Journal of Enzyme Inhibition and Medicinal Chemistry, August 2003 VOL. 18 (4), pp. 339–347

Taylor & Francis healthsciences

Monoamine Oxidase Inhibitory Properties of Optical Isomers and *N*-substituted Derivatives of 4-methylthioamphetamine

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(Received 29 January 2003; In final form 10 March 2003)

(±)-4-Methylthioamphetamine (MTA) was resolved into its enantiomers, and a series of *N*-alkyl derivatives of the parent compound, as well as its α-ethyl analogue, were prepared. The monoamine oxidase (MAO) inhibitory properties of these substances were evaluated *in vitro*, using a crude rat brain mitochondrial suspension as the source of enzyme. All compounds produced a selective, reversible and concentration-related inhibition of MAO-A. (+)-MTA proved to be the most potent inhibitor studied, while all the other derivatives were less active than the parent compound, with (−)-MTA being about 18 times less potent than the (+) isomer. The analysis of structure–activity relationships indicates that the introduction of alkyl substituents on the amino group of MTA leads to a reduction in the potency of the derivatives as MAO-A inhibitors, an effect which increases with the size of the substituent.

Keywords: Monoamine oxidase; 4-methylthioamphetamine; MAO inhibitors; Amphetamine derivatives; Structure–activity relationships; Antidepressants

INTRODUCTION

Monoamine oxidase (EC 1.4.3.4, amine: O_2 oxido-reductase, MAO), which catalyzes the oxidative deamination of a variety of monoamines such as catecholamines and serotonin (5-HT), exists in two different isoforms (MAO-A and -B) that are distinguishable by their substrate selectivity, inhibitor sensitivity and amino acid sequence.[1–3] Non-selective and irreversible MAO inhibitors (MAOI) have been used as effective antidepressants, but severe side effects have limited their use.[4–6] More recently developed, selective and reversible inhibitors of the A-isoform (MAOI-A) exhibit antidepressant actions while they appear to have less side effects than their irreversible predecessors.[7–9]

An extensive series of phenylisopropylamines, including amphetamine itself, has been evaluated as MAOI.[10–14] Several of these studies have assessed the influence of different substituents on the aromatic ring of the phenylisopropylamine molecule (in particular at the *para* position), upon MAO inhibitory properties. However, there is no consistent information about how the alkylation of the amino group of phenylisopropylamines might modify the potency and selectivity of these molecules.

Several years ago, (±)-4-methylthioamphetamine (MTA) was shown to be a potent, selective, non-neurotoxic inducer of serotonin (5-HT) release from rat frontal cortical slices.[15] More recently, microdialysis studies in anesthetized rats showed that MTA produces a rapid and persistent increase in 5-HT basal release in the hippocampus, and this drug was also found to be a potent, selective, reversible inhibitor of MAO-A,[14,16] suggesting that it might serve as a lead for the development of novel antidepressants with a short onset of action. All these results, however, were obtained with the racemic

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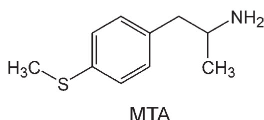
ISSN 1475-6366 print/ISSN 1475-6374 online © 2003 Taylor & Francis Ltd
DOI: 10.1080/1475636031000118437

modification of the drug. In addition, MTA has recently gained certain notoriety as a street drug, and one case of poisoning has been attributed to its ingestion.[17,18,19]



Based on these precedents, the goal of the present study was to evaluate the MAO inhibitory properties of the optical isomers and of a series of *N*-alkyl derivatives of MTA, as well as its α-ethyl homologue, in order to contribute to a better understanding of the structural requirements necessary for effective inhibition of the enzyme by phenylisopropylamines. Finally, some structure–activity relationships for this series of drugs are discussed.

MATERIALS AND METHODS

Reagents

All the chemicals used were of the highest grade commercially available. Tetrahydrofuran and acetonitrile were Merck HPLC grade. 5-HT, 5-hydroxyindoleacetic acid, yeast aldehyde dehydrogenase and β-nicotinamide dinucleotide were from Sigma (St. Louis, MO, USA). *l*-Deprenyl was generously donated by Prof. J. Knoll (Semmelweis University of Medicine, Hungary). 4-Methylthiobenzaldehyde, 4-dimethylaminophenylacetic acid and all other reagents were purchased from Aldrich Chemical Co. (Milwaukee, WI, USA).

General Methods

Melting points were determined on a Reichert-Jung Galen III Kofler hot stage and are uncorrected. Optical rotations were determined with a Schmidt-Haensch Polartronic electronic polarimeter. NMR spectra were recorded in $CDCl_3$ or D_2O using a Bruker AMX 300 instrument, operating at 300.13 (^1H) or 75.03 (^{13}C) MHz. Chemical shifts are reported in δ values (ppm relative to tetramethylsilane as an internal reference).

Synthesis

(±)-1-(4-Methylthiophenyl)-2-aminopropane (MTA)

A mixture of 4-methylthiobenzaldehyde (10 mL, 75 mmol), dry ammonium acetate (6.0 g, 81 mmol), nitroethane (55 mL) and toluene (100 mL) was refluxed overnight under a Dean–Stark trap. The mixture was concentrated to 70 mL and stored overnight at −20°C. 1-(4-Methylthiophenyl)-2-nitropropene was collected by filtration (8.5 g) as bright yellow crystals. The mother liquors were evaporated under reduced pressure, and the dark reddish brown oily residue was diluted with hot methanol (80 mL). On cooling, another fraction of the nitropropene crystallized (5.3 g) sufficiently pure for use in the next synthetic step. After removal of the solvent, the residue was partitioned between H_2O and $CHCl_3$, and the organic layer was dried with Na_2SO_4, concentrated and fractionated over a silica gel column, eluting with $CHCl_3$. In this way, additional nitropropene was recovered (0.5 g) which was recrystallized from methanol (total yield 91%) m.p. 73–74.5°C; ^1H NMR ($CDCl_3$) δ 2.46 (s, 3H, S-CH_3), 2.52 (s, 3H, C-CH_3), 7.28–7.36 (A_2B_2 system, 4H, $J = 8$ Hz, Ar-*H*), 8.04 (s, 1H, Ar-C*H*); ^{13}C NMR ($CDCl_3$) δ 14.09 (S-CH_3), 14.95 (C-1), 125.81 (C-2′/C-6′), 128.51 (C-2), 130.44 (C-3′/C-5′), 142.12 (C-1′), 146.80 (C-4′). A solution of the nitropropene (13.0 g, 62 mmol) in dry THF (100 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (13.0 g, 342 mmol) in dry THF (200 mL). The reaction mixture was refluxed in an oil bath for 24 h and then cooled in an ice/water bath and the reaction quenched by cautious addition of H_2O (15 mL), 40% NaOH (13 mL) and again H_2O (45 mL). The suspension was filtered, rinsing the cake well with THF. The solvent was removed under reduced pressure to yield MTA as a light yellow oil which was distilled under vacuum (150°C, 0.1 Torr) giving a colorless product (10.0 g, 55 mmol, 81%). ^1H NMR ($CDCl_3$) δ 1.08 (d, 3H, $J =$ 6.3 Hz, CHCH_3), 2.44 (s, 3H, S-CH_3), 2.47 (dd, 1H, $J =$ 13.4 Hz, $J' = 8.0$, CH_2CH), 2.64 (dd, 1H, $J = 12.8$, $J' =$ 7.9 Hz, CH_2CH), 3.11 (m, 1H, 6.3 Hz, CH_3C*H*), 7.08–7.19 (A_2B_2 system, 4H, $J = 8.2$ Hz, Ar-*H*); MTA·HCl (*i*-PrOH-Et_2O) m.p. 190–192°C, ^1H NMR (D_2O) δ 1.22 (d, 3H, $J = 6.6$ Hz, CHCH_3), 2.42 (s, 3H, S-CH_3), 2.84 (d, 2H, $J = 7.1$ Hz, CH_2CH), 3.55 (m, 1H, 6.8 Hz, CH_3C*H*), 7.19 (d, 2H, $J = 8.2$ Hz, Ar-*H*), 7.36 (d, 2H, $J = 8.2$ Hz, Ar-*H*). Found C, 55.20; H, 7.42; N, 6.68; S, 12.84. $C_{10}H_{16}ClNS$ requires C, 55.16; H, 7.41; N, 6.43; S, 14.72%.

(±)-N-Methyl-1-(4-methylthiophenyl)-2-aminopropane (NMMTA)

To a solution of MTA (1.8 g, 9.7 mmol) in $CHCl_3$ (30 mL), ethyl chloroformate (5 mL, 52 mmol) was added. The reaction was refluxed for 8 h and the solvent was removed to give *N*-ethoxycarbonyl-MTA (2.2 g, 89%) as a colorless oil which was used without further purification; ^1H NMR ($CDCl_3$) δ 1.10 (d, 3H, $J = 6.6$ Hz, CHCH_3), 1.21 (t, 3H, $J = 7.1$ Hz, O-CH_2CH_3), 2.48 (s, 3H, S-CH_3), 2.64 (dd, 1H, $J =$ 13.5 Hz, $J' = 7.1$, CH_2CH), 2.80 (dd, 1H, $J = 13.5$, $J' =$ 5.6 Hz, CH_2CH), 3.93 (m, 1H, CH_3C*H*), 4.08 (q, 2H, $J = 7.1$ Hz, O-C$H_2$$CH_3$), 4.52 (br s, 1H, N-H), 7.10 (d, 2H, $J = 8.2$ Hz, Ar-*H*), 7.20 (d, 2H, $J = 8.2$ Hz, Ar-*H*). To a stirred suspension of $LiAlH_4$ (2.6 g, 68 mmol) in

anhydrous ethyl ether (150 mL), a solution of the former product (3.0 g, 12 mmol) in anhydrous ethyl ether (50 mL) was added. The mixture was refluxed for 24 h and the excess hydride was destroyed by addition of dilute H_2SO_4 (20 g in 500 mL H_2O) until a clear solution was obtained. The organic phase was separated and the aqueous layer was extracted with ethyl ether (70 mL) and then with CH_2Cl_2 (2 × 80 mL). The mixture was made basic to pH 9 with 40% NaOH and extracted with CH_2Cl_2 (3 × 150 mL). These extracts were pooled, dried with anhydrous Na_2SO_4 and the solvent removed under vacuum. The residual light yellow oil was distilled under reduced pressure (150°C, 0.1 Torr) to afford a colorless product (1.5 g, 68%). ^1H NMR ($CDCl_3$) δ 1.04 (d, 3H, $J = 6.1$ Hz, CHCH_3), 2.43 (s, 3H, N-CH_3), 2.47 (s, 3H, S-CH_3), 2.58 (dd, 1H, $J = 12.9$ Hz, $J' = 6.3$ Hz, CH_2CH), 2.68 (dd, 1H, $J = 13.2$ Hz, $J' = 6.8$ Hz, CH_2CH), 2.75 (m, 1H, $J = 6.4$ Hz, CH_3CH), 7.11 (d, 2H, $J = 8.2$ Hz, Ar-H), 7.20 (d, 2H, $J = 8.2$ Hz, Ar-H). NMMTA·HCl (*i*-PrOH-Et_2O) m.p. 169–171°C; ^1H NMR (D_2O) δ 1.22 (d, 3H, $J = 6.6$ Hz, CHCH_3), 2.46 (s, 3H, S-CH_3), 2.67 (s, 3H, N-CH_3), 2.82 (dd, 1H, $J = 13.8$ Hz, $J' = 6.3$ Hz, CH_2CH), 3.01 (dd, 1H, $J = 13.8$ Hz, $J' = 6.1$ Hz, CH_2CH), 3.47 (m, 1H, $J = 6.4$ Hz, CH_3CH), 7.22 (d, 2H, $J = 8.2$ Hz, Ar-H), 7.30 (d, 2H, $J = 8.2$ Hz, Ar-H). Found C, 57.09; H, 7.88; N, 6.31; S, 12.40. $C_{11}H_{18}ClNS$ requires C, 57.00; H, 7.83; N, 6.05; S, 13.83%.

(±)-N,N-Dimethyl-1-(4-methylthiophenyl)-2-aminopropane (DMMTA)

To a stirred solution of MTA hydrochloride (0.20 g, 0.11 mmol) in a mixture of MeOH (8 mL) and 40% formaldehyde solution (2.4 mL) was added $NaCNBH_4$ (0.90 g, 14 mmol). The pH was kept near 6 by the occasional addition of HCl. When the pH was stable (after about 48 h), the reaction mixture was poured into H_2O (70 mL) and made strongly basic by the addition of aqueous NaOH. The solution was extracted with CH_2Cl_2 (3 × 20 mL), the extracts pooled, and extracted with dilute H_2SO_4 (3 × 20 mL). The pooled acidic extracts were made basic and again extracted with CH_2Cl_2, and the solvent was removed under vacuum to give 0.17 g (73%) of a colorless oil. ^1H NMR ($CDCl_3$) δ 1.00 (d, 3H, $J = 6.6$ Hz, CHCH_3), 2.43 (dd, 1H, $J = 12.9$ Hz, $J' = 2.8$ Hz, CH_2CH), 2.45 (s, 6H, N-$(CH_3)_2$), 2.47 (s, 3H, S-CH_3), 2.95 (m, 1H, CH_3CH), 3.10 (dd, 1H, $J = 13.0$ Hz, $J' = 4.2$ Hz, CH_2CH), 7.11 (d, 2H, $J = 8.2$ Hz, Ar-H), 7.20 (d, 2H, $J = 8.2$ Hz, Ar-H). DMMTA·HCl (*i*-PrOH-Et_2O) m.p. 163–165°C; ^1H NMR (D_2O) δ 1.18 (d, 3H, $J = 6.6$ Hz, CHCH_3), 2.44 (s, 3H, S-CH_3), 2.80 (s, 6H, N-$(CH_3)_2$, partially masking m, 1H, CH_2CH), 3.06 (dd, 1H, $J = 13.6$ Hz, $J' = 5.2$ Hz, CH_2CH), 3.61 (m, 1H, CH_3CH), 7.22 (d, 2H, $J = 8.2$ Hz, Ar-H), 7.28 (d, 2H, $J = 8.2$ Hz, Ar-H). Found C, 58.53; H, 8.21; N, 5.95; S, 10.88. $C_{12}H_{20}ClNS$ requires C, 58.64; H, 8.20; N, 5.70; S, 13.04%.

(±)-N-Ethyl-1-(4-methylthiophenyl)-2-aminopropane (NEMTA)

To a stirred solution of MTA (1.0 g, 5.5 mmol) in pyridine (5.2 mL), was added acetic anhydride (0.7 g, 6.7 mmol) and the mixture was stirred at room temperature for 30 min. The mixture was poured into H_2O (60 mL) and made acidic with HCl. The aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL), the extracts pooled, washed with dilute HCl and dried with anhydrous Na_2SO_4. The solvent was removed under vacuum to give 1.1 g (89%) of 1-(4-methylthiophenyl)-2-acetamidopropane, pure enough for the next synthetic step. ^1H NMR ($CDCl_3$) δ 1.09 (d, 3H, $J = 6.7$ Hz, CHCH_3), 1.93 (s, 3H, COCH_3), 2.47 (s, 3H, S-CH_3), 2.67 (dd, 1H, $J = 13.5$ Hz, $J' = 7.2$ Hz, CH_2CH), 2.79 (dd, 1H, $J = 13.6$ Hz, $J' = 5.7$ Hz, CH_2CH), 4.23 (m, 1H, $J = 6.9$ Hz, CH_3CH), 7.09 (d, 2H, $J = 8.2$ Hz, Ar-H), 7.20 (d, 2H, $J = 8.2$ Hz, Ar-H). To a stirred suspension of $LiAlH_4$ (1.0 g, 26 mmol) in anhydrous THF (80 mL), a solution of the former product (1.1 g, 4.9 mmol) in anhydrous THF (5 mL) was added. The mixture was refluxed for 4 days and the excess hydride was carefully destroyed by addition of H_2O (1 mL), followed by 40% NaOH (1 mL) and additional H_2O (3 mL). The solid was filtered and washed with THF (20 mL). The solvent was removed under vacuum to give 0.92 g of a light brown oil. This product was distilled under vacuum (180°C, 0.1 mm Hg) yielding 0.75 g (73%) of a colorless oil. ^1H NMR ($CDCl_3$) δ 1.06 (overlapping d and t, 6H, CHCH_3 and N-CH_2CH_3), 2.46 (s, 3H, S-CH_3), 2.58 (overlapping m, 2H, N-C$H_2$$CH_3$ and CH_2CH), 2.71 (overlapping m, 2H, N-C$H_2$$CH_3$ and CH_2CH), 2.89 (m, 1H, $J = 6.4$ Hz, CH_3CH), 7.10 (d, 2H, $J = 8.2$ Hz, Ar-H), 7.20 (d, 2H, $J = 8.2$ Hz, Ar-H). NEMTA·HCl (*i*-PrOH-Et_2O) m.p. 184–187°C; ^1H NMR (D_2O) δ 1.2 (overlapping d and t, 6H, CHCH_3 and N-CH_2CH_3), 2.44 (s, 3H, S-CH_3), 2.74 (dd, 1H, $J = 13.5$ Hz, $J' = 8.9$ Hz, CH_2CH), 3.08 (overlapping m, 3H, N-C$H_2$$CH_3$ and CH_2CH), 3.48 (m, 1H, $J = 6.4$ Hz, CH_3CH), 7.20 (d, 2H, $J = 8.2$ Hz, Ar-H), 7.28 (d, 2H, $J = 8.2$ Hz, Ar-H). Found C, 58.56; H, 8.23; N, 5.97; S, 11.42. $C_{12}H_{20}ClNS$ requires C, 58.64; H, 8.20; N, 5.70; S, 13.04%.

(±)-N,N-Diethyl-1-(4-methylthiophenyl)-2-aminopropane (DEMTA)

To molecular sieves (1.0 g) in DMF (15 mL), KOH (0.25 g, 4.5 mmol) was added and the suspension was vigorously stirred for 10 min. MTA (0.8 g, 4.5 mmol) was added and stirring was continued for 30 min. Finally, iodoethane (1.0 mL, 7.7 mmol) was added. The reaction mixture was left at room temperature

for 24 h. The solid was filtered and washed with EtOAc. The solvent was removed under vacuum, NaOH (2N, 40 mL) was added and the mixture was extracted with EtOAc (4 × 20 mL). The extracts were pooled, washed with saturated brine and dried with anhydrous Na_2SO_4. The solvent was removed under vacuum and the crude mixture was purified over a flash column eluting with $CHCl_3$/MeOH/NH_3 (90/9/1), to give 0.37 g (35%) of DEMTA. ^{1}H NMR ($CDCl_3$) δ 0.91 (d, 3H, *J* = *6.5* Hz, CHC*H*$_3$), 1.05 (t, 6H, *J* = 7.1 Hz, N-(CH_2C*H*$_3$)$_2$), 2.35 (dd, 1H, *J* = 12.9 Hz, *J*′ = 9.4 Hz, C*H*$_2$CH), 2.46 (s, 3H, S-C*H*$_3$), 2.54 (m, 4H, N-(C*H*$_2$$CH_3$)$_2$), 2.88 (dd, 1H, *J* = 12.7 Hz, *J*′ = 4.2 Hz, C*H*$_2$CH), 2.98 (m, 1H, *J* = 6.5 Hz, CH_3C*H*), 7.09 (d, 2H, *J* = 8.2 Hz, Ar-*H*), 7.19 (d, 2H, *J* = 8.2 Hz, Ar-*H*). DEMTA• HBr (*i*-PrOH-Et_2O) m.p. 149–151°C; ^{1}H NMR (D_2O) δ 1.19 (d, 3H, *J* = *6.7* Hz, CHC*H*$_3$), 1.29 (t, 6H, *J* = 5.7 Hz, N-(CH_2C*H*$_3$)$_2$), 2.45 (s, 3H, S-C*H*$_3$), 2.81 (dd, 1H, *J* = 13.4 Hz, *J*′ = 9.8 Hz, C*H*$_2$CH), 3.08 (dd, 1H, *J* = 13.5 Hz, *J*′ = 5.0 Hz, C*H*$_2$CH), 3.24 (m, 4H, N-(C*H*$_2$$CH_3$)$_2$), 3.72 (m, 1H, *J* = 6.3 Hz, CH_3C*H*), 7.24 (d, 2H, *J* = 8.2 Hz, Ar-*H*), 7.32 (d, 2H, *J* = 8.2 Hz, Ar-*H*). Found C, 52.92; H, 7.68; N, 4.63; S, 8.36; $C_{14}H_{24}BrNS$ requires C, 52.83; H, 7.60; N, 4.40; S, 10.07%.

N-Propyl-1-(4-methylthiophenyl)-2-aminopropane (NPMTA)

To molecular sieves (1.0 g) in DMF (15 mL), KOH (0.25 g, 4.5 mmol) was added and the suspension was vigorously stirred for 10 min. MTA (0.8 g, 4.5 mmol) was added and stirring was continued for 30 min. Finally, bromopropane (1.0 mL, 7.7 mmol) was added. The reaction mixture was left at room temperature for 24 h. The solid was filtered and washed with EtOAc. The solvent was removed under vacuum, NaOH (2N, 40 mL) was added and the mixture was extracted with EtOAc (4 × 20 mL). The extracts were pooled, washed with saturated brine and dried with anhydrous Na_2SO_4. The solvent was removed under vacuum and the crude mixture was purified over a flash column eluting with $CHCl_3$/MeOH/NH_3 (94/5/1), to give 0.37 g (35%) of NPMTA. ^{1}H NMR ($CDCl_3$) δ 0.87 (t, 3H, *J* = 7.4 Hz, N-CH_2CH_2C*H*$_3$), 1.05 (d, 3H, *J* = 6.2 Hz, CHC*H*$_3$), 1.45 (m, 2H, N-CH_2C*H*$_2$$CH_3$), 2.46 (s, 3H, S-C*H*$_3$), 2.5–2.7 (overlapping m, 4H, N-C*H*$_2$$CH_2CH_3$ and C*H*$_2$CH), 2.87 (m, 1H, C*H*CH_3), 7.10 (d, 2H, *J* = 8.2 Hz, Ar-*H*), 7.20 (d, 2H, *J* = 8.2 Hz, Ar-*H*). NPMTA·HCl (*i*-PrOH-Et_2O) m.p. 173–175°C; ^{1}H NMR (D_2O) δ 0.91 (t, 3H, *J* = 7.5 Hz, N-CH_2CH_2-C*H*$_3$), 1.20 (d, 3H, *J* = *6.6* Hz, CHC*H*$_3$), 1.63 (m, 2H, N-CH_2C*H*$_2$$CH_3$), 2.45 (s, 3H, S-C*H*$_3$), 2.76 (dd, 1H, *J* = 13.7 Hz, *J*′ = 8.9 Hz, C*H*$_2$CH), 3.0 (overlapping m, 3H, N-C*H*$_2$$CH_2CH_3$ and C*H*$_2$CH), 3.50 (m, 1H, CH_3C*H*), 7.22 (d, 2H, *J* = 8.2 Hz, Ar-*H*), 7.30 (d, 2H, *J* = 8.3 Hz, Ar-*H*). Found C, 59.82; H, 8.35; N, 5.79; S, 10.93. $C_{13}H_{22}ClNS$ requires C, 60.32; H, 8.18; N, 5.41; S, 12.38%.

N-Allyl-1-(4-methylthiophenyl)-2-aminopropane (NAMTA) And N,N*-diallyl-1-(4-methylthiophenyl)-2-aminopropane (DAMTA)*

To molecular sieves (0.3 g) in DMF (6 mL) was added KOH (0.06 g, 1.1 mmol) and the suspension was vigorously stirred for 10 min. MTA (0.20 g, 1.1 mmol) was added and stirring was continued for 30 min. Finally, allyl bromide (0.3 mL, 3.3 mmol) was added. The reaction mixture was left at room temperature for 24 h. The solid was filtered and washed with EtOAc. The solvent was removed under vacuum, NaOH (2N, 40 mL) was added, and the mixture was extracted with EtOAc (4 × 20 mL). The extracts were pooled, washed with saturated brine and dried with anhydrous Na_2SO_4. The solvent was removed under vacuum and the mixture of products was fractionated over a flash column eluting with (EtOAc/EtOH 9:1) to give 0.06 g (25%) of NAMTA and 0.14 g (49%) of DAMTA. NAMTA: ^{1}H NMR ($CDCl_3$) δ 1.06 (d, 3H, *J* = *6.3* Hz, CHC*H*$_3$), 2.47 (s, 3H, S-C*H*$_3$), 2.59 (dd, 1H, *J* = 13.4 Hz, *J*′ = 6.9 Hz, C*H*$_2$CH), 2.76 (dd, 1H, *J* = 13.4 Hz, *J*′ = 6.5 Hz, C*H*$_2$CH), 2.95 (m, 1H, *J* = 6.5 Hz, CH_3C*H*), 3.23 (dd, 1H, *J* = 13.9 Hz, *J*′ = 5.4 Hz, N-C*H*$_2$CH=CH_2), 3.34 (dd, 1H, *J* = 13.9 Hz, *J*′ = 5.9 Hz, N-C*H*$_2$CH=CH_2), 5.09 (dd, 1H, *J* = 13.8 Hz, *J*′ = 1.2 Hz, *cis*CH=C*H*$_2$), 5.15 (dd, 1H, *J* = 17.2 Hz, *J*′ = 1.5 Hz, *trans*CH=C*H*$_2$), 5.86 (m, 1H, C*H* = CH_2), 7.11 (d, 2H, *J* = 8.2 Hz, Ar-*H*), 7.20 (d, 2H, *J* = 8.2 Hz, Ar-*H*). NAMTA·HCl (*i*-PrOH-Et_2O) m.p. 171–173°C; ^{1}H NMR (D_2O) δ 1.22 (d, 3H, *J* = *6.6* Hz, CHC*H*$_3$), 2.46 (s, 3H, S-C*H*$_3$), 2.78 (dd, 1H, *J* = 13.8 Hz, *J*′ = 8.7 Hz, C*H*$_2$CH), 3.07 (dd, 1H, *J* = 13.8 Hz, *J*′ = 5.6 Hz, C*H*$_2$CH), 3.54 (dd, 1H, *J* = 14.0 Hz, *J*′ = 6.3 Hz, N-C*H*$_2$CH=CH_2), 3.66 (overlapping m, 2H, CH_3C*H* and N-C*H*$_2$CH=CH_2), 5.43 (d, 1H, *J* = 3.2 Hz, *cis*CH=C*H*$_2$), 5.48 (d, 1H, *J* = 10.1 Hz, *trans*CH=C*H*$_2$), 5.85 (m, 1H, C*H* = CH_2), 7.22 (d, 2H, *J* = 8.2 Hz, Ar-*H*), 7.30 (d, 2H, *J* = 8.2 Hz, Ar-*H*). Found C, 60.62; H, 7.84; N, 5.74; S, 10.83. $C_{13}H_{20}ClNS$ requires C, 60.56; H, 7.82; N, 5.43; S, 12.44%.

DAMTA: ^{1}H NMR ($CDCl_3$) δ 0.92 (d, 3H, *J* = *6.6* Hz, CHC*H*$_3$), 2.36 (dd, 1H, *J* = 13.1 Hz, *J*′ = 9.0 Hz, C*H*$_2$CH), 2.46 (s, 3H, S-C*H*$_3$), 2.87 (dd, 1H, *J* = 13.1 Hz, *J*′ = 5.1 Hz, C*H*$_2$CH), 3.09 (overlapping m, 5H, CH_3C*H* and N-(C*H*$_2$CH=CH_2)$_2$), 5.08 (apparent d, 2H, *J* = 10.0 Hz, *cis*CH=C*H*$_2$), 5.16 (dd, 2H, *J* = 17.2 Hz, *J*′ = 5.2 Hz, *trans*CH=C*H*$_2$), 5.84 (m, 2H, C*H* = CH_2), 7.06 (d, 2H, *J* = 8.2 Hz, Ar-*H*), 7.17 (d, 2H, *J* = 8.2 Hz, Ar-*H*). DAMTA·HCl (*i*-PrOH-Et_2O) m.p. 136–138°C; ^{1}H NMR (D_2O) δ 1.25 (d, 3H, *J* = *6.6* Hz, CHC*H*$_3$), 2.46 (s, 3H, S-C*H*$_3$), 2.81 (dd, 1H, *J* = 13.3 Hz, *J*′ = 10.0 Hz, C*H*$_2$CH), 3.11 (dd, 1H, *J* = 13.5 Hz, *J*′ = 4.7 Hz, C*H*$_2$CH), 3.76

(overlapping m, 5H, CH_3CH and N-(CH_2-$CH{=}CH_2$)$_2$), 5.58 (m, 2H, *cis*$CH{=}CH_2$), 5.58 (m, 2H, *trans*$CH{=}CH_2$), 5.58 (m, 2H, $CH = CH_2$), 7.20 (d, 2H, $J = 8.2$ Hz, Ar-*H*), 7.28 (d, 2H, $J = 8.2$ Hz, Ar-*H*). Found C, 64.29; H, 7.99; N, 5.06; S, 8.91. $C_{16}H_{25}ClNS$ requires C, 64.51; H, 8.12; N, 4.70; S, 10.76%.

N,N-Dipropyl-1-(4-methylthiophenyl)-2-aminopropane (DPMTA)

DAMTA (1.2 g, 4.59 mmol) was hydrogenated catalytically with Pd-C 10% in methanol for 24 h, after that the catalyst was removed by filtration over celite. The solvent was removed under vacuum to give 1.1 g (90 %). ^{1}H NMR ($CDCl_3$) δ 0.85 (t, 6H, $J = 7.4$ Hz, N-($CH_2CH_2CH_3$)$_2$), 0.90 (d, 3H, $J = 6.5$ Hz, $CHCH_3$), 1.42 (sex, 4H, $J = 7.4$ Hz, N-(CH_2-CH_2CH_3)$_2$), 2.3–2.4 (overlapping m, 5H, N-(CH_2-CH_2CH_3)$_2$ and CH_2CH), 2.44 (s, 3H, S-CH_3), 2.8–3.0 (overlapping m, 2H, CH_2CH and $CHCH_3$), 7.08 (d, 2H, $J = 8.2$ Hz, Ar-*H*), 7.17 (d, 2H, $J = 8.2$ Hz, Ar-*H*). DPMTA·Malonate (*i*-PrOH-Et_2O) m.p. 109–111°C; ^{1}H NMR (D_2O) δ 0.91 (t, 3H, $J = 7.3$ Hz, N-$CH_2CH_2CH_3$), 0.94 (t, 3H, $J = 7.3$ Hz, N-$CH_2CH_2CH_3$), 1.20 (d, 3H, $J = 6.6$ Hz, $CHCH_3$), 1.7 (m, 4H, N-($CH_2CH_2CH_3$)$_2$), 2.45 (s, 3H, S-CH_3), 2.82 (dd, 1H, $J = 13.4$, $J' = 9.7$ Hz, CH_2CH), 3.0–3.3 (overlapping m, 5H, N-($CH_2CH_2CH_3$)$_2$ and CH_2CH), 3.72 (m, 1H, $CHCH_3$), 7.23 (d, 2H, $J = 8.3$ Hz, Ar-*H*), 7.30 (d, 2H, $J = 8.3$ Hz, Ar-*H*); ^{1}H NMR (DMSO-d_6) δ δ 0.91 (t, 6H, $J = 7.4$ Hz, N-$CH_2CH_2CH_3$), 1.07 (d, 3H, $J = 6.4$ Hz, $CHCH_3$), 1.62 (m, 4H, N-($CH_2CH_2CH_3$)$_2$), 2.46 (s, 3H, S-CH_3), 2.63 (dd, 1H, $J = 13.8$ Hz, $J' = 6.4$ Hz, CH_2CH), 2.85 (s, 2H, $CH_2(CO_2H)_2$), 2.95 (dd, 1H, $J = 13.8$, J' 9.5 Hz, CH_2CH), 2.80–2.94 (m, 4H, N-($CH_2CH_2CH_3$)$_2$, 3.87 (m, 1H, $CHCH_3$), 7.21 (s, 4H, Ar-*H*). Found C, 60.96; H, 8.30; N, 3.96; S, 7.82. $C_{19}H_{31}NO_4S$ requires C, 61.76; H, 8.46; N, 3.79; S, 8.68%.

1-(4-Methylthiophenyl)-2-aminobutane (MTAB)

A mixture of 4-methylthiobenzaldehyde (1.3 mL, 10 mmol), *N,N*-dimethylethylenediamine (1.1 mL, 10 mmol), nitropropane (4.5 mL, 41 mmol) and toluene (10 mL) was refluxed overnight under a Dean–Stark trap. The solvent was removed under vacuum and the crude mixture (1.2 g, 54%) was fractionated over a flash column, eluting with $CHCl_3$, to obtain (*E*)-1-(4-methylthiophenyl)-2-nitrobutene (1.1 g, 91% of the mixture) and its (*Z*) isomer (0.1 g, 9% of the mixture), each geometrical isomer identified by its NOESY spectrum. (*E*) isomer ^{1}H NMR ($CDCl_3$) δ 1.28 (t, 3H, $J = 7.4$ Hz, CH_2CH_3), 2.52 (s, 3H, S-CH_3), 2.88 (q, 2H, $J = 7.4$ Hz, $CH_3CH_2C{=}CH$), 7.29 (d, 2H, $J = 8.5$ Hz, H3′ and H5′), 7.36 (d, 2H, $J = 8.5$ Hz, H2′ and H6′), 7.98 (s, 1H, Ar-$CH = C$). (*Z*) isomer ^{1}H NMR ($CDCl_3$) δ 1.20 (t, 3H, $J = 7.4$ Hz, CH_2CH_3), 2.46 (s, 3H, S-CH_3), 2.67 (q, 2H, $J = 7.4$ Hz, CH_3CH_2-$C{=}CH$), 6.29 (s, 1H, Ar-$CH = C$), 7.16 (s, 4H, $J = 9.2$ Hz, Ar-*H*). To a stirred suspension of $LiAlH_4$ (2.2 g, 58 mmol) in anhydrous THF (80 mL), a solution of the (Z) and (E) nitrobutene mixture (2.3 g, 10 mmol) in anhydrous THF (20 mL) was added dropwise. The mixture was refluxed for 24 h. The excess hydride was carefully destroyed by cautious addition of H_2O (2.5 mL), 40% NaOH (2 mL) and additional H_2O (8 mL). The solid was filtered and washed with THF (20 mL). The solvent was removed under vacuum to obtain MTAB as a light brown oil, which was distilled under vacuum (155–160°C, 0.1 mmHg) yielding a colorless oil (1.8 g, 9.3 mmol, 90%). ^{1}H NMR ($CDCl_3$) δ 0.97 (t, 3H, $J = 7.4$ Hz, CH_2CH_3), 1.44 (m, 2H, CH_2CH_3), 2.41 (dd, 1H, $J = 13.4$ Hz, $J' = 8.6$ Hz, CH_2CH), 2.43 (s, 3H, SCH_3), 2.75 (dd, 1H, $J = 13.4$ Hz, $J' = 4.7$ Hz, CH_2CH), 2.87 (m, 1H, CH_3CH_2-CH), 7.11 (d, 2H, $J = 8.2$ Hz, Ar-*H*), 7.20 (d, 2H, $J = 8.2$ Hz, Ar-*H*). MTAB·HCl (*i*-PrOH-Et_2O) m.p. 159–161°C; ^{1}H NMR (D_2O) δ 0.95 (t, 3H, $J = 7.4$ Hz, CH_2CH_3), 1.65 (qd, 2H, $J = 14.7$ Hz, $J' = 7.6$ Hz, CH_2CH_3), 2.43 (s, 3H, SCH_3), 2.78 (dd, 1H, $J = 14.3$ Hz, $J' = 7.9$ Hz, CH_2CH), 2.96 (dd, 1H, $J = 14.3$ Hz, $J' = 6.2$ Hz, CH_2CH), 3.40 (m, 1H, $J = 6.5$ Hz, CH_3CH_2CH), 7.20 (d, 2H, $J = 8.2$ Hz, Ar-*H*), 7.27 (d, 2H, $J = 8.2$ Hz, Ar-*H*). Found C, 56.85; H, 7.82; N, 6.29; S, 12.09. $C_{11}H_{18}ClNS$ requires C, 57.00; H, 7.83; N, 6.05; S, 13.83%.

Enantiomeric Resolution of MTA

A solution of (±)-MTA (3.1 g, 17 mmol) in *i*-PrOH (10 mL) was added to a solution of (+)-*O,O′*-di-*p*-toluoyltartaric acid (6.7 g, 17 mmol) in boiling *i*-PrOH (15 mL), and the reaction mixture was boiled for 5 min. After cooling, the precipitated salt was filtered and dried for 48 h in a vacuum over H_2SO_4, and then for 2 h at 66°C. The mixture of diastereomeric MTA salts (7.2 g, 73%) was then dissolved in boiling MeOH (620 mL). This solution was allowed to cool to room temperature and then kept at −20°C for a fortnight. The precipitated salt was filtered and dried for 48 h in a vacuum over H_2SO_4 (1.45 g, 40%). The base was liberated by dissolving the salt in 2N NaOH and extracting with $CHCl_3$ (4 × 20 mL), washing with 10% Na_2CO_3 (10 mL) and finally with distilled H_2O. The organic phase was dried with anhydrous Na_2SO_4 and the solvent was removed under vacuum. In this way partially resolved (+)-MTA was obtained (0.69 g), $[\alpha]_D^{22} = +24°$ ($c = 5$, MeOH).

The mother liquors were concentrated to dryness and the free base was liberated from the residue (5.7 g) to afford MTA enriched in the (−) isomer (1.33 g). This base was used to prepare the (−)-*O,O′*-di-*p*-toluoyltartaric salt in MeOH (750 mL) as described above for the (+) enantiomer. The crystalline salt was collected by filtration (1.05 g, 32%) and

the free base was released as before to yield partially resolved (−)-MTA (513 mg), $[\alpha]_D^{22} = -23.4°$ ($c = 5.1$, MeOH). To determine the enantiomeric excesses, Mosher's amides were prepared by reacting either the racemic mixture or each of the enriched enantiomers with (−)-α-methoxy-α-trifluoromethyl-phenylacetyl chloride[20] and ^{1}H-NMR spectra were recorded. All three amide spectra showed methyl group resonances as two doublets centered at 1.21 and 1.14 ppm ($J = 6.6$ Hz), and methoxyl singlets at 3.31 and 3.26 ppm. The integrals of these signals for both enantiomerically enriched MTA isomers allowed an ee of 90% to be calculated. MTA hydrochlorides were prepared by adding an equimolar amount of 37% HCl to a concentrated solution of each enantiomer in *i*-PrOH and subsequent addition of a few drops of Et_2O. The salts were recrystallized in *i*-PrOH to afford (+)-MTA·HCl, $[\alpha]_D^{22} = +21.5°$ ($c = 2.0$, H_2O) and (−)-MTA·HCl, $[\alpha]_D^{22} = -22.0°$, ($c = 2.0$, H_2O).

Enzymatic Assays

The effects of the MTA enantiomers and derivatives on MAO-A or MAO-B activities were studied using a crude rat brain mitochondrial suspension (male Sprague–Dawley rats weighing 180–220 g, sacrificed by decapitation), using 5-HT (100 μM) and 4-dimethylaminophenethylamine (DMAPEA, 5 μM) as selective substrates for MAO-A and −B, respectively, and detecting these compounds and their metabolites by HPLC with electrochemical detection (HPLC-ED) as described previously.[14]

IC_{50} values were determined using Prism Graph Pad software, from plots of inhibition percentages (calculated in relation to a sample of the enzyme treated under the same conditions without inhibitors) versus −log inhibitor concentration. The time course of MAO inhibition by the drugs was assessed by preincubating the reaction mixture with different compounds, at appropriate concentrations, for 30 min. After preincubation, MAO activity was measured as described.[14,21] The reversibility of the inhibitory process was assessed after repeated washing of the mitochondrial suspension, after preincubation for 10 min with drugs at appropriate concentrations. The preparations were washed three times (centrifugation and resuspension) with 0.1 M sodium phosphate buffer, pH 7.4. Finally, MAO activity was measured again, using HPLC-ED. Control samples, in which the inhibitor solution was replaced by an equal volume of water, were treated in the same way.[21]

Chromatographic Conditions

A C_{18} reverse phase column (Macrosphere 250 mm × 4.6 mm, Alltech, USA), an amperometric detector (Merck-Recipe L3500A), and a chromatographic integrator (Merck-Hitachi D2500) were used to analyze the reaction mixtures. All other conditions were as previously described.[14]

Statistical Analysis

IC_{50} values are given as the mean ± SD of at least two independent experiments, each in triplicate. The statistical significance was determined using Student's *t*-test. In all cases the significance level was found to be $P < 0.05$.

RESULTS

Table I shows the structures of the compounds studied.

Chemistry

The synthesis of (±)-(MTA) *via* the corresponding arylnitropropene, had been reported[22] in 1963 in a low overall yield (26%), which we were able to improve to 68% (including the crystallization step to obtain the hydrochloride) using a different basic catalyst in the crucial nitroaldol condensation step. With the exception of MTA itself and its *N*-methyl derivative,[23,24] all the molecules reported here have not been described previously. Racemic MTA, its enantiomers and all its derivatives were stored and used as hydrochloride salts, except DEMTA (as the hydrobromide) and DPMTA (as the malonate).

All the phenylisopropylamine free bases synthesized here present the characteristic chemical shifts of a 1,4-disubstituted aromatic system, resonating at 7.10 to 7.20 ppm with a coupling constant of 8.3 Hz. In the hydrochlorides this pattern is shifted downfield, presumably due to deshielding by the positively charged nitrogen atom interacting directly with the aromatic ring. In the *N*-monoalkyl-MTA series both benzylic proton resonances are shifted slightly downfield with regard to the corresponding MTA signals, suggesting that both protons lie closer to the ring plane than in MTA. On the contrary, in the *N*,*N*-dialkyl-MTA series the benzylic proton resonances are indicative of a more pronounced conformational change, with one of them moving downfield and the other one moving upfield. The ^{1}H NMR spectrum of DPMTA malonate in D_2O did not show any resonance assignable to the malonate methylene hydrogens, presumably due to rapid exchange with the solvent. In DMSO-d_6 the expected signal was observed at 2.85 ppm, confirming the identity of the salt.

TABLE I Structural description of MTA and derivatives, and their IC_{50} values for MAO inhibition

Compound	R_1	R_2	R_3	IC_{50} [μM] MAO-A	IC_{50} [μM] MAO-B
(±)-MTA	H	H	CH_3	0.25 ± 0.02	NE
(±)-NMMTA	H	CH_3	CH_3	0.89 ± 0.39	NE
(±)-DMMTA	CH_3	CH_3	CH_3	2.10 ± 0.22	NE
(±)-NEMTA	H	CH_2CH_3	CH_3	1.80 ± 0.24	NE
(±)-DEMTA	CH_2CH_3	CH_2CH_3	CH_3	6.45 ± 0.18	NE
(±)-NPMTA	H	$CH_2\ CH_2CH_3$	CH_3	2.41 ± 0.50	>10
(±)-DPMTA	$CH_2\ CH_2CH_3$	$CH_2\ CH_2CH_3$	CH_3	>10	NE
(±)-NAMTA	H	$CH_2CH{=}CH_2$	CH_3	3.50 ± 1.22	>10
(±)-DAMTA	$CH_2CH{=}CH_2$	$CH_2CH{=}CH_2$	CH_3	>10	NE
(±)-MTAB	H	H	CH_2CH_3	0.84 ± 0.16	NE
(+)-MTA				0.11 ± 0.03	NE
(−)-MTA				2.04 ± 0.40	NE
l-Deprenyl				>10	0.007

The IC_{50} values were calculated from the inhibition *vs* −log concentration curves, obtained from at least two independent experiments, with each concentration assayed in triplicate. N.E. = No Effect at 10 μM. (±)-MTA and *l*-deprenyl were used as positive controls for MAO-A and MAO-B inhibition, respectively.

MAO Inhibition

Table I summarizes the *in vitro* MAOI effects of (±)-MTA, its enantiomers, its *N*-alkyl derivatives and MTAB. (+)-MTA was the most potent MAOI-A, followed by its racemic modification which was about half as potent (Figure 1). (−)-MTA was about eighteen times less potent than its enantiomer. Most of the derivatives had no effect on MAO-B with the exception of NPMTA and NAMTA which showed weak inhibitory activity.

A representative sample of the drugs was tested regarding the reversibility of their inhibitory properties upon MAO-A. As shown in Table II, all the compounds proved to be reversible MAOI-A, as evidenced by the recovery of the enzyme activity measured after repeated washing of the preparation.

Since the lack of effect of these compounds toward MAO-B might be due to time dependency of the inhibitory process (as occurs in the case of suicide inhibitors such as deprenyl), we evaluated the effect of incubating the enzyme with the drugs for 0 or 30 min. As shown in Table III, none of the compounds inhibited MAO-B under these conditions. As expected, the MAO-B inhibitory profile of *l*-deprenyl (used as a positive control) was time-dependent, showing significantly stronger effects after 30 minutes preincubation.

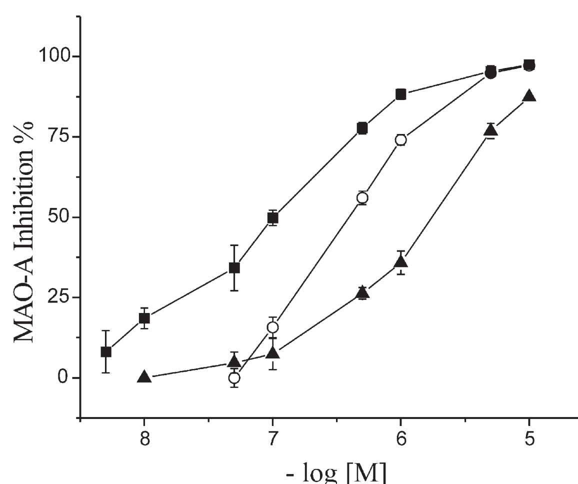


FIGURE 1 Effects of (±)-MTA (○) and its (*S*)(+)- (■) and (*R*)(−)- (▲) isomers upon MAO-A. Enzyme inhibition is represented as the percentage of inhibition of deamination of 5-HT, as measured by HPLC-ED. Each point is the mean ± SD of three determinations.

TABLE II Reversibility of MAO-A inhibition produced by some substituted derivatives of MTA, as determined by repeated washing

Compound [10^{-5} M]	Percent Inhibition: Before washing	Percent Inhibition: After washing
NAMTA	74.2 ± 1.5	0.0 ± 8.3
NEMTA	81.4 ± 1.4	0.0 ± 8.8
DMMTA	79.7 ± 1.4	31.0 ± 17.6
MTAB	91.2 ± 1.0	21.4 ± 5.8

Crude mitochondrial suspensions were preincubated for 10 min with inhibitor and then the preparation was washed three times by centrifugation and resuspension. MAO-A activity of the preparation and of the controls was determined by HPLC-ED using 5-HT as selective substrate. Each value is the mean ± SD of triplicate determinations.

TABLE III Effect of preincubation on the inhibition of MAO-B by MTA and derivatives

Compound [10^{-5} M]	Percent inhibition of MAO-B Preincubation time (min)	
	0	30
MTA	3.8 ± 5.16	3.7 ± 6.4
NMMTA	15.6 ± 3.1	9.7 ± 5.7
DMMTA	14.4 ± 1.6	2.3 ± 4.0
NEMTA	17.8 ± 4.2	15.0 ± 5.8
DEMTA	21.2 ± 1.4	32.5 ± 4.3
NPMTA	32.9 ± 1.8	30.0 ± 5.2
DPMTA	7.1 ± 2.6	12.9 ± 4.3
NAMTA	35.6 ± 3.6	34.3 ± 9.0
DAMTA	5.8 ± 5.4	2.3 ± 4.0
MTAB	0.0 ± 2.7	5.7 ± 7.4
(−)-MTA	2.0 ± 3.4	3.0 ± 3.0
(+)-MTA	2.0 ± 3.3	13.7 ± 12.7
l-Deprenyl [10^{-8} M]	2.0 ± 0.2	65.3 ± 4.0*

Crude mitochondrial suspensions were preincubated at 37°C with compounds for the times indicated. Percent of MAO-B inhibition was determined by HPLC-ED. *l*-Deprenyl was used as a positive control. The values are means ± SD of triplicate determinations. *$P < 0.05$ (Student's *t*-test), compared with 0 min preincubation.

DISCUSSION

The first important finding of this work was that the presence of a substituent on the amino group of the MTA side chain decreases its activity as a MAOI-A, and that the magnitude of this effect increases with the size of the substituent. Thus, an almost linear increase of IC_{50} for MAO-A inhibition was observed when a methyl (NMMTA), an ethyl (NEMTA), a propyl (NPMTA) or an allyl (NAMTA) group was placed on the nitrogen atom. The introduction of a second alkyl substituent led to a greater increase in the IC_{50} values (as compared to the corresponding monoalkyl derivative), with the rank order of potencies being DMMTA > DEMTA > DPMTA ≅ DAMTA. Replacement of the methyl group on the α-carbon of the side chain by an ethyl group (MTAB *vs* MTA) also resulted in decreased potency. These results are in agreement with previously reported data, describing the effects of *N*-substitution upon the MAOI properties of a small number of amphetamine derivatives.[16,25,26] The most likely explanation of these results seems to be that the substituents on the amino group sterically hinder its approach to a complementary residue of the enzyme, although electronic contributions of the substituents cannot be discarded. Similar behavior, *i.e.* a decrease of MAOI-A properties, was observed after lengthening the alkyl chain bound to the α-carbon of the MTA molecule. This might also be a consequence of steric hindrance around the nitrogen atom which is presumably a key binding feature, limiting access to a pharmacophoric conformation.[27] These preliminary observations call for analogous experiments with derivatives bearing bulkier substituents on the nitrogen or on the α-carbon atom. Nevertheless, it is worth pointing out that, although modifications of the MTA structure studied by us generated less active drugs as compared to the parent compound, some of the derivatives are still potent MAOI-A *i.e.* MTAB, NMMTA, DMMTA, NEMTA, NPMTA, NAMTA. As is the case of MTA, all the compounds evaluated by us proved to be reversible and very selective MAOI-A. In addition, it was demonstrated for most of these substances that the lack of effects upon MAO-B was not due to time-dependence of the inhibitory process, as happens with irreversible inhibitors.

The other noteworthy result of this study was that (+)-MTA is about 18 times more potent than (−)-MTA and is therefore twice as potent as the racemic mixture. This confirms a trend observed with several other phenylisopropylamines such as amphetamine and deprenyl,[10,26] amiflamine and its analogs[28,29] and methylenedioxymethamphetamine (MDMA),[30] showing in all cases that the (*S*)-isomers (which are always dextrorotatory) are the eutomers. It is interesting to note that the (*S*)-isomers of these amphetamine derivatives are the eutomers, both as MAOI-A and as 5-HT releasing agents, the latter acting *via* their 5-HT transporter substrate character.[31] The present results might therefore be relevant to the dissociation of the 5-HT releasing and MAOI-A properties actions of MTA, which is desirable in the perspective of understanding the structure–activity relationships of its congeners and the possible development of antidepressants with a dual mechanism of action.

Acknowledgements

The authors thank Ms. Rut Arancibia for excellent technical assistance. This work was supported by the Presidential Chair in Science (BKC, 1996), ICM grant N° P99-031-F, FONDECYT grant N° 1000776 and DICYT grant N° 029901RP.

References

[1] Murphy, D.L. (1978) *Biochem. Pharmacol.* **27**, 1889–1893.
[2] Johnston, J.P. (1968) *Biochem. Pharmacol.* **17**, 1285–1297.
[3] Bach, A.W.J., Lan, N.C., Johanson, D.L., Abell, C.W., Bembenek, M.E., Kwan, S.W., Seeburg, P.H. and Shih, J.C. (1988) *Proc. Natl. Acad. Sci. USA* **85**, 4934–4938.
[4] Youdim, M.B.H. (1983) *Mod. Prob. Pharmacopsychiat.* **19**, 63–74.
[5] Murphy, D.L., Aulakh, C.S., Garrik, N.A. and Sunderland, T. (1987) In: Meltzer, H.Y., ed, *Psychopharmacology: The Third Generation of Progress* (Raven Press, New York), pp 545–552.
[6] Shulman, K.I. (1994) In: Kennedy, S.H., ed, *Clinical Advances in Monoamine Oxidase Inhibitor Therapies* (American Psychiatric Press, Washington, DC), pp 111–124.
[7] Möller, H.-J., Paykel, E.S., eds. (1992) *Renaissance of Monoamine Oxidase Inhibitors: the New Selective and Reversible Generation* (Royal Society of Medicine, London).

[8] Waldmeier, P.C., Amrein, R. and Schmid-Burgk, W. (1994) In: Kennedy, S.H., ed, *Clinical Advances in Monoamine Oxidase Inhibitor Therapies* (American Psychiatric Press, Washington, DC), pp 33–59.
[9] Bieck, P.R. and Antonin, K-H. (1994) In: Kennedy, S.H., ed, *Clinical Advances in Monoamine Oxidase Inhibitor Therapies* (American Psychiatric Press, Washington, DC), pp 83–110.
[10] Mantle, T.J., Tipton, K.F. and Garrett, N.J. (1976) *Biochem. Pharmacol.* **25**, 2073–2077.
[11] Florvall, L., Ask, A-L., Ögren, S-O. and Ross, S.B. (1978) *J. Med. Chem.* **21**, 56–63.
[12] Fuller, R.W. and Hemrick-Luecke, S.K. (1982) *Res. Commun. Substance Abuse* **3**, 159–164.
[13] Green, A.L. and El Hait, M.A.S. (1980) *J. Pharm. Pharmacol.* **32**, 262–266.
[14] Scorza, M.C., Carrau, C., Silveira, R., Zapata-Torres, G., Cassels, B.K. and Reyes-Parada, M. (1997) *Biochem. Pharmacol.* **54**, 1361–1369.
[15] Huang, X., Marona-Lewicka, D. and Nichols, D.E. (1992) *Eur. J. Pharmacol.* **229**, 31–38.
[16] Scorza, M.C., Silveira, R., Nichols, D. and Reyes-Parada, M. (1999) *Neuropharmacol.* **38**, 1055–1061.
[17] Elliott, S.P. (2000) *J. Anal. Toxicol.* **24**, 85–89.
[18] Elliott, S.P. (2001) *Ann. Clin. Biochem.* **38**, 339–347.
[19] Winstock, A.R., Wolf, K. and Ramsey, J. (2002) *Drug Alcohol Depend.* **67**, 111–115.
[20] Dale, J.A. and Mosher, H.S. (1973) *J. Am. Chem. Soc.* **92**, 512–519.
[21] Reyes-Parada, M., Scorza, M.C., Silveira, R., Dajas, F., Costa, G., Tipton, K.F. and Cassels, B.K. (1994) *Biochem. Pharmacol.* **47**, 1365–1371.
[22] Holland, G.F., Buck, C.J. and Weissman, A. (1963) *J. Med. Chem.* **6**, 519–524.
[23] Murphy, J.E.J., Flynn, J.J., Cannon, D.M., Guiry, P.J., McCormack, P., Baird, A.W., McBean, G.J. and Keenan, A.J. (2002) *Eur. J. Pharmacol.* **444**, 61–67.
[24] Dukat, M., Young, R. and Glennon, R.A. (2002) *Pharmacol. Biochem. Behav.* **72**, 299–305.
[25] Florvall, L., Ask, A-L., Ross, S.B., Ögren, S-O. and Holm, A-Ch. (1983) *Acta. Pharm. Suec.* **20**, 255–270.
[26] Robinson, J.B. (1985) *Biochem. Pharmacol.* **34**, 4105–4108.
[27] Aliste, M.P. and Cassels, B.K. (2001) *J. Chem. Soc., Perkin Trans.* **2**, 906–915.
[28] Ask, A-L., Fagervall, I., Florvall, L., Ross, S.B. and Ytterborn, S. (1985) *Br. J. Pharmacol.* **85**, 683–690.
[29] Fowler, C.J. and Oreland, L. (1981) *J. Pharm. Pharmacol.* **33**, 403–406.
[30] Leonardi, E.T.K. and Azmitia, E.C. (1994) *Neuropsychopharmacol.* **10**, 231–237.
[31] Nichols, D.E. (1994) In: Cho, A.K. and Segal, D.S., eds, *Amphetamine and Its Analogs. Psychopharmacology Toxicology and Abuse* (Academic Press, San Diego, California), pp 3–41.

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