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

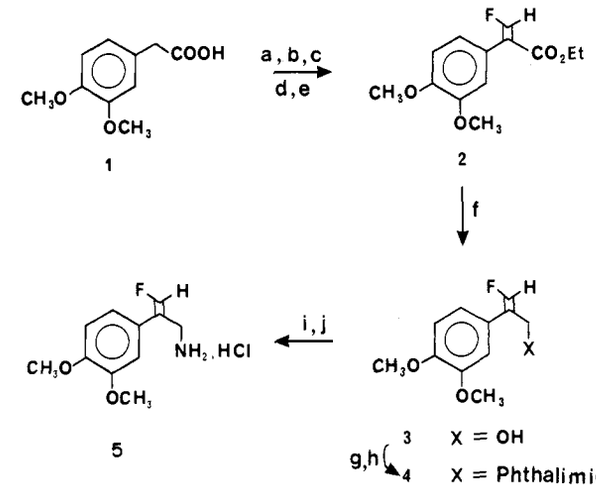
Sir:

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 inhibitors[6] of MAO.

We have prepared a series of substituted allylamines[7] 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 **2**[9] from commercially available **1** followed essentially known chemistry developed in our laboratory[10] and elsewhere.[11] Selective reduction of **2** was achieved with diisobutylaluminium hydride in hexane, followed by acidic workup. The resulting alcohol **3**[9] was most conveniently converted to the phthalimide **4**[9] via the bromide. Deprotection afforded **5**, which was purified as its hydrochloride salt[9] (mp 216–217 °C). The *E* configuration of the double bond was established on the basis of NMR data and confirmed by X-ray structural analysis.[12]

Scheme I[a]



[a] a = *tert*-butyl acetate, $HClO_4$; b = LDA, $ClCO_2Et$; c = sodium *tert*-butoxide, $ClCHF_2$; d = CF_3CO_2H; e = NaOH; f = DIBAL; g = PBr_3; h = potassium phthalimide; i = NH_2NH_2; j = HCl.

Incubation of a preparation of rat brain mitochondrial MAO[13] 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

(1) Singer, T. P.; Von Korff, R. W.; Murphy, D. L. Eds. "Monoamine Oxidase: Structure, Function and Altered Functions"; Academic Press, New York, 1979.
(2) Quitkin, F.; Rifkin, A.; Klein, D. F. *Arch. Gen. Psychiatry* **1979**, *36*, 749.
(3) Blackwell, B. *Lancet* **1963**, *2*, 849.
(4) Johnston, P. J. *Biochem. Pharmacol.* **1968**, *17*, 1285.
(5) Knoll, J. *Trends Neurosci.* **1979**, 111.
(6) Knoll, J. In "Enzyme-Activated Irreversible Inhibitors"; Seiler, N.; Jung, M. J.; Koch-Weser, J., Eds; Elsevier/North Holland Biomedical Press: Amsterdam, 1978; p 253.
(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.
(10) Bey, P.; Schirlin, D. *Tetrahedron Lett.* **1978**, 5225.
(11) (a) Shen, T. Y.; Lucas, S.; Sarett, L. H. *Tetrahedron Lett.* **1961**, 43. (b) Kosuge, S.; Nakai, H.; Kurono, M. *Prostaglandins* **1979**, *18*, 737.
(12) An X-ray structural analysis of **5** was kindly undertaken by Professor R. Weiss at the Laboratoire de Cristallochimie, Institut Le Bel, Université Louis Pasteur, Strasbourg.
(13) Rat brain mitochondria were prepared[16] 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[^{14}C]-tryptamine (10 μM) and [^{14}C]phenethylamine (5 μM) as selective substrates for type A and type B, respectively.
(14) Kitz, R.; Wilson, I. B. *J. Biol. Chem.* **1962**, *237*, 3245.

0022-2623/84/1827-0009$01.50/0

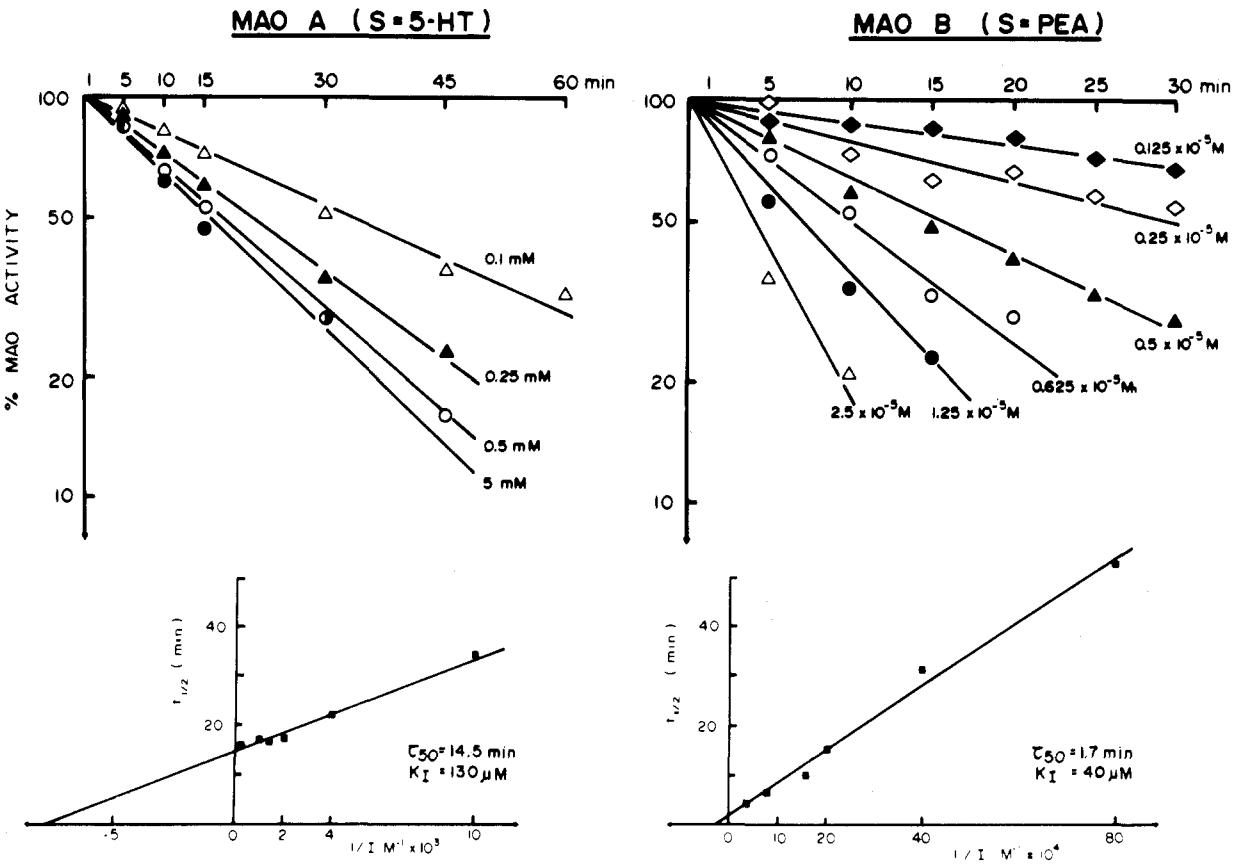


Figure 1. Time- and concentration-dependent inhibition of MAO A and MAO B by (*E*)-2-(3,4-dimethoxyphenyl)-3-fluoroallylamine (**5**). Rat brain mitochondrial MAO was preincubated with **5** at various concentrations at 10 °C in 0.1 M phosphate buffer (pH 7.2).[13] Kinetic parameters were calculated 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.

inhibitor[15] 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 μg/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 antidepressant[18] 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.

Acknowledgment. The authors thank S. Baltzer, Mrs. M. F. Jauch, and Mrs. M. L. Part for valuable technical assistance.

Registry No. 1, 93-40-3; 2, 85277-77-6; 3, 85277-86-7; 4, 85277-95-8; 5, 85278-66-6; monoamine oxidase, 9001-66-5.

(15) Abeles, R. H.; Maycock, A. L. *Acc. Chem. Res.* **1976**, *9*, 313.
(16) Christmas, A. J.; Coulson, C. J.; Maxwell, D. R.; Riddell, D. *Br. J. Pharmacol.* **1972**, *45*, 490.
(17) Fozard, J. R.; Spedding, J.; Palfreyman, M. G.; Wagner, J.; Möhring, J.; Koch-Weser, J. *J. Cardiovasc. Pharmacol.* **1980**, *2*, 229.
(18) Mann, J.; Gershon, S. *Life Sci.* **1980**, *26*, 877.
(19) Youdin, M. B. H.; Riederer, P.; Birkmayer, W.; Mendlewicz, J. In ref 1, p 477.
(20) Sandler, M.; Glover, V.; Elsworth, J. D.; Lewinsohn, R.; Reveley, M.A. In ref 1, p 447.

Philippe Bey, John Fozard, Jean Michel Lacoste
Ian A. McDonald,* Monique Zreika
Michael G. Palfreyman*
Merrell International Research Center
67084 Strasbourg Cedex, France
Received July 5, 1983