STEREOSELECTIVITY AND ISOENZYME SELECTIVITY OF MONOAMINE OXIDASE INHIBITORS: ENANTIOMERS OF α-METHYLBENZYLAMINE AND OTHER N-ALKYL DERIVATIVES

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Differentiation of the isoenzyme forms of MAO is accomplished by the use of specific substrates and inhibitors. Thus, 5-hydroxytryptamine (5-HT) is metabolized by MAO-A whereas ß-phenylethylamine (PEA) and benzylamine are specific substrates for MAO-B. Clorgyline and [R]-(-)-Deprenyl (N-propargyl-N-methylamphetamine) are highly selective irreversibe inhibitors of MAO-A and MAO-B respectively. This non-competitive irreversible inhibition by Clorgyline, Deprenyl and other propargylamine derivatives is preceded however by a competitive reversible phase (Fowler et al 1982).

The enantiomers of amphetamine, N-methylamphetamine and Deprenyl (which are homologues of PEA) have previously been studied as competitive inhibitors of MAO-A and MAO-B using a solubilised rat liver MAO preparation and shown to display considerable variation in their stereoselectivity and isoenzyme selectivity (Robinson 1985). The K_i values for the competitive inhibition of MAO-A and MAO-B by the enantiomers of α-methylbenzylamine, N-methyl- α-methylbenzylamine and N-methyl-N-propargyl- α-methylbenzylamine (α-Methyl-Pargyline) are now reported using a solubilised rat liver MAO preparation at 37° and pH 7.4 (Table I).

For the enantiomeric pairs of inhibitors studied in this report, inhibitors of the [R]-configuration were more potent inhbitors of both MAO-A and MAO-B and the MAO-B isoenzyme form was more sensitive to inhibition than MAO-A.

The high stereoselectivity and isoenzyme selectivity shown by [R]-(+)-α-methyl-Pargyline suggests that (±)-α-methyl-Pargyline would be an appropriate substitute for [R]-(-)-Deprenyl for the specific labelling of the MAO-B active site. However, further studies of the irreversible inhibition phase are required for confirmation.

Because of the stereoselectivity and isoenzyme selectivity of the above enantiomeric inhibitors and the related amphetamine derivatives, repetition of the above studies using a rat liver mitochondrial MAO preparation should aid in the detection of any possible enzyme structural changes accompanying membrane disruption and solubilisation of MAO.

	MAO-A	R/S	MAO-B	R/S	$\frac{\text{MAO-A}}{\text{MAO-B}}$
	K_m(5-HT) 327(±6)μM		K_m(PEA) 6.4(±.5)μM		
	K_i(μM)(±SD)		K_i(μM)(±SD)		
[R]-(+)-	331 (20)		42.9 (3.7)		7.72
α-Me-Benzylamine		.1790		.041	
[S]-(-)-	1851 (112)	R>S	1035 (88)	R>>S	1.79
[R]-(+)-	674 (38)		437 (66)		1.54
N-Me-α-Me-Benzylamine		.488			.27
[S]-(-)-	1378 (53)	R>S	1609 (42)	R>S	.86
[R]-(+)-	35.1 (1.9)		.193 (.03)		182
α-Me-Pargyline		.091		.00185	
[S]-(-)-	385 (10)	R>>S	104 (10)	R>>S	3.7

Table I. K_i values (competitive inhibition) of enantiomeric α-Me-Benzylamines towards MAO-A and MAO-B in a solubilised rat liver mitochondrial MAO preparation.

Fowler, C.J. et al (1982) Biochem. Pharmacol. 31:3555-3561
Robinson, J.B. (1985) Ibid. in press.