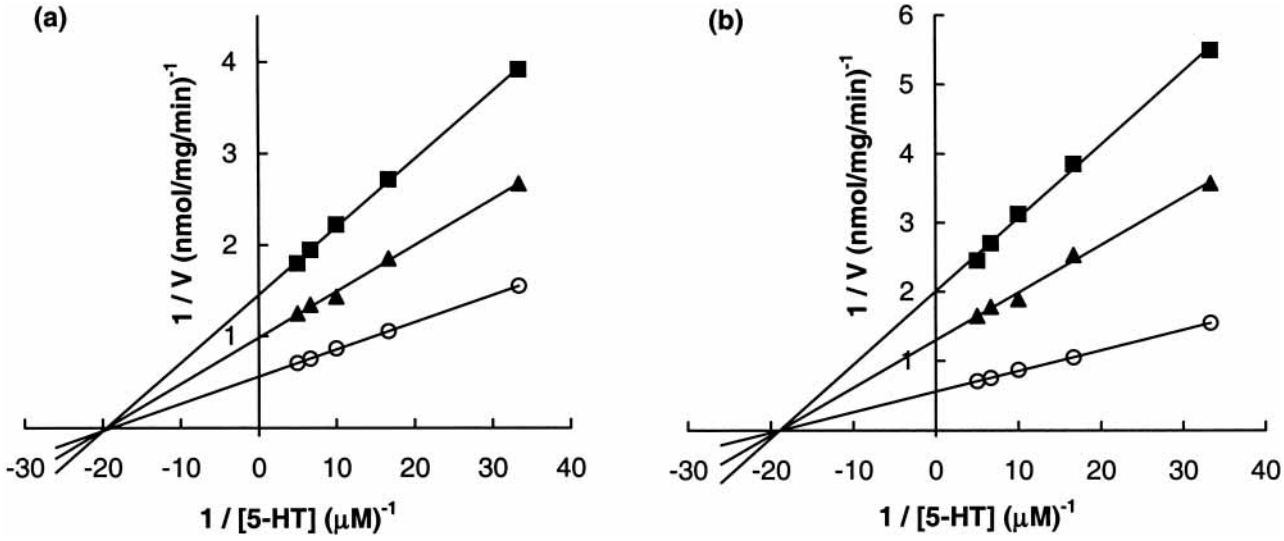



Fig. 4. Lineweaver-Burk plot of inhibition of rat brain mitochondrial MAO-A by (a) psoralen and (b) isopsoralen. MAO-A assays were performed as described under Materials and Methods at different concentrations of the substrate [$^{14}$C] 5-hydroxytryptamine (5-HT). Each experiment contained three sets of data: control without any inhibitor (○), in the presence of 12.4 μM psoralen or 7.1 μM isopsoralen (▲), and in the presence of 18.3 μM psoralen or 10.7 μM isopsoralen (■). Enzyme activities were expressed in nmol per mg protein per min. The Lineweaver-Burk transformed data were plotted, followed by linear regression of the points. Data represent the average of 3 experiments.

Kinetic studies were performed on MAO-A at different concentrations of the substrate in the absence or presence of the inhibitors. Lineweaver-Burk plots of the data are shown in fig. 4a (for psoralen) and fig. 4b (for isopsoralen). It appears that both compounds act as non-competitive inhibitors of MAO-A. The $K_i$ for psoralen was calculated to be 14.0 μM and the $K_i$ for isopsoralen was 6.5 μM.

On the other hand, when such kinetic studies were performed on MAO-B, an entirely different pattern of inhibition has emerged. Lineweaver-Burk plots of the data are shown in fig. 5a (for psoralen) and fig. 5b (for isopsoralen). In this case, both compounds act as competitive inhibitors of MAO-B. The $K_i$ for psoralen was calculated to be 58.1 μM and the $K_i$ for isopsoralen was 10.8 μM.

A comparison of the inhibitory characteristics of the two compounds is summarised in table 1.

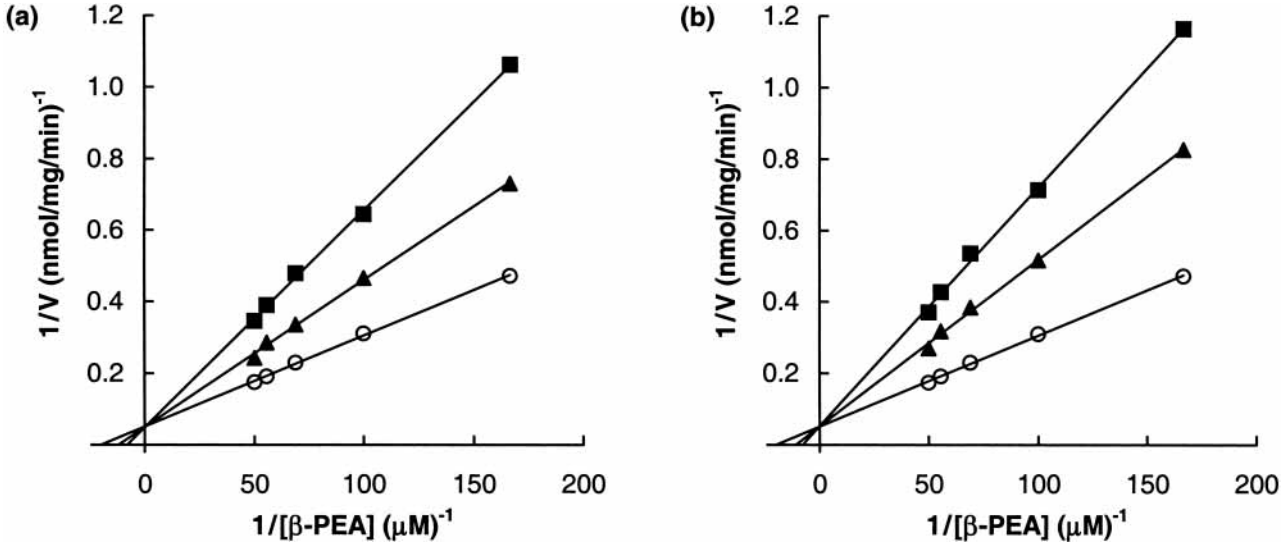



Fig. 5. Lineweaver-Burk plot of inhibition of rat brain mitochondrial MAO-B by (a) psoralen and (b) isopsoralen. MAO-B assays were performed as described under Materials and Methods at different concentrations of the substrate [$^{14}$C] β-phenylethylamine (β-PEA). Each experiment contained three sets of data: control without any inhibitor (○), in the presence of 49.4 μM psoralen or 8.5 μM isopsoralen (▲), and in the presence of 74.2 μM psoralen or 15.4 μM isopsoralen (■). Enzyme activities were expressed in nmol per mg protein per min. The Lineweaver-Burk transformed data were plotted, followed by linear regression of the points. Data represent the average of 3 experiments.

*Table 1.*

Inhibition of monoamine oxidase by psoralen and isopsoralen: a comparison.

| | MAO-A | | | MAO-B | | |
|---|---|---|---|---|---|---|
| Inhibitor | $IC_{50}$ (μM) | Mode of inhibition | $K_i$ (μM) | $IC_{50}$ (μM) | Mode of inhibition | $K_i$ (μM) |
| Psoralen | 15.2 | Non-competitive | 14.0 | 61.8 | Competitive | 58.1 |
| Isopsoralen | 9.0 | Non-competitive | 6.5 | 12.8 | Competitive | 10.8 |

## Discussion

MAO inhibitors currently in clinical use have undesirable side-effects (Rabkin *et al.* 1984 & 1985; Remick *et al.* 1989) which often lead to drug intolerance and even discontinuation despite favourable therapeutic response. Adverse drug effects frequently seen during treatment with phenelzine, a clinically used MAO inhibitor, were hypertensive reactions, orthostatic reactions, confusion, oedema, weight gain, urinary retention and sexual dysfunction. For tranylcypromine, another MAO inhibitor in clinical use, though oedema and weight gain were not observed, and sexual dysfunction was less common, but orthostatic reactions were even more pronounced than phenelzine. Also, the irreversible nature of these drugs caused cumulative effects and wash-out problems (Felner & Waldmeier 1979). In addition, for other MAO inhibitors such as iproniazid, the sporadic occurrence of acute hepatotoxicity is also a problem (Da Prada *et al.* 1989). Thus, the search for other MAO inhibitors with better pharmacological and toxicological profiles is highly warranted.

In the present investigation, psoralen and isopsoralen, isolated from the dried seeds of *P. corylifolia*, were found to exhibit potent inhibitory activities against both MAO-A and MAO-B. The mode of inhibition of both compounds towards MAO-A is non-competitive in nature while the inhibition of MAO-B is competitive in nature. The molecular basis of this divergent action on the two isoforms of MAO is not understood. Judged by the $IC_{50}$ and $K_i$ values (table 1), these naturally occurring compounds appear to preferentially inhibit MAO-A than MAO-B. In this context, this relative preference towards MAO-A is similar to other classes of non-hydrazine reversible MAO inhibitors currently under investigation such as N-methylisoquinolinium ion ($NMIQ^+$), isoquinolines, and quinolines (Naoi *et al.* 1993), and the cerebral antiischaemic agent ifenprodil (Arai *et al.* 1991). The preference and the non-competitive nature of inhibition towards MAO-A suggest that these compounds could be employed in situations where a more selective mode of inhibition is warranted. The specific action of MAO-A on norepinephrine, epinephrine and serotonin suggests that psoralen and isopsoralen might be useful in the perturbation of the level of these biogenic amines in the human brain under physiological or pathological conditions. It is interesting to note that these experimental results corroborate the traditional use of *P. corylifolia* in China, otherwise known as Buguzhi in Chinese medicine, to treat various symptoms associated with ageing (Chang & But 1986). It is worth noting that no overt toxicity has been reported on the use of *P. corylifolia.* That they might be safer confers a great advantage on these natural compounds.

At this juncture, it is noteworthy to mention two *in vivo* studies relevant to our work. The first one reports that a derivative of psoralen could modulate CNS activity when administered to a number of laboratory animals including dogs, cats, rats, mice and hamsters (Sethi *et al.* 1992). The second study is a clinical finding in Finland where oral administration of psoralen is suggested to be beneficial to patients suffering from seasonal affective disorders (Partonen 1998). Partonen hypothesised that inhibition of hepatic melatonin metabolism might be involved. Our experimental findings reported in the present investigation suggest that inhibition of MAO in the CNS might provide an alternative explanation. Confirmation of this awaits further *in vivo* studies.

Chemically, psoralen and isopsoralen belong to the class of tricyclic furocoumarins (fig. 1). It has been reported earlier that simple coumarins do not possess any MAO inhibitory activity (Hossain *et al.* 1996). It seems that other criteria such as ring conjugation or the presence of other side chains are necessary in order to make coumarins active against MAO, in line with previous reports (Thull & Testa 1994; Hossain *et al.* 1996; Löscher *et al.* 1999). Our data are the first demonstration that furocoumarins possess potent MAO inhibitory activities.

In order to evaluate the potential of any lead compounds to develop into therapeutically useful agents, their toxicological profiles must be thoroughly studied. In this respect, existing data on the toxicity of furocoumarins are inconsistent. On one hand, there are reports indicating that they do not exhibit any observable toxicity upon administration to various experimental animals (Chang & But 1986; Wall *et al.* 1988; Sethi *et al.* 1992). On the contrary, other reports have indicated that these compounds might possess genotoxic activities (Lagatolla *et al.* 1998), or might act as ovarian toxicants (Diawara *et al.* 1999), or could inactivate cytochrome P-450 2B1 in the liver (Koenigs & Trager 1998). Furocoumarins were reported to possess antiproliferative activity (Song & Tapley 1978) due to their ability to bind DNA upon ultraviolet A light (UVA) irradiation (Ben-Hur & Song 1984). In fact, photochemotherapy with psoralen derivatives and UVA has been successfully employed in the treatment of psoriasis and other dermatological diseases

(Wolff & Honigsmann 1984). However, the photoactivation of psoralen to produce toxic derivatives may be a problem (Stern *et al.* 1998). Thus, a recent approach in photochemotherapy is to study the structure-function relationship of various psoralen derivatives in order to arrive at compounds of much less toxicity (Conconi *et al.* 1996 & 1998). It is worth noting that the photoactivity of isopsoralen appears to be much less than that of psoralen (Alcalay *et al.* 1989), and this could be an advantage for isopsoralen in situations where such photoactivity is considered undesirable.

The same principle can be applied to MAO inhibition. Coumarins are one of the most common plant secondary metabolites found in nature, with over 800 of them reported. In addition, numerous non-natural occurring coumarins have also been synthesised. In view of the purported toxicities of some furocoumarins, this repertoire of natural or synthetic compounds should be exploited to screen for compounds with more favourable efficacy/toxicity ratios. In addition, psoralen and isopsoralen exhibit rather different preference towards MAO-A and MAO-B despite their structural similarity. Psoralen exhibits a preference towards MAO-A than MAO-B, with a difference by four times in the $IC_{50}$ values (table 1). On the other hand, although isopsoralen is a more potent inhibitor in its own right, its differential selectivity towards MAO-A is less (table 1). This structure-function relationship should be further exploited in order to arrive at compounds which are more efficacious and selective.

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