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EFFECT OF STRUCTURAL MODIFICATION OF ALKYL *N*-PROPARGYLAMINES ON THE SELECTIVE INHIBITION OF MONOAMINE OXIDASE B ACTIVITY

PETER H. YU,* BRUCE A. DAVIS and ALAN A. BOULTON

Neuropsychiatric Research Unit, Department of Psychiatry, University of Saskatchewan, Saskatoon, Saskatchewan, Canada S7N 0W0

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Abstract—A series of alkyl *N*-methyl-propargylamine derivatives has been discovered recently to be very potent selective irreversible monoamine oxidase B inhibitors (MAO-B). In the present study, we used a simple compound in this series, namely *N*-2-butyl-*N*-methylpropargylamine·HCl (2-BuMP), as the basic structure to investigate the effect of structural modification on the effectiveness and selectivity of the inhibition of MAO activities. When the *N*-methyl group was replaced by a hydrogen atom, an ethyl group or a propargyl group, MAO inhibitory activity was abolished. The modification of the propargyl group, e.g. to 3-butynyl, *N*-cyanomethyl or to allyl groups, also destroyed the inhibitory activity. The potency of the inhibitors was related to the carbon chain length of the alkyl group as well as to the substitution of the alpha or the terminal carbon atoms. Substitution of hydroxyl, carboxyl or carboethoxyl groups on the terminal carbon of the alkyl chain drastically reduced the inhibitory activity. More potent MAO inhibitory activity was observed for molecules with a single methyl group substitution on the alpha carbon in comparison with those substituted with two hydrogen or two methyl groups. Other branched alkyl *N*-methylpropargylamines, e.g. *N*-methyl-*N*-(3-pentyl)propargylamine, appeared to be slightly less selective in the inhibition of MAO-B activity. Some of these alkyl propargylamine MAO-B inhibitors, which do not possess the amphetamine-like moiety of L-deprenyl, may have significant neuropsychopharmacological implications.

Monoamine oxidase (MAO†; EC 1.4.3.4) is an enzyme that oxidizes monoamine neurotransmitters and neuromodulators, as well as exogenous bioactive monoamines [1, 2]; MAO inhibitors have been employed in the treatment of depression [3] for a number of years. MAO exists in two forms, namely MAO-A and MAO-B [4], which are now known to be derived from distinctly different gene loci [5]; these two forms are differentially distributed in neuronal and non-neuronal structures. MAO-A deaminates preferentially 5-hydroxytryptamine (5-HT) and is very sensitive to selective MAO-A inhibitors, such as clorgyline [*N*-(2,4-dichlorophenoxy-*n*-propyl)-*N*-methylpropargylamine]. MAO-B deaminates preferentially 2-phenylethylamine (PE) and is very sensitive to MAO-B inhibitors, such as deprenyl [phenylisopropyl-*N*-methylpropargylamine] [2]. Because MAO-A metabolizes 5-HT and noradrenaline and is a neuronal enzyme, it was only natural that most drug research emphasized MAO-A inhibitors. Relatively few MAO-B inhibitors have been developed.

The MAO-B inhibitor L-deprenyl (selegiline) has been used as an effective adjuvant to *l*-DOPA in the treatment of Parkinson's disease [6], reducing the requirement for *l*-DOPA in those cases where *l*-DOPA is being ingested. Recently, it has been reported that L-deprenyl by itself can delay significantly the onset of disability associated with early, otherwise untreated, cases of Parkinson's disease [7, 8]. L-Deprenyl, as well as other MAO inhibitors, has been shown to prevent 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridinium (MPTP) induced Parkinson-like neurotoxicity in animals [9]. MPTP itself does not cause the toxic effects, but is converted to toxic 1-methyl-4-phenylpyridine (MPP^+) by MAO-B in the brain. L-Deprenyl has been shown to rescue neurons by a mechanism not yet fully understood, which appears to be unrelated to the inhibition of MAO-B activity [10], and has also been found to improve the clinical condition of some Alzheimer's patients [11, 12] and depressives [13] and has been observed to prolong life span and improve sexual activity in rodents [14, 15] and humans [16]. Unlike MAO-A inhibitors, MAO-B inhibitors do not usually cause hypertensive crises (except after chronic large doses) and so possess the potential to become very useful neuropsychiatric and geriatric drugs.

MAO is known to be capable of deaminating aliphatic amines [17–19]. Recently, it has been demonstrated that straight chain aliphatic amines (number of carbon atoms ranging from 4 to 12) are readily metabolized by MAO-B [20]. The affinity of MAO-B for these aliphatic amines is quite high, i.e. the K_m values are in the low micromolar range, much lower than for other biogenic amines. The high affinity of these alkyl amines for the MAO-B site has led us recently to develop some *N*-alkyl *N*-methylpropargylamine derivatives as highly potent

* Corresponding author. Tel. (306) 966-8816; FAX (306) 966-8830.

† Abbreviations: MAO, monoamine oxidase; 5-HT, 5-hydroxytryptamine; PE, 2-phenylethylamine; and 2-BuMP, *N*-(2-butyl)-*N*-methylpropargylamine·HCl.

irreversible MAO-B inhibitors [21]. L-Deprenyl is a structural analog of amphetamine. It can be converted to *l*-methamphetamine and *l*-amphetamine *in vivo* [22, 23]. It has been suggested that the efficacy of deprenyl as an anti-Parkinson drug may result from its conversion to amphetamine [24]. L-Deprenyl is converted to *l*-amphetamine, which is, however, a behaviorally inactive form and does not cause withdrawal syndromes [25]. Unlike L-deprenyl, these alkyl *N*-methylpropargylamines do not possess the amphetamine moiety, which may have important neuropharmacological implications. In the present paper, further investigation of the relationship between the structures of the alkyl *N*-propargylamines and their inhibitory effects on MAO activity is described.

MATERIALS AND METHODS

Preparation of rat liver mitochondrial MAO. The liver mitochondrial fractions were prepared by differential centrifugation as previously described [2]. Mitochondrial membrane fragments were obtained by lysing the mitochondria in chilled distilled water followed by centrifugation at 105,000 *g* for 30 min. The membrane preparations were further washed, twice, by suspension in water followed by centrifugation. The resultant pellets were homogenized in water by repeated ultrasonic disruption at 75 W peak envelope power for 5 sec several times, using a needle probe tip (Braunsonic 1510, San Francisco, CA).

Rat liver MAO-A and MAO-B were obtained by treatments using selective MAO inhibitors. The mitochondrial membrane enzyme preparations were incubated with either L-deprenyl (1×10^{-6} M), an MAO-B inhibitor, or clorgyline (5×10^{-7} M), an MAO-A inhibitor, at room temperature for 30 min.

Monoamine oxidase assays. The radio-enzymatic assay for monoamine oxidase using ^{14}C-labeled substrates has been described previously [2]. The enzyme preparations were incubated at 37° for 30 min in the presence of the MAO-A substrate 5-HT (5×10^{-4} M, 0.1 μCi) and the MAO-B substrate PE (1×10^{-5} M, 0.1 μCi) in a final volume of 200 μL. The reactions were terminated by the addition of 200 μL of 2 M citric acid. The oxidized products were extracted into 1 mL toluene : ethyl acetate (1 : 1, v/v), of which 600 μL was then transferred to a counting vial containing 10 mL of Omnifluor fluid (New England Nuclear, Boston, MA, U.S.A.). Radioactivity was assessed by liquid scintillation spectrometry (Beckman LS-7500).

Synthesis of N-*alkyl*-N-*methylpropargylamines.* The new compounds were prepared by the general procedure as previously described [21]. Briefly, the appropriate alkyl bromides were condensed with *N*-propargylamine in the presence of a base, which may be either an extra equivalent of *N*-propargylamine or anhydrous sodium carbonate. Any unreacted *N*-methylpropargylamine (b.p. 82–84°) is readily removed during distillation of the solvent and in the water wash (solubility in water is infinite). The reaction may be carried out in ethanol, acetone or benzene, but yields are highest with absolute ethanol. *N*-Propargyl- and *N,N*-dipropargyl-*t*-amylamine were prepared by reaction of *t*-amylamine with one or two equivalents, respectively, of propargyl bromide in ethanol containing sodium bicarbonate. The compounds were crystallized as hydrochloride or oxalate salts.

The structural identities of the described compounds were ascertained by mass spectrometry, elemental analysis and PMR spectra. The mass spectra of all the compounds were characterized by a small molecular ion (typically less than 10% relative intensity) and a base peak (relative intensity 100%) arising by bond cleavage of the alkyl chain alpha to the nitrogen atom. Elemental analysis of carbon, nitrogen and hydrogen was conducted by Microanalysis Laboratories Ltd. (Markham, Ontario, Canada). The analyses were all within acceptable limits (± 0.4%). The PMR spectra were recorded by Dr. K. Brown (Department of Chemistry, University of Saskatchewan, Saskatoon, Saskatchewan, Canada), and provided confirmation of structural assignments by means of the chemical shifts and couplings of the alkyl or alkenyl group protons. The chemical shifts of the *N*-methyl and propargyl protons were affected very little by the different alkyl groups.

RESULTS AND DISCUSSION

The alkyl propargylamine inhibitors (at concentrations from 1×10^{-10} to 1×10^{-3} M) were preincubated with the MAO for 20 min at room temperature, and then the residual enzyme activities

Table 1. Structural relationship of alkyl propargylamines and MAO-B inhibitory activities

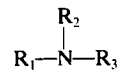
Inhibitors*	Functional groups†			MAO inhibition (IC_{50})	
	R_1	R_2	R_3	MAO-B	MAO-A
2-BuMP‡	$CH_3CH_2\underset{\displaystyle CH_3}{\underset{\vert}{CH}}-$	$-CH_3$	$-CH_2C{\equiv}CH$	$(1.4 \pm 0.1) \times 10^{-6}$ M	$(1.9 \pm 0.2) \times 10^{-5}$ M
1-BuMP‡	$CH_3CH_2CH_2CH_2-$	$-CH_3$	$-CH_2C{\equiv}CH$	$(1.4 \pm 0.1) \times 10^{-6}$ M	$(9.8 \pm 0.1) \times 10^{-5}$ M
2-BuPP	$CH_3CH_2\underset{\displaystyle CH_3}{\underset{\vert}{CH}}-$	$-H$	$-CH_2C{\equiv}CH$	$>1 \times 10^{-3}$ M	$>1 \times 10^{-3}$ M
1-BuEP	$CH_3CH_2CH_2CH_2-$	$-CH_2CH_3$	$-CH_2C{\equiv}CH$	$>1 \times 10^{-3}$ M	$>1 \times 10^{-3}$ M
2-ButPP	$CH_3CH{=}CHCH_2-$	$-CH_3$	$-CH_2C{\equiv}CH$	$(2.7 \pm 0.1) \times 10^{-6}$ M	$>1 \times 10^{-4}$ M
3-ButPP	$CH_2{=}CHCH_2CH_2-$	$-CH_3$	$-CH_2C{\equiv}CH$	$(3.2 \pm 0.2) \times 10^{-6}$ M	$>1 \times 10^{-4}$ M

Table 1. Continued

Inhibitors*	Functional groups†			MAO inhibition (IC_{50})	
	R_1	R_2	R_3	MAO-B	MAO-A
2-BuEP	$CH_3CH_2\underset{\displaystyle CH_3}{\overset{\displaystyle CH_3}{\underset{\displaystyle |}{CH}}}-$	$-CH_2CH_3$	$-CH_2C\equiv CH$	$>1 \times 10^{-4}$ M	$>1 \times 10^{-4}$ M
3-BuBuM	$CH_3CH_2\underset{\displaystyle CH_3}{\overset{\displaystyle CH_3}{\underset{\displaystyle |}{CH}}}-$	$-CH_3$	$-CH_2CH_2C\equiv CH$	$>1 \times 10^{-3}$ M	$>1 \times 10^{-3}$ M
CM2Bu	$CH_3CH_2\underset{\displaystyle CH_3}{\overset{\displaystyle CH_3}{\underset{\displaystyle |}{CH}}}-$	$-CH_3$	$-CH_2C\equiv N$	$>1 \times 10^{-3}$ M	$>1 \times 10^{-3}$ M
t-AMP	$CH_3CH_2\underset{\displaystyle CH_3}{\overset{\displaystyle CH_3}{\underset{\displaystyle |}{C}}}-$	$-CH_3$	$-CH_2C\equiv CH$	$(4.2 \pm 0.2) \times 10^{-5}$ M	$>1 \times 10^{-3}$ M
t-ADPP	$CH_3CH_2\underset{\displaystyle CH_3}{\overset{\displaystyle CH_3}{\underset{\displaystyle |}{C}}}-$	$-CH_2C\equiv CH$	$-CH_2C\equiv CH$	$>1 \times 10^{-3}$ M	$>1 \times 10^{-3}$ M
2-ABM	$CH_3CH_2\underset{\displaystyle CH_3}{\overset{\displaystyle CH_3}{\underset{\displaystyle |}{C}}}-$	$-CH_3$	$-CH_2C=CH_2$	$>1 \times 10^{-3}$ M	$>1 \times 10^{-3}$ M
2-HxMP‡	$CH_3(CH_2)_3\underset{\displaystyle CH_3}{\overset{}{\underset{\displaystyle |}{CH}}}-$	$-CH_3$	$-CH_2C\equiv CH$	$(8.3 \pm 0.2) \times 10^{-8}$ M	$(9.0 \pm 0.4) \times 10^{-5}$ M
1-HxMP	$CH_3(CH_2)_4\underset{\displaystyle CH_2CH_3}{\overset{}{\underset{\displaystyle |}{CH}}}-$	$-CH_3$	$-CH_2C\equiv CH$	$(3.1 \pm 0.1) \times 10^{-7}$ M	$(3.9 \pm 0.2) \times 10^{-4}$ M
M-3-PP‡	$CH_3CH_2\underset{\displaystyle CH_3}{\overset{}{\underset{\displaystyle |}{CH}}}-$	$-CH_3$	$-CH_2C\equiv CH$	$(1.8 \pm 0.1) \times 10^{-7}$ M	$(2.4 \pm 0.3) \times 10^{-6}$ M
3-MBMP	$CH_3\underset{\displaystyle OH}{\overset{}{\underset{\displaystyle |}{CH}}}CH_2CH_2-$	$-CH_3$	$-CH_2C\equiv CH$	$(8.9 \pm 0.9) \times 10^{-7}$ M	$(4.7 \pm 0.2) \times 10^{-5}$ M
6OH1HxMP‡	$\underset{\displaystyle OH}{\overset{}{\underset{\displaystyle |}{CH_2(CH_2)_5}}}-$	$-CH_3$	$-CH_2C\equiv CH$	$(1.2 \pm 0.1) \times 10^{-4}$ M	$>1 \times 10^{-3}$ M
6OH2HxMP‡	$\underset{\displaystyle OH}{\overset{}{\underset{\displaystyle |}{CH_2(CH_2)_3}}}\underset{\displaystyle CH_3}{\overset{}{\underset{\displaystyle |}{CH}}}-$	$-CH_3$	$-CH_2C\equiv CH$	$(1.3 \pm 0.1) \times 10^{-4}$ M	$>1 \times 10^{-3}$ M
3-CP-MPP‡	$-OOC(CH_2)_3\underset{\displaystyle C_2H_5}{\overset{}{\underset{\displaystyle |}{CH}}}-$	$-CH_3$	$-CH_2C\equiv CH$	$>1 \times 10^{-3}$ M	$>1 \times 10^{-3}$ M
5-CE2P-MP‡	$OOC(CH_2)_3\underset{\displaystyle CH_3}{\overset{}{\underset{\displaystyle |}{CH}}}-$	$-CH_3$	$-CH_2C\equiv CH$	$>1 \times 10^{-4}$ M	$>1 \times 10^{-4}$ M

* 2-BuMP: *N*-(2-butyl)-*N*-methylpropargylamine · HCl
1-BuMP: *N*-(1-butyl)-*N*-methylpropargylamine · HCl
2-BuPP: *N*-(2-butyl)-propargylamine · HCl
1-BuEP; *N*-(1-butyl)-*N*-ethylpropargylamine · oxalate
2-ButPP: *N*-(2-buten-1-yl)-*N*-methylpropargylamine · HCl
3-ButPP: *N*-(3-buten-1-yl)-*N*-methylpropargylamine · HCl
2-BuEP: *N*-(2-butyl)-*N*-ethylpropargylamine · oxalate
3-BuBuM: *N*-(3-butynyl)-*N*-(2-butyl)-methylamine · HCl
CM2Bu: *N*-cyanomethyl-*N*-(2-butyl)-methylamine · oxalate
t-AMP: *N*-(*t*-amyl)-*N*-methylpropargylamine · HCl
t-ADPP: *N*,*N*-dipropargyl-*t*-amylamine · HCl
2-ABM: *N*-allyl-*N*-(2-butyl)methylamine · HCl
2-HxMP: *N*-(2-hexyl)-*N*-methylpropargylamine · HCl
1-HxMP: *N*-(1-hexyl)-*N*-methylpropargylamine · HCl
M-3-PP: *N*-(3-pentyl)-*N*-methylpropargylamine · oxalate
3-MBMP: *N*-(3-methylbutyl)-*N*-methylpropargylamine · HCl
6OH1HxMP: *N*-(6-hydroxyl-1-hexyl)-*N*-methylpropargylamine · HCl
6OH2HxMP: *N*-(6-hydroxyl-2-hexyl)-*N*-methylpropargylamine · HCl
3-CP-MPP: *N*-(3-carboxy-1-propyl)-*N*-methylpropargylamine · oxalate
5-CE2P-MP: *N*-(5-carbethoxy-2-pentyl)-*N*-methylpropargylamine · HCl

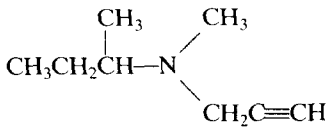
† General formula of the compounds:



‡ Data have been reported previously [21] and are listed here for the purpose of comparison of the structure–activity relationship for the series of compounds.

were determined. MAO-A and MAO-B activities from rat liver mitochondrial membranes were assessed using 5-HT (5×10^{-4} M) and PE (1×10^{-5} M) as substrates, respectively. The straight-chain unsubstituted aliphatic propargylamines are all selective MAO-B inhibitors with MAO-A/MAO-B ratios of their IC_{50} values ranging from 10 to 1000 [21]. We have synthesized thirteen new alkyl propargylamine derivatives structurally closely related, and their inhibitory activities (IC_{50}) towards MAO-A and MAO-B have been compared. As can be seen in Table 1, these alkyl *N*-propargylamines exhibited quite variable inhibitory activity towards the MAOs.

The structure of the known MAO-B inhibitor, *N*-(2-butyl)-*N*-methylpropargylamine · HCl (2-BuMP), i.e.



was modified in each of the three groups attached to the nitrogen atom. Thus, *N*-(2-butyl)-propargylamine and *N*-(2-butyl)-*N*-ethylpropargylamine, which are different from 2-BuMP in that the *N*-methyl group has been replaced by a hydrogen atom or an ethyl group, respectively, were totally inactive towards MAO. The propargyl group was also essential for MAO inhibition, since replacing it with a 3-butynyl group, i.e. *N*-(3-butynyl)-*N*-(2-butyl)-methylamine, also caused a complete loss of MAO inhibitory activity. That *N*-allyl-*N*-(2-butyl)methylamine and *N*-cyanomethyl-*N*-methyl-2-butylamine were incapable of inactivating MAO demonstrates that the propargyl triple bond is essential.

Regarding substitutions at the alpha carbon, short alkyl chain compounds, such as the *N*-butyl derivatives, exhibited no apparent difference from the straight chain *N*-(1-butyl)-*N*-methylpropargylamine and the branched chain 2-BuMP in the inhibition of MAO-B activity. Substitution at the alpha carbon of alkyl *N*-propargylamines with a longer alkyl chain (i.e. three or more carbon atoms), however, did have an effect in that compounds with a methyl group on the alpha carbon were more potent inhibitors than those without. *N*-(2-Hexyl)-*N*-methylpropargylamine, for example, was more potent than *N*-(1-hexyl)-*N*-methylpropargylamine (Table 1), which is consistent with our earlier findings with regard to the pentyl and heptyl *N*-methylpropargylamines [21]. When two methyl groups were present on the alpha carbon [i.e. *N*-(*t*-amyl)-*N*-methylpropargylamine], the MAO-B inhibition potency was reduced considerably. Substitution with two propargyl groups, e.g. *N,N*-dipropargyl-*t*-amylamine, abolished the MAO inhibitory activity. *N*-(3-Pentyl)-*N*-methylpropargylamine, a compound in which an ethyl group has been attached to the alpha carbon, also exhibited a quite potent MAO-B inhibiting effect; its selectivity, however, appeared to be decreased considerably. If the branching is at the carbon terminal as is the case for *N*-(3-methylbutyl)-*N*-methylpropargylamine, the MAO-B inhibition selectivity was not affected. An olefinic bond in the alkyl side chain, e.g. *N*-(3-buten-1-yl)-*N*-methylpropargylamine and *N*-(2-buten-1-yl)-*N*-methylpropargylamine, affected neither the potency nor the selectivity of inhibition of MAO-B activity. The introduction of a double bond in the aliphatic chain, however, reduced the inhibitory activity towards MAO-A. Such a modification would make the aliphatic chain more rigid and somewhat less lipophilic, which may cause a reduction in the affinity between the inhibitors and the MAO-A site. 2-ButPP and 3-ButPP are, therefore, more selective MAO-B inhibitors than 2-BuMP.

Introduction of a hydroxyl group on the carbon terminal reduced the MAO inhibitory activity. When the carbon terminal was substituted with a carboxyl or a carboethoxy group, however, the MAO inhibitory activity was reduced even more. It is unknown whether this was due to incompatibility of configuration or altered lipophilicity that affected the binding of these compounds with MAO.

A number of *N*-methylpropargylamine derivatives have been discovered to be either MAO-A or MAO-B inhibitors [26–29]. For the most part these compounds contain an aromatic moiety, such as phenyl, furanyl or indanyl [27, 30]. We have shown recently that the aromatic group can be replaced by simple alkyl groups without affecting MAO inhibitory activity [21]. Since alkyl amines with 5 to 10 carbons possess a very high affinity for the MAO-B site [20], it was not unexpected that alkyl *N*-methyl-propargylamines turned out to be quite potent and selective MAO-B inhibitors. A series of these alkyl *N*-propargylamines has now been employed in the investigation of the relationship of structure to the inhibition of MAO activity. It can be concluded that the presence of both a propargyl group and a methyl group on the nitrogen atom is essential for providing an optimal configuration that is compatible with the flavine site on both MAO-A and MAO-B. Both MAO-A and MAO-B possess the same primary structure adjacent to the flavine site [31, 32], and therefore these flavine sites should possess a similar configuration so as to fit the *N*-methylpropargyl moiety of the inhibitors. The remainder of the molecule, that is the alkyl or aromatic groups, determines the affinity and selectivity with respect to MAO-A or MAO-B substrate sites. Although the tertiary structures of the amine substrate sites have not been established, MAO-A and MAO-B substrate sites appear to possess different hydrophobicity. Alkyl alcohols, such as hexan-1-ol and octan-1-ol, exhibit a selective and reversible, although rather weak, inhibitory effect on MAO-B [33]. When the carbon chain length of the aliphatic alcohols is decreased, the potency of inhibition of MAO-B activity is reduced. This phenomenon is consistent with the observed tendency of MAO-B inhibition by the alkyl *N*-methylpropargylamines to be also related to the carbon chain length; however, the propargyl compounds are highly potent and irreversible inhibitors [21]. There is evidence that the nature of the lipid environment may influence inhibitor specificity and sensitivity [34]. The possibility that the high affinity of alkyl groups towards MAO-B sites may be due to an interaction

with the lipid micro-environment cannot be ruled out. The potency of the alkyl *N*-propargylamine derivatives in inhibiting MAO-B activity may, therefore, be related to the local inhibitor concentration in the region of the active centers of the enzyme due to enhanced lipid partition of the alkyl compounds.

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