

deficiencies after the protozoa lived in a luxurious environment for a while. This revelation may suggest that future chemotherapeutic studies on parasitic helminths can utilize free-living helminths as models to eliminate

many unnecessary technical difficulties. Also, there perhaps could be a further classification among the parasites to term the protozoa "true parasites" and the helminth "pseudo-parasites" from the viewpoint of chemotherapy.

Communications to the Editor

(*E*)-2-(3,4-Dimethoxyphenyl)-3-fluoroallylamine: A Selective, Enzyme-Activated Inhibitor of Type B Monoamine Oxidase

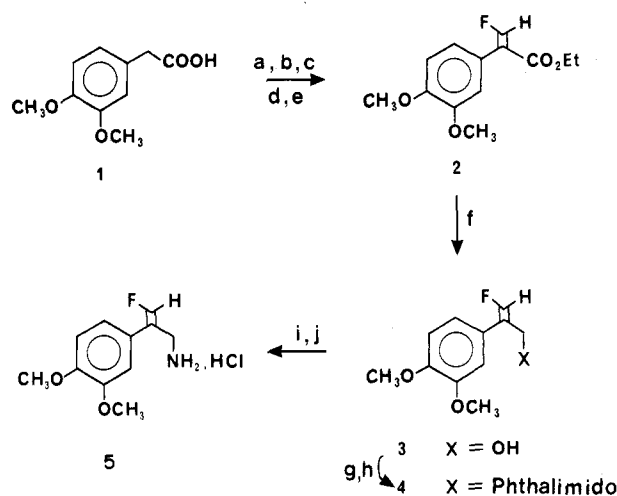
Sir:

The search for clinically effective inhibitors of monoamine oxidase [amine:oxygen oxidoreductase (deaminating, flavin-containing); EC 1.4.3.4; MAO] has been one of the continuing themes of drug research for the past 3 decades.¹ While the therapeutic advantages of MAO inhibitors are generally well accepted,² one problem that has not yet been satisfactorily resolved is the so-called "cheese effect".³

An attractive approach to the design of clinically safe MAO inhibitors is to take advantage of the occurrence of two forms of MAO: type A and type B.⁴ On the basis of the substrate specificity of MAO A and B and the relative distribution of the two enzyme forms in different body organs, it has been reasonably postulated that a selective inhibitor of the B form would be largely free of the cheese effect.⁵ This concept has played a role in the development of some selective inhibitors⁶ of MAO.

We have prepared a series of substituted allylamines⁷ as enzyme-activated inhibitors of MAO. Of most interest is (*E*)-2-(3,4-dimethoxyphenyl)-3-fluoroallylamine (5),⁸ synthesized according to the route in the Scheme I. The preparation of 2⁹ from commercially available 1 followed essentially known chemistry developed in our laboratory¹⁰ and elsewhere.¹¹ Selective reduction of 2 was achieved with diisobutylaluminum hydride in hexane, followed by acidic workup. The resulting alcohol 3⁹ was most conveniently converted to the phthalimide 4⁹ via the bromide. Deprotection afforded 5, which was purified as its hydrochloride salt (mp 216–217 °C). The *E* configuration of

Scheme I^a



^a a = *tert*-butyl acetate, HClO_4 ; b = LDA, ClCO_2Et ; c = sodium *tert*-butoxide, ClCHF_2 ; d = $\text{CF}_3\text{CO}_2\text{H}$; e = NaOH; f = DIBAL; g = PBr_3 ; h = potassium phthalimide; i = NH_2NH_2 ; j = HCl.

the double bond was established on the basis of NMR data and confirmed by X-ray structural analysis.¹²

Incubation of a preparation of rat brain mitochondrial MAO¹³ with varying concentrations of 5 resulted in a time-dependent loss of enzyme activity, which followed pseudo-first order kinetics for more than 2 half-lives (Figure 1). The minimum half-life (τ_{50}) at saturating concentration and the apparent dissociation constant (K_I) of 5, determined at 10 °C according to the method of Kitz and Wilson,¹⁴ are 14.5 min and 130 μM and 1.7 min and 40 μM for the A and B forms of MAO, respectively. Protection against inactivation of either the A or the B form of the enzyme can be demonstrated by preincubation with the corresponding substrate 5-HT (type A) or benzylamine (type B). Enzyme activity is not recovered after extensive dialysis or after treatment with benzylamine,^{7b} indicating that the inhibition is irreversible. These results strongly suggest that 5 is an enzyme-activated irreversible

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- (7) For other examples of allylamines that inhibit MAO, see: (a) Rando, R. R. *J. Am. Chem. Soc.* 1973, 95, 4438. (b) Rando, R. R.; Eigner, A. *Mol. Pharmacol.* 1977, 13, 1005.
- (8) Compound 5 has been assigned the code number MDL 72145.
- (9) All new compounds gave spectral data and C, H, and N combustion analyses consistent with the structure.
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- (12) An X-ray structural analysis of 5 was kindly undertaken by Professor R. Weiss at the Laboratoire de Cristallographie, Institut Le Bel, Université Louis Pasteur, Strasbourg.
- (13) Rat brain mitochondria were prepared¹⁶ in 0.1 M phosphate buffer (pH 7.2). Aliquots of mitochondrial suspension were preincubated at 37 or at 10 °C for different times with a range of concentrations of 5. After extensive dilution (100- to 250-fold), the remaining MAO activity of the type A and type B forms of the enzyme were determined with 5-hydroxy[¹⁴C]-tryptamine (10 μM) and [¹⁴C]phenethylamine (5 μM) as selective substrates for type A and type B, respectively.
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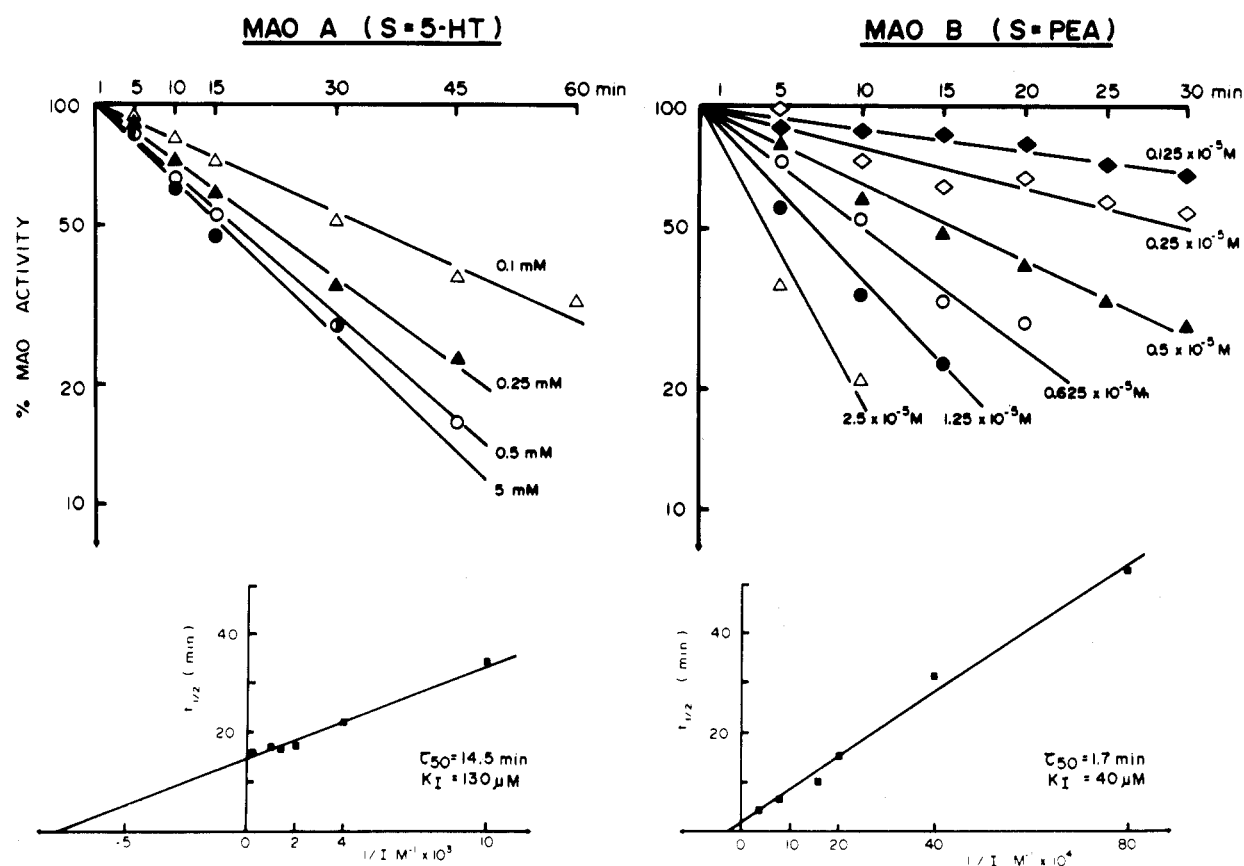


Figure 1. Time- and concentration-dependent inhibition of MAO A and MAO B by (*E*)-2-(3,4-dimethoxyphenyl)-3-fluoroallylamine (5). Rat brain mitochondrial MAO was preincubated with 5 at various concentrations at 10 °C in 0.1 M phosphate buffer (pH 7.2).¹³ Kinetic parameters were calculated by the method of Kitz and Wilson.¹⁴ τ_{50} is the half-life of enzyme activity at infinite concentration of inhibitor. K_I is the apparent dissociation constant.

inhibitor¹⁵ of MAO, highly selective for the B form of the enzyme.

The compound is active in vivo by both the intraperitoneal (ip) and the oral (po) routes of administration. Over a dose range of 0.25 to 2.5 mg/kg po, selective type B inhibition in the brain is observed. At doses of 10 mg/kg po, this selectivity is largely lost. Upon repeated administration of 0.5 mg/(kg day) po, type B MAO is inhibited by greater than 85% and type A by less than 15%. At 2.5 mg/(kg day) po, the type A inhibition increases to about 50 %.

In order to assess the potential of 5 to provoke the "cheese reaction", rats were pithed and set up for recording blood pressure and heart rate.¹⁷ Tyramine was administered either intravenously (iv) or intraduodenally (id) in ascending doses (1.25–80 μ g/kg iv and 1–50 mg/kg id), and the blood pressure and heart-rate responses were recorded. Pretreatment of the animals with 5 [0.5 mg/(kg day) for 5 days po] produced only minimal potentiation of the cardiovascular responses to tyramine challenge. This effect was similar to that obtained with L-deprenyl [10 mg/(kg day) for 5 days po] but contrasted to the marked potentiation of the tyramine response seen with the type A

selective inhibitor clorgyline [5.0 mg/(kg day) for 5 days po].

The therapeutic possibilities of selective type B MAO inhibition have been studied mainly with L-deprenyl,⁵ and this drug has been reported to be an effective antidepressant¹⁸ and to be useful as an adjunct to the L-Dopa treatment of Parkinsonism.¹⁹ However, L-deprenyl has several actions in addition to selective type B MAO inhibition, which could conceivably be important to its therapeutic efficacy.²⁰ The fact that 5 is a selective type B inhibitor devoid of the secondary properties of L-deprenyl should help clarify the role of type B MAO in these disease states.

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