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# Synthesis of α- and β-Methyl Derivatives of 2-[(5-Methoxy-1-methyl)indol-2-yl]ethylamine as Selective Inhibitors of Monoamine Oxidases A and B.

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*Key Words*: α- and β-methyl 2-[(5-methoxy-1-methyl)indol-2-yl]ethylamines, Monoamine Oxidases A and B, Inhibitors.

**Abstract:** We report the synthesis of some α- and β-methyl derivatives **2** and **3** of 2-[(5-methoxy 1-methyl)indol-2-yl]ethylamine. The *in vitro* screening shows that all these compounds are effective inhibitors of MAO. However, none of them are MAO-B selective inhibitors but the α-methyl secundary amine **3d** and the β-methyl tertiary amines **2c** and **2d** are MAO-A selective inhibitors.

## INTRODUCTION

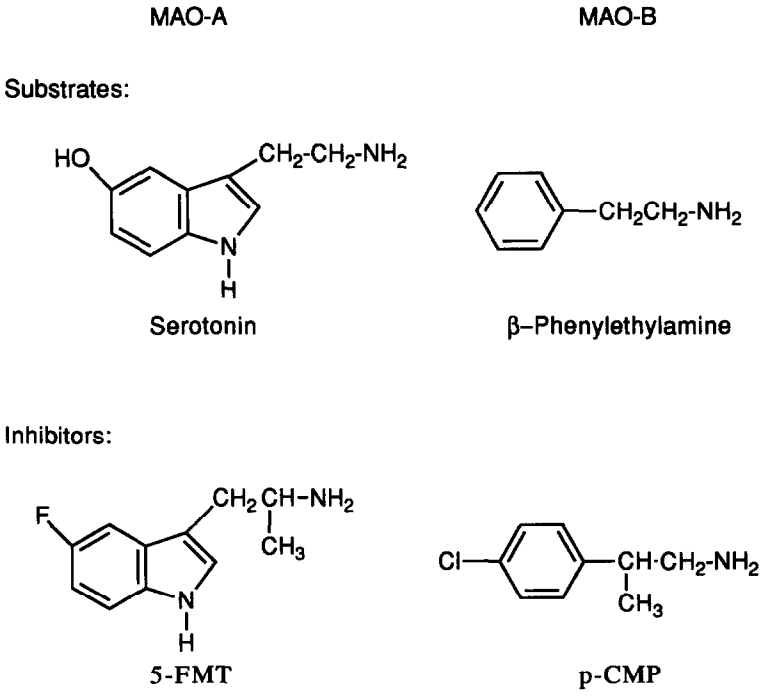
Monoamine oxidase (MAO, EC 1.4.3.4) is a flavoprotein enzyme tightly bound to the outer mitocondrial membrane[1]. The first indication that monoamine oxidase might have an important function in central amine neurotransmission began with the observation that Iproniazid brought about a "lightening effect" in patients; Zeller showed also its high potent MAO inhibitory action[2]. Monoamine oxidase exists in two different forms: MAO-A and MAO-B. They are defined by their different substrate specificities and their respective sensitivities to inhibition by Clorgyline (MAO-A) and *l*-Deprenyl[3] (MAO-B). In addition to these selective MAO inhibitors there are now many other MAO inhibitors that are selective for either type of MAO[4]. Many of the reversible MAO-A selective inhibitors are simple α-methyl substrate analogues of MAO[5-9].On the other hand, there are very few useful reversible MAO-B selective inhibitors. MAO-A selective inhibitors are of interest as antidepressive agents while the MAO-B selective inhibitor, *l*-Deprenyl, is being used together with *l*-Dopa in the treatment of the Parkinson's disease.

Previous *in vitro* studies have shown that an α–methyl substrate analogue, 5-fluoro-α–methyltryptamine (5-FMT, Fig. 1), was a reversible competitive MAO-A selective inhibitor and the β–methyl analogue, p-chloro-β-methylphenethylamine (p-CMP, Fig. 1), was a MAO-B selective inhibitor[8-9]. This observation have been confirmed by *ex vivo* studies[10].

In view of this and continuing our studies on the synthesis of selective MAO inhibitors[11-13], we report now the preparation and preliminary *in vitro* screening of compounds **2** and **3** (Fig. 2). These derivatives of 2-[(5-methoxy-1-methyl)indol-2-yl]ethylamine are α and β-methyl homoanalogues of compound **1**[12] (Fig. 2),

which is known to be 2.5 fold more selective inhibitors for MAO-A than Clorgyline[12]. In addition,it is well known that 2-propynyl- and 2,3-butadienylamine derivatives are irreversible, mechanism-based MAO inhibitors[13,14].

**Figure 1**

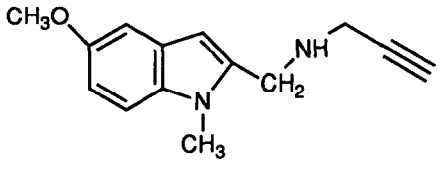



## RESULTS AND DISCUSSION

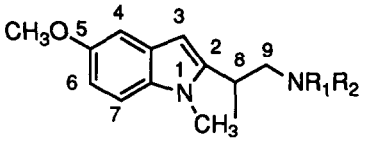
The synthesis of compounds **2** was carried out using as precursor methyl [(5-methoxy)indol-2-yl]acetate **4** (Scheme 1), which can be obtained in a six-steps sequence starting from commercially available 3-methyl-4-nitroanisole[15]. Conversion of **4** to the N,C-dimethyl derivative **5** (60%) was achieved at 0°C by using sodium hydride and methyl iodide in N,N-dimethylformamide; the only detectable by-product was a small amount of compound **6** [$^1$H-NMR (90 MHz, $CDCl_3$): δ 7.10 (d, H-7, J= 9), 7.0 (d, H-4, J=3), 6.77 (dd, H-6, J= 9, J= 3), 6.25 (s, H-3), 3.84 (s, N(1)$CH_3$), 3.69 (s, $OCH_3$), 3.56 (s, 3H, $COOCH_3$), 1.67 (s, 6H, $(CH_3)_2$)].

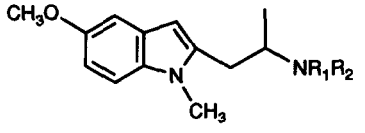
The aminolysis of **5** with ammonia and methylamine, under potassium cyanide catalysis[16], yielded the amides **7** and **8**, respectively. These compounds were reduced with lithium aluminium hydride in boiling tetrahydronfuran to give the amines **2a** and **2b** (Fig. 2) The amine **2b** was N-alkylated with 2-propynyl or 2,3-butadienyl bromide giving the acetylenic and allenic amines **2c** and **2d** (Fig. 2) in 60% and 63% yield, respectively.

**Figure 2**




**1**



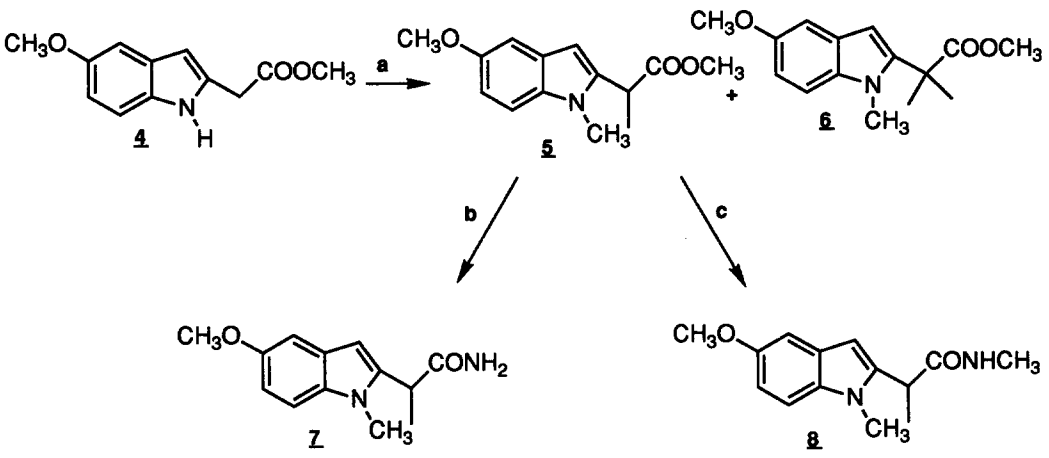

**2 a:** $R_1$= H, $R_2$= H
**2 b:** $R_1$= H, $R_2$= $CH_3$
**2 c:** $R_1$= propargyl, $R_2$= $CH_3$
**2 d:** $R_1$= 2,3-butadienyl, $R_2$= $CH_3$

**3 a:** $R_1$= H, $R_2$= H
**3 b:** $R_1$= H, $R_2$= $CH_3$
**3 c:** $R_1$= 2-propynyl, $R_2$= H
**3 d:** $R_1$= 2,3-butadienyl, $R_2$= H
**3 e:** $R_1$= 2-butynyl, $R_2$= H
**3 f:** $R_1$= 2-propynyl, $R_2$= $CH_3$
**3 g:** $R_1$= 2,3-butadienyl, $R_2$= $CH_3$
**3 h:** $R_1$= 2-butynyl, $R_2$= $CH_3$

We have approached the synthesis of compounds **3** starting from ethyl [(5-methoxy-1-methyl)indol-2-yl]carboxylate **9**[12] (Scheme 2). After reduction with lithium aluminium hydride and oxidation with manganese oxide[17], aldehyde **11** was obtained. The Henry reaction between the aldehyde **11** and nitroethane gave the nitrovinyl derivative **12** (90%) as a pure isomer, whose configuration at the double bond has not been established. This compound treated with lithium aluminiun hydride afforded the amine **3a** (Fig. 2) in 85% yield.

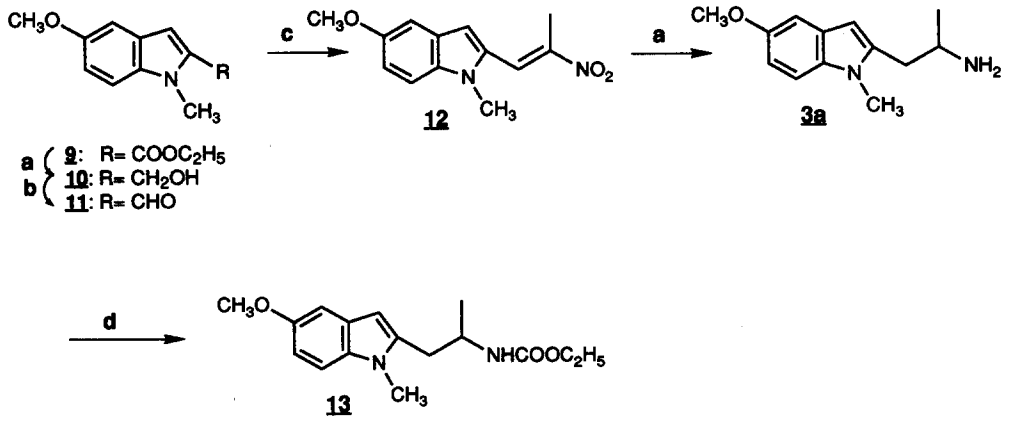
The N-methylamine **3b** (Fig. 2) was formed by reduction of the N-ethoxycarbonylcarbamate **13** which was synthesized from amine **3a** and ethoxycarbonyl chloride.

**Scheme 1**




**a:** NaH, $CH_3I$, 0°C; **b:** $NH_3$, NaCN, $CH_3OH$; **c:** $NH_2CH_3$, NaCN, $CH_3OH$.

**Scheme 2**




**a:** $AlLiH_4$, THF, Δ; **b:** $MnO_2$, ClNa; **c:** $CH_3CH_2NO_2$, $NH_4AcO$; **d:** $ClCOOC_2H_5$, NaOH.

**Table: $^1$H-RMN data of compounds 2 and 3.**

| Compound | Solvent (MHz, °C) | $^1$H-RMN ($\delta$ ppm, J Hz) |
|---|---|---|
| **2a** | $CDCl_3$ (300, rt) | 7.09 (d, H-7, J= 8.8), 6.96 (d, H-4, J= 2.4),6.76 (dd, H-6, J= 8.8, J= 2.4), 6.13 (s, H-3), 3.70 (s, $NCH_3$), 3.60 (s, $OCH_3$), 2.92 (m, $CH_2$(9)), 2.81 (m, CH(8)), 1.23 (d, $CH_3$-C(8)). |
| **2b*** | DMSO (300, rt) | 7.32 (d, H-7, J= 8.7), 6.98 (d, H-4, J= 0.6), 6.74 (dd, H-6, J= 8.7, J= 0.6), 3.73 (s, N(1)$CH_3$), 3.67 (s, $OCH_3$), 3.34 (m, CH(8)-$CH_2$(9)), 2.57 (s, $NCH_3$), 1.32 (d, $CH_3$-C(8)). |
| **2c** | $CDCl_3$ (300, rt) | 7.09 (d, H-7, J= 8.7), 6.95 (d, H-4, J= 2.4), 6.74 (dd, H-6, J= 8.7, J= 2.4), 6.14 (s, H-3), 3.76 (s, N(1)$CH_3$), 3.62 (s, $OCH_3$), 3.36 (dd, C<u>H</u>H-C≡, J= 17, J= 2.3), 3.28 (dd, CH<u>H</u>-C≡, J= 17, J= 2.3), 2.99 (m, CH(8)), 2.67 (dd, C<u>H</u>H(9), J= 12.4, J=5.4), 2.43 (dd, CH<u>H</u>(9), J= 12.4, J= 9), 2.27 (s, $NCH_3$), 2.15 (t, ≡CH, J= 2.3), 1.28 (d, $CH_3$-C(8), J= 6.7). |
| **2d*** | $(CD_3)_2CO$ (200, rt) | 7.45 (d, H-7, J= 8.9), 7.21 (d, H-4, J= 2.4), 7.00 (dd, H-6, J= 8.9, J= 2.4), 6.55 (s, H-3), 5.55 (m, CH=C=, J= 6.7), 5.23 (m, =C=$CH_2$), 3.98 (s, N(1)$CH_3$), 3.93 (s, $OCH_3$), 3.71 (m, C<u>H</u>$_2$=CH=, CH(8)-$CH_2$(9)), 3.04 (s, $NCH_3$), 1.58 (d, $CH_3$-C(8), J= 6.3). |
| **3a*** | DMSO (300, rt) | 7.28 (d, H-7, J= 9.0), 6.97 (d, H-4, J= 2.2), 6.73 (dd, H-6, J= 9.0, J= 2.2), 6.23 (s, H-3), 4.81 (s (broad), $NH_2$), 3.72 (s, $NCH_3$), 3.64 (s, $OCH_3$), 3.45 (m, CH(9)), 3.12 (m, C<u>H</u>H(8)), 2.89 (m, CH<u>H</u>(8)), 1.19 (d, 3H, $CH_3$-C(9)), J= 6.5). |
| **3b*** | $CDCl_3$ (300, rt) | 7.29 (d, H-7, J= 8.7), 6.97 (d, H-4, J= 2.2), 6.74 (dd, H-6, J= 8.7, J= 2.2), 6.24 (s, H-3), 3.72 (s, N(1)$CH_3$), 3.65 (s, $OCH_3$), 3.46 (m, CH(9), J= 9.3, J= 6.3, J=4.4), 3.24 (dd, C<u>H</u>H(8), J= 14.7, J= 4.4), 2.90 (dd, CH<u>H</u>(8), J= 14.7, J= 9.3), 2.60 (s, $NCH_3$), 1.19 (d, $CH_3$-C(9), J= 6.3). |
| **3c*** | DMSO (300, rt) | 7.28 (d, H-7, J= 8.7), 6.97 (d, H-4, J= 2.3), 6.73 (dd, H-6, J= 8.7, J= 2.3), 6.22 (s, H-3), 3.92 (m, $CH_2$-C≡), 3.77 (s, N(1)$CH_3$), 3.64 (s, $OCH_3$), 3.61 (t, ≡CH, J= 2.5), 3.49 (m, CH(9)), 3.24 (dd, C<u>H</u>H(8), J= 14.7, J= 4.6), 2.86 (dd, CH<u>H</u>(8), J= 14.7, J= 9.5), 1.18 (d, $CH_3$-C(9), J= 6.4). |

**Table** (continued)

| | | |
|---|---|---|
| **3d*** | DMSO (300, 30°C) | 7.28 (d, H-7, J= 8.8), 6.97 (d, H-4, J= 2.3), 6.73 (dd, H-6, J= 8.8, J= 2.3), 6.23 (s, H-3), 5.38 (m, CH=C=, J= 6.8), 5.04 (d (broad), =C=$CH_2$, J= 6.8), 3.72 (s, N(1)$CH_3$), 3.65 (s, $OCH_3$), 3.63 (m, C$\underline{H}_2$-CH=C=), 3.48 (m, CH(9)), 3.28 (dd, C$\underline{H}$H(8), J= 14.6, J= 3.2), 2.89 (dd, CH$\underline{H}$(8), J= 14.6, J= 10.0), 1.20 (d, $CH_3$C(9), J= 6.3). |
| **3e*** | DMSO (200, rt) | 7.29 (d, H-7, J= 8.9), 6.98 (d, H-4, J= 2.3), 6.74 (dd, H-6, J= 8.9, J= 2.3), 6.23 (s, H-3), 3.87 (m, $CH_2$-C≡), 3.65 (s, N(1)$CH_3$), 3.65 (s (broad), $OCH_3$, CH(9)), 3.26 (dd, C$\underline{H}$H(8), J= 14.7, J= 3.2), 2.86 (dd, CH$\underline{H}$(8), J= 14.7, J= 9.1), 1.87 (t, $CH_3$-C≡, J= 2.3), 1.19 (d, $CH_3$-C(9), J= 6.3). |
| **3f*** | DMSO (300, 30°C) | 7.28 (d, H-7, J= 8.7), 6.97 (d, H-4, J= 2,3), 6.73 (dd, H-6, J= 8.7, J= 2.3), 6.22 (s, H-3), 3.92 (m, 2H, $CH_2$-C≡), 3.72 (s, N(1)$CH_3$), 3.64 (s, $OCH_3$), 3.61 (t, ≡CH, J=2.5), 3.24 (m, CH(9)), 3.12 (dd, C$\underline{H}$H(8), J= 14.7, J= 4.6), 2.95 (dd, CH$\underline{H}$(8), J= 14.7, J= 9.5), 2.56 (s, $NCH_3$), 1.18 (d, $CH_3$-C(9), J= 6.4). |
| **3g*** | DMSO (300, 30°C) | 7.28 (d, H-4, J= 8.8), 6.97 (d, H-4, J= 2.5), 6.73 (dd, H-6, J= 8.8, J= 2.5), 6.22 (s, H-3), 5.38 (m, CH=C=, J= 7.1), 5.07 (d (broad), =C=$CH_2$, J= 6.7), 3.72 (s, N(1)$CH_3$), 3.66 (s, $OCH_3$, CH(9), C$\underline{H}_2$-CH=C=), 3.23 (dd, C$\underline{H}$H(8), J= 14.6, J= 3.5), 2.92 (dd, CH$\underline{H}$(8), J= 14.6, J= 10.7), 2.66 (s, $NCH_3$), 1.15 (d, $CH_3$-C(9), J= 6.5). |
| **3h*** | DMSO (200, rt) | 7.27 (d, H-7, J= 8.8), 6.96 (d, H-4, J= 2.4), 6.72 (dd, H-6, J= 8.8, J= 2.4), 6.21 (s, H-3), 3.87 (t, $CH_2$-C≡, J= 2.1), 3.72 (s, N(1)$CH_3$), 3.66 (s, $OCH_3$), 3.60 (m, CH(9)), 3.22 (dd (broad), C$\underline{H}$H(8), J= 14.5, J= 3.4), 2.86 (dd (broad), CH$\underline{H}$(8), J= 14.5, J= 10.5), 2.65 (s, $NCH_3$), 1.87 (t, $CH_3$-C≡, J= 2.1), 1.13 (d, $CH_3$-C(9), J= 6.5). |

* $^1$H-RMN spectra of the hydrochloride or acid oxalate.

The amines **3a** and **3b** were N-alkylated by 2-propynyl, 2,3-butadienyl and 2-butynyl bromide in the presence of *t*-butylamine giving amines **3c-h** (Fig. 2) in good yield. The N-alkylation of compound **3a** also gave the bisalkylation products in small amount.

All new compounds showed correct analytical and spectroscopic data. The $^1$H-NMR data of compounds **2** and **3** are summarized in the Table.

## BIOLOGICAL ACTIVITY

Compounds **2a-d** and **3a-h** were tested *in vitro* on bovine brain MAO types A and B. The *in vitro* screening indicated that all the compounds were effective inhibitors of MAO. The **2a, b** and **3a, b** were weak non selective reversible inhibitors of MAO-A and B ($IC_{50}$= 63μM to 10μM). However, the amines **2c,d** and **3c-h** were from moderate to potent ($IC_{50}$ = 0.012 μM for **3e**) irreversible non selective MAO inhibitors, with the exception of compounds **2c,d** and **3d** which showed selectivity for MAO-A with $IC_{50}$ values of 1.2 μM (MAO-A), 316 μM (MAO-B); 0.16 μM (MAO-A) , 63 μM (MAO-B) and 0.079 μM (MAO-A), 40 μM (MAO-B), respectively. None of them were MAO-B selective inhibitors.

## EXPERIMENTAL SECTION

Melting points were determined on a Gallenkamp apparatus (open capillar) or a Koffler apparatus (heating block) and are uncorrected. Elemental analysis were obtained from vacuum dried samples on a Perkin-Elmer 240 automatic analyzer. IR spectra were recorded on a Perkin-Elmer 681 spectrometer; frequences (ν) are given in $cm^{-1}$. $^1$H-NMR spectra were recorded on a Varian EM (90 MHz), a Varian XL-300 (300 MHz) or a Bruker AM-200 (200 MHz) instrument with tetramethylsilane (TMS) as internal standard; chemical shifts (δ) are given in ppm and coupling constants (J) in Hz. $^{13}$C-NMR spectra were recorded on a Bruker AM-200 (50 MHz). Preparative column chromatography was run on silica gel (Merck, Kieselgel 60, 70-230 mesh).

**Methyl 2-[(5-methoxy-1-methyl)indol-2-yl]propionate** (**5**). The indole derivative **4** (3g, 13.6 mmol) was dissolved in N,N-dimethylformamide (30 mL) and added to sodium hydride (653 mg, 27.2 mmol) suspended in DMF (20 mL) at 0°C under argon. After 15 min, methyl iodide (4.2 mL, 65 mmol) was added and the mixture was allowed to come to room temperature for 3 h. Water and diethyl ether were added and the mixture stirred for 30 min; the layers were separated and the aqueous phase was extracted with diethyl ether; the organic layer was dried over $Na_2SO_4$, filtered and evaporated to dryness. Flash chromatography, eluting with ethyl acetate / hexane 1:5, yielded **5** (2 g, 60%) and **6** (0.4 g, 14%). (**5**): white solid, m.p. 95°C (from ethyl acetate-hexane); IR (KBr) ν 1780 (C=O); $^1$H-NMR (90 MHz, $CDCl_3$) δ 7.20 (d, H-7, J= 9), 7.05 (d, H-4, J=

2.2), 6.85 (dd, H-6, J= 9, J= 2.2), 6.35 (s, H-3), 3.91 (q, CH (8), J= 7.5), 3.82 (s, N(1)$CH_3$), 3.62 (s, $OCH_3$, $COOCH_3$), 1.60 (d, $CH_3$-C(8), J= 7.5).
Anal. Calcd. for $C_{14}H_{17}NO_3$: C, 68.01; H, 6.88; N, 5.66. Found: C, 68.04, H, 5.59; N, 5.69.

**General procedure for the synthesis of the amides 7 and 8.** A mixture of ester **5** (1 mol) and sodium cyanide (0.1 mol) in 9 M dried ammonia (or methylamine) in methanol (50 mL) was heated to 45°C in a sealed glass flask for 4 days (or 2 days). The solvent was evaporated, the residue dissolved in $CH_2Cl_2$ and washed with water. The aqueous layer was extracted with $CH_2Cl_2$, the organic phases combined, dried over $Na_2SO_4$, filtered and evaporated. Crystallization was used for product isolation.
**2-[(5-Methoxy-1-methyl)indol-2-yl]propionamide (7).** The ester **5** (575 mg, 2.3 mmol) was treated with 9 M dried ammonia in methanol (50 mL) and cyanide catalyst following the general procedure. Crystallization from methanol afforded the amide **7** (378 mg, 70%): m.p. 169°C; IR (KBr): ν 3500-3200 ($NH_2$), 1655 (C=O); $^1$H-NMR (300 MHz, DMSO): δ 7.37 (s (broad), $NH_2$), 7.26 (d, H-7, J= 8.8) 7.01 (s (broad), $NH_2$), 6.98 (d, H-4, J= 2.4), 6.22 (s, H-3), 3.78 (q, CH(8), J= 7.1), 3.72 (s, N(1)$CH_3$), 3.63 (s, $OCH_3$), 1.44 (d, $CH_3$-C(8), J= 7.1).
Anal. Calcd. for $C_{13}H_{16}N_2O_2$: C, 67.24; H, 6.89; N, 12.06. Found: C, 66.98; H, 6.86; N, 11.91.
**N-Methyl-2-[(5-methoxy-1-methyl)indol-2-yl]propionamide (8).** The amide **8** was obtained in 84% yield, according to the general procedure: m.p. 165°C (from methanol); IR (KBr): ν 3300 ($NH_2$), 1650 (C=O); $^1$H-NMR (300MHz, DMSO): δ 7.26 (d, H-7, J= 8.8), 7.04 (d, H-4, J= 2.3), 6.80 (dd, H-6, J= 8.8, J= 2.3), 6.33 (s (broad), H-3), 3.86 (q, CH(8), J= 7.3), 3.81 ( s, N(1)$CH_3$), 3.69 (s, $OCH_3$), 2.71 (d, $NCH_3$), J= 4.7), 1.58 (d, $CH_3$-C(8), J= 7.3).
Anal. Calcd. for $C_{14}H_{18}N_2O_2$: C, 68.29; H, 7.31; N, 11.38. Found: C, 67.99 H, 7.40; N, 11.39.

**2-[(5-Methoxy-1-methyl)indol-2-yl]propylamine (2a).** A suspension of lithium aluminium hydride (310 mg, 8.1 mmol) in dry THF (15 mL) was cooled at 0°C and a solution of the amide **7** (378 mg, 1.62 mmol) in dry THF (15 mL) was added dropwise with stirring. The temperature was allowed to rise and when the addition was finished the mixture was boiled for two days to complete the reduction. The mixture was cooled and standard workup was done. Flash chromatography, eluting with chloroform/methanol 1:1, provided **2a** (200 mg, 56%) as a yellow oil which was dissolved in diethyl ether and added over a solution of oxalic acid in diethyl ether. Evaporation to dryness and recrystallization from ethanol-ether yielded the acid oxalate of **2a**: m.p. 178°C; $^1$H-NMR data are given in Table.
Anal. Calcd. for $C_{15}H_{20}N_2O_5$: C, 58.44; H, 6.49; N, 9.09. Found: C, 58.40; H, 6.40; N, 9.00.

**N-Methyl-2-[(5-methoxy-1-methyl)indol-2-yl]propylamine (2b).** The amide **8** (480 mg, 1.9 mmol) was reduced with lithium aluminium (369 mg, 9.7 mmol) following the procedure used for **2a**. The obtained crude was flash-chromatographed ($CHCl_3$/$CH_3OH$ 3:1) to give the amine **2b** (315 mg, 70%) as an oil whose acid oxalate was recrystallized from ethanol-ether: m.p. 136°C; $^1$H-NMR data are summarized in Table; $^{13}$C-NMR (50 MHz, DMSO): δ 164.46 (C=O), 153.73 (C5) 135.83 (C2), 132.95 (C7a), 123.63 (C3a), 11.89, 110.75, 102.01 (C7 C4 C6), 101.75 (C3) 55.90 ($OCH_3$), 54.05 (N(1)$CH_3$), 30.17 (C8), 25.74 (C9) 18.59 ($CH_3$-C8).
Anal. Calcd. for $C_{16}H_{22}N_2O_5$: C, 59.63; H, 6.83; N, 8.69. Found: C, 59.45; H, 6.80; N, 8.41.

**[(5-Methoxy-1-methyl)indol-2-yl]methylalcohol (10).** A suspension of lithium aluminium hydride (20 g, 0.5 mol) in dry THF (500 mL) was cooled at 0°C and a solution of the ester **9** (23 g, 0.1 mol) in dry THF (100 mL) was added dropwise with stirring. The temperature was allowed to rise and when the addition was finished the mixture was boiled. After stirring for 2 h, the mixture was hydrolyzed by careful dropwise addition of water, filtered through Celite and the solvent removed in vacuum to afford the alcohol **10** (16.5 g, 81%): m.p. 106°C (from benzene); $^1$H-NMR (90 MHz, $CDCl_3$): δ 7.15 (d, H-7, J= 9), 7.0 (d, H-4, J= 3), 6.85 (dd, H-6, J= 9, J= 3), 6.3 (s, H-3), 4.65 (s, 2H, $CH_2OH$), 3.8 (s, N(1)$CH_3$), 3.62 (s, $OCH_3$).
Anal. Calcd. for $C_{11}H_{13}NO_2$: C, 69.10; H, 7.18; N, 7.10. Found: C, 68.92; H, 6.88; N, 7.32.

**[(5-Methoxy-1-methyl)indol-2-yl]carbaldehyde (11).** To a solution of **10** (16 g, 84 mmol) in dry ehter/THF (3:1) was added manganese dioxide (Merck, 73 g, 840 mmol) and sodium chloride (19.6 g, 336 mmol). The reaction was stirred for 12 h at room temperature. The mixture was filtered through silica gel and concentrated. Recrystallization from ethanol provided the aldehyde **11** (12 g, 76%): m.p. 88°C; IR (KBr): ν 1685 (C=O); $^1$H-NMR (90 MHz, $CDCl_3$): δ 9.8 (s, 1H, CHO), 7.3-6.9 (4H, indole),3.9 (s, N(1)$CH_3$), 3.7 (s, $OCH_3$).
Anal. Calcd. for $C_{11}H_{11}NO_2$: C, 69.84; H, 5.82; N, 7.40. Found: C, 69.70; H, 6.01; N, 7.10.

**1-[(5-Methoxy-1-methyl)indol-2-yl]-2-nitropropene (12).** A mixture of the [(5-methoxy-1-methyl) indol-2-yl]carbaldehyde (**11**, 3 g, 16 mol), nitroethane (2 g, 25 mmol) and ammoniun acetate (0.44 g, 5 mmol) in ethanol (15 mL) was refluxed for 3 h. The solution was concentrated under reduced pressure and the crude was washed with water and recrystallized from ethanol-benzene afforded **12** (3.5 g, 90%): m.p. 170-2°C; IR (KBr) ν 1620 ($NO_2$), 1310 ($NO_2$); $^1$H-NMR (90 MHz, $CDCl_3$): δ 8.12 (s, CH(8)=C), 7.2-6.8 (m, 4H, indole), 3.80 (s, N(1)$CH_3$), 3.70 (s, $OCH_3$), 2.50 (s, $CH_3$-C(9)=).
Anal. Calcd. for $C_{13}H_{14}N_2O_3$: C, 63.41; H, 5.69; N, 11.38. Found: C, 63.34; H, 5.57; N, 11.16.

**α-Methyl-2-[(5-Methoxy-1-methyl)indol-2-yl]ethylamine (3a).** To a suspension of lithium aluminium hydride (4 g, 0.11 mol) in dry THF (100 mL) was added dropwise a solution of compound **12** (3.5 g, 0.014 mol) in dry THF (50 mL). When the addition was finished the mixture was boiled for 3 h and then stirred overnight at room temperature. The mixture was hydrolyzed by careful dropwise addition of water, filtered through Celite and the solvent removed in vacuum to afford the amine **3a** which was isolated as acid oxalate: m.p. 160°C (from ethanol-ether); IR (KBr): ν 3500-3350 ($NH_2$); $^1$H-NMR (Table); $^{13}$C-NMR (50 MHz, $D_2O$): δ 166.61 (C=O), 154.32 (C5), 137.49 (C2), 134.45 (C7a), 128.65 (C3a), 112.18, 111.83 (C6 C7 C4), 103.89 (C3), 57.34 ($OCH_3$) 48.32 (N(1)$CH_3$), 32.49 (C8), 30.53 (C9), 18.92 ($\underline{C}H_3$-C9).
Anal. Calcd. for $C_{15}H_{19}N_2O_5$: C, 58.44; H, 6.49; N, 9.09. Found: C, 58.17; H, 6.70; N, 8.93.

**N-Ethoxycarbonyl-α-methyl-2-[(5-methoxy-1-methyl)indol-2-yl]ethylamine (13).** To a suspension of amine **3a** (acid oxalate, 2 g, 6.5 mmol) in 2 N sodium hydroxide (20 mL), diethyl ether (15 mL) was added. The mixture was cooled at 0°C and a solution of ethoxycarbonyl chloride (0.86 g, 8 mmol) in dry ether (5 mL) was added dropwise with stirring. The temperature was allowed to rise and the stirring was continued for 3 h at room temperature. When the reaction was complete, the organic layer was separated and the

aqueous solution was extracted twice with ether. The combined organic extracts were washed with water, dried ($Na_2SO_4$) and the solvent removed in vacuum. The residue was compound **13** pure (1.5 g, 79%): m.p. 81-2°C (hydroscopic); IR (KBr): ν 3340 (NH), 1690 (C=O), 1270 (C-N); $^1$H-NMR (90 MHz, $CDCl_3$): δ 7.15 (d, H-7, J= 9), 7.00 (d, H-4, J= 3), 6.80 (dd, H-6, J= 9, J= 3), 6.20 (s, H-3), 4.05 (q, $CH_2$ (Et), J= 6), 3.75 (s, N(1)$CH_3$), 3.61 (s, $OCH_3$), 3.60 (m, CH(9)), 2.85 (m, $CH_2$(8)), 1.15 (s, $CH_3$-C9), 1.15 (t, $CH_3$ (Et), J= 6).
Anal. Calcd. for $C_{16}H_{22}N_2O_3$: C, 66.20; H, 7.58; N, 9.65. Found: C, 66.50; H, 7.55; N, 9.65.

**N,α-Dimethyl-2-[(5-methoxy-1-methyl)indol-2-yl]ethylamine (3b).** The carbamate **13** (0.8 g, 3.1 mmol) was reduced with lithium aluminium hydride (240 mg, 6.2 mmol) in boiling THF (20 mL) for 3 h under stirring. After standard workup, the crude was added over a solution of oxalic acid in ether to give the acid oxalate of **3b** (0.7 g, 78%): m.p. 85°C (from ethanol-ether); IR (KBr): ν 3500-3400 (NH); $^1$H-NMR (Table); $^{13}$C-NMR (50 MHz, $D_2O$): δ 167.14 (C=O), 154.77 (C5), 137.45 (C2), 134.81 (C7a), 129.04 (C3a), 112.53, 112.07, 104.44 (C7 C4 C6 C3), 57.80 ($OCH_3$), 56.12 (N(1)$CH_3$), 31.53 ($NCH_3$), 31.44 (C8), 30.86 (C9), 16.73 ($\underline{C}H_3$-C9).
Anal. Calcd. for $C_{16}H_{22}N_2O_5$: C, 59.62; H, 6.83; N, 8.69. Found: C, 59.45; H, 7.06; N, 8.50.

**General procedure for the N-alkylation of 2 and 3.** A solution of the respective amine **2** or **3** (1 mmol) in dry THF (50 mL) and *t*-butylamine (1.5 mmol) was cooled at 0ºC. To the stirred mixture a solution of the appropriated allenic or acetylenic bromide (1.2 mmol) was added dropwise. The mixture was stirred at room temperature until the reaction was complete. The solvent was removed in vacuum and the residue treated with water and extracted with ether. Flash chromatography was used for product isolation. The $^1$H-NMR data are summarized in Table.
**N-Methyl-N-(2-propynyl)-2-[(5-methoxy-1-methyl)indol-2-yl]propylamine (2c).** The amine **2b** (65 mg, 0.28 mmol) was N-alkylated with propargyl bromide (0.025 ml, 0.03 mmol) following the general procedure. Flash chromatography using hexane/ethyl acetate 5:1 as the eluent, provied the amine **2c** (50 mg, 60%) as a yellow oil. The acid oxalate was prepared: m.p. 115°C (from ethanol/ ether).
Anal. Calcd. for $C_{19}H_{24}N_2O_5$: C, 63.33; H, 6.66; N, 7.77. Found: C, 63.60; H, 6.80; N, 7.99.
**N-(2,3-Butadienyl)-N-methyl-2-[(5-methoxy-1-methyl)indol-2-yl]propylamine (2d).** Following the general procedure, the amine **2b** (250 mg, 1.mmol) was N-alkylated with 2,3-butadienyl bromide (172.7 mg, 1.3 mmol). Chromatography using hexane/ ethyl acetate 3:1 as the eluent gave the desired amine **2d** (195 mg, 63%) as an oil. The acid oxalate was prepared: m.p. 125°C (from ethanol/ ether).
Anal. Calcd. for $C_{20}H_{26}N_2O_5$: C, 64.17; H, 6.95; N, 7.48. Found: C, 64.20; H, 6.88; N, 7.21.
**N-(2-Propynyl)-α-methyl-2-[(5-methoxy-1-methyl)indol-2-yl]ethylamine (3c).** N-alkylation of **3a** (1.5 g, 5 mmol) with 0.4 ml (5.5mmol) of propargyl bromide yieled, after chromatography eluting with chloroform/ methanol 6:1 and formation of the acid oxalate, **3c** (1.1 g, 70%): m.p. 130ºC (from ethanol/ether); IR (KBr): ν 3500-3400 (NH), 3250 (≡C-H), 2140 (C≡C); $^{13}$C-NMR (50 MHz, DMSO): δ 164.11 (C=O), 153.55 (C5), 136.28 (C2), 132.51 (C7a), 127.52 (C3a), 110.49, 110.17, 101.59 (C7 C6 C4), 100.42 (C3), 78.24 (≡CH), 76.55 (C≡), 55.32 ($OCH_3$), 51.57 (N(1)$CH_3$), 33.58 (N-$CH_2$-C≡), 30.40 (C8), 29.61 (C9), 16.19 ($CH_3$-C9).
Anal. Calcd. for $C_{18}H_{22}N_2O_5$: C, 62.42; H, 6.35; N, 8.09. Found: C, 62.26; H, 6.52; N, 8.13.

**N-(2,3-Butadienyl)-α-methyl-2-[(5-methoxy-1-methyl)indol-2-yl)]ethylamine (3d).** N-alkylation of **3a** (2g, 6.8 mmol) with 2,3-butadienyl bromide (1 g, 7.5 mmol), after chromatography using $CHCl_3$/ $CH_3OH$ 6:1 as eluent and acid oxalate formation, yielded **3d** (1.26 g, 55%): m.p. 137°C (from ethanol/ether); IR (KBr): ν 1940 (C=C=C).

Anal. Calcd. for $C_{19}H_{24}N_2O_5$. 1 1/4 $H_2O$: C, 59.60; H, 6.90; N, 7.30. Found: C, 59.67; H, 6.63; N, 7.11.

**N-(2-Butynyl)-α-methyl-2-[(5-methoxy-1-methyl)indol-2-yl]ethylamine (3e).** The amine **3a** (2 g, 6.8 mmol) was N-alkylated with 2-butynyl bromide (1g, 7.5 mmol). Flash chromatography ($CHCl_3$/$CH_3OH$ 6:1) provided the amine **3e** (1.6 g, 70%) as an oil. The acid oxalate: m p. 127°C (from ethanol/ ether); IR (KBr): ν 3500-3400 (NH).

Anal. Calcd. for $C_{19}H_{24}N_2O_5$.1/2 $H_2O$: C, 61.78; H, 6.77; N, 7.58. Found: C, 61.93; H, 6.44; N, 7.86.

**N,α-Dimethyl-N-(2-propynyl)-2-[(5-methoxy-1-methyl)indol-2-yl]ethylamine (3f).** N-alkylation of **3b** (1 g, 4.5 mmol) with propargyl bromide (0.4 ml, 5.4 mmol) gave **3f** (0.8 g, 80%). The acid oxalate was prepared: m.p. 106°C (from ethanol/ ether); IR (KBr): ν 2140 (≡C-H).

Anal. Calcd. for $C_{19}H_{24}N_2O_5$. $1H_2O$: C, 60.31; H, 6.87; N, 7.40. Found: C, 60.37; H, 6.80; N, 7.26.

**N-(2,3-Butadienyl)-N,α-dimethyl-2-[(5-methoxy-1-methyl)indol-2-yl]ethylamine (3g).** The N-alkylation of **3b** (1.85 g, 8 mmol) with 2,3-butadienyl bromide (1.27 g, 9.6 mmol) gave **3g** (1.7 g, 80%). The acid oxalate melts at 127-8°C (from ethanol/ ether); IR (KBr): ν 1960 (C=C=C).

Anal. Calcd. for $C_{20}H_{26}N_2O_5$. 1/4 $H_2O$: C, 63.49; H, 7.01; N, 7.40. Found: C, 63.56; H, 7.21; N, 7.19.

**N-(2-Butynyl)-N,α-dimethyl-2-[(5-methoxy-1-methyl)indol-2-yl)]ethylamine (3h).** The N-alkylation of **3b** was carried out as described above, and **3h** was obtained in 85% yield. The acid oxalate was prepared: m.p. 170°C (hydroscopic); IR (KBr): ν 2250 (C≡C).

Anal. Calcd. for $C_{20}H_{26}N_2O_5$.11/2 $H_2O$: C, 60.15; H, 7.01; N, 7.26. Found: C, 60.45; H, 7.00; N, 7.11.

## Enzymatic assays:

Mitochondrial MAO was prepared from bovine brain according to the method described by Reynolds[18]. The isolated mitochondria was dispersed in ice-cold 5mM potassium phosphate buffer, pH 7.3, to give a preparation containing about 23.6 mg/mL of protein, using bovine serum albumin as standard[19]; 0.5 mL samples were placed in vials and frozen at -20°C. For standardization, MAO-B activity was estimated by Tabor's spectrophotometric method[20] in UT/mL.

For each assay, a suspension containing 1 UT/mL and 0.5 mg/mL of protein was preincubated in potassium phosphate buffer 30mM, pH 7.3 for 20 min at 37°C with several inhibitor concentration (from 0.01 nM to 1.0 mM). The inhibitor was added to the reaction mixture in aqueous or DMSO solution. The remaining activity was determined isotopically in potassium phosphate buffer 30 mM, pH 7.3 (0.5 mL), with 0.5 mM $^{14}$C-tyramine·HCl (0.8 Ci/mol, Amersham) by described methods[21] with the suitable modification reported by us[11-13]. $IC_{50}$ values were obtained graphically from residual activity percentage *versus* -log [I] plots.

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