Synthesis and Evaluation of Iodinated Benzamide Derivatives as Selective and Reversible Monoamine Oxidase B Inhibitors

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A new series of iodinated analogues of *N*-(2-aminoethyl)benzamide was synthesized and evaluated for inhibitory potency and specificity toward monoamine oxidase type-B (MAO-B). Among them, *N*-(2-aminoethyl)-2-chloro-4-iodobenzamide hydrochloride (**2d**) showed high inhibitory potency and selectivity against MAO-B. The type of MAO-B inhibition by **2d** was non-competitive and the inhibition constant (K_i) was 0.80 μ M. Strong and selective *in vivo* MAO-B inhibition by **2d** was also confirmed. The brain MAO-B inhibition by **2d** was reversible and the enzyme activity completely returned to the control value 24 h after administration. Compound **2d** was, therefore, considered to be a candidate for advanced development as a radioiodinated ligand that may be useful for functional MAO-B studies in the living brain using single photon emission computer tomography.

Keywords monoamine oxidase B; specific inhibitor; *N*-(2-aminoethyl)-4-chlorobenzamide hydrochloride (Ro 16-6491); iodinated derivative; single photon emission computer tomography

Monoamine oxidase (MAO) [EC 1.4.3.4] is a flavin-containing enzyme that catalyzes the oxidative deamination of endogenous neurotransmitter amines as well as exogenous amines. It exists in two subtypes, MAO-A and MAO-B, on the basis of their different specificities toward substrates and inhibitors.¹⁾ Clorgyline and *l*-deprenyl irreversibly and selectively inhibit MAO-A and MAO-B, respectively, by binding covalently to the flavin coenzyme of MAO.²⁾ They behave as mechanism-based enzyme inhibitors and are also termed suicide substrates.³⁾

Positron emission tomography (PET) and single photon emission computer tomography (SPECT) provide the capability of noninvasively examining biochemical transformation in the intact living system utilizing organic molecules labeled with a positron emitter or a single photon emitter. For the direct and noninvasive mapping and functional studies of MAO activity in the living brain, ¹¹C labeled clorgyline and *l*-deprenyl⁴⁾ and radioiodinated clorgyline⁵⁾ have been investigated as radio-ligands for PET and SPECT studies, respectively.

Recently, a new generation of short-acting MAO inhibitors with high selectivity toward the two different forms of MAO has been developed, and their usefulness as an antidepressant and as an anti-Parkinsonian drug is currently being evaluated.⁶⁾ Among the new class of potent and specific MAO-B inhibitors, Ro 16-6491 [*N*-(2-aminoethyl)-4-chlorobenzamide hydrochloride, **2e** (Chart 1)] is a reversible and highly selective MAO-B inhibitor.⁷⁾ It counteracts the neurotoxic effects induced by 1-methyl-

4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a suspected Parkinsonism inducing drug.⁸⁾ Moreover, tritium-labeled Ro 16-6491 binds specifically and with high affinity to MAO-B.⁹⁾

These characteristics of Ro 16-6491 indicate that it appears to be suitable as a prototype or template for the design of analogues that may be labeled with imaging radionuclides for use as new radiopharmaceuticals for functional MAO-B studies in the living brain with PET and SPECT. Moreover, such a radioligand with high specific radioactivity would also be useful for a variety of molecular biology and biochemical applications. The radioiodine, ¹²³I possesses very suitable radiation properties, half-life of 13 h and gamma ray energy of 159 keV, for SPECT imaging, and ¹²⁵I is also a useful radionuclide for *in vitro* studies. We report here the syntheses of a novel series of iodinated Ro 16-6491 analogues amenable to radiolabeling with ¹²³I or ¹²⁵I. The preliminary *in vitro* and *in vivo* studies on the inhibitory potency and selectivity toward MAO-B were also performed in order to select a new ligand candidate for ¹²³I or ¹²⁵I labeling.

Synthesis The iodinated analogues of Ro 16-6491 (**2a—d**) were prepared by the reactions outlined in Chart 1. Treatment of the appropriately substituted benzoic acids (**1a—e**) with thionyl chloride generated acid chlorides, which were then reacted with *N*-acetylenediamine in the presence of triethylamine in anhydrous chloroform to yield corresponding *N*-(2-acetylaminoethyl)benzamides. Hydrolysis of these intermediates in 2 N hydrochloric acid and ethanol provided the desired compounds (**2a—e**) in a 44—64% overall yield.

Biological Results and Discussion

The inhibitory potency of the iodinated analogues, **2a—d**, and Ro 16-6491 (**2e**) against MAO-A and MAO-B activities in rat liver homogenates were selectively measured *in vitro* using a combination of kynuramine as a substrate and clorgyline or *l*-deprenyl as a specific MAO-A or MAO-B inhibitor, respectively, according to a modified fluorometric procedure.¹⁰⁾ These results are summarized as concentration-dependent inhibition curves in Fig. 1. *N*-(2-

Chart 1

Fig. 1. Concentration-Dependent Inhibition Curves of MAO-A (Right) and MAO-B (Left) by **2a** (■), **2b** (▲), **2c** (□), **2d** (●), and **2e** (○) in Rat Liver Homogenate *in Vitro*

MAO-A and MAO-B activities in rat liver homogenates were selectively measured after treatment with various concentrations of each compound using kynuramine as a substrate in the presence of *L*-deprenyl or cloglyline as described under Experimental. Each point is the mean value of triplicate determinations.

Fig. 2. Double-Reciprocal Plots for the Inhibition of MAO-B by **2d** in Rat Liver Homogenate

MAO-B activity in rat liver homogenates was measured in the absence (○) or presence of 1 (●), 2 (□), or 3 (■) μM of **2d** using kynuramine and cloglyline as described under Experimental. Ordinate: $1/\{\text{initial velocity (nmol/mg protein/min)}\}$. Abscissa: $1/\{\text{kynuramine concentration (mM)}\}$. Each point represents the mean of triplicate determinations.

Aminoethyl)-2-chloro-4-iodobenzamide hydrochloride (**2d**) was found to have high inhibitory potency against MAO-B, and its IC_{50} value was calculated as $0.40 \mu\text{M}$ from the results shown in Fig. 1, fully comparable to Ro 16-6491 ($\text{IC}_{50} 0.35 \mu\text{M}$) examined under the same conditions. The ratio of IC_{50} for MAO-A to that for MAO-B of **2d** was 450, indicating its high selectivity toward MAO-B. However, compounds **2a**, **2b** and **2c** were found to be relatively weak MAO-B inhibitors ($\text{IC}_{50} 1.4\text{--}2.7 \mu\text{M}$). Interestingly, **2a**, bearing iodine at the *meta* position on the benzene ring, showed no selectivity for MAO-B (IC_{50} ratio of MAO-A to MAO-B 1.7).

Thus, the most potent compounds, **2d**, among the iodinated Ro 16-6491 derivatives tested *in vitro*, was chosen for further evaluation. The results of kinetic studies on the MAO-B inhibition by **2d** are shown as double-reciprocal plots in Fig. 2. These data indicated that the type of inhibition of rat liver MAO-B by **2d** was non-competitive. The inhibition constant (K_i) value was calculated as $0.80 \mu\text{M}$.

The *in vivo* inhibitory potency and specificity of **2d** against MAO-B activity in the brain were examined using brain homogenates from **2d** administered mice. Mice were treated with graded doses ($0.1\text{--}200 \mu\text{mol/kg}$) of **2d**. After 1 h, the brain homogenates were prepared and the MAO-A and

Fig. 3. Dose-Response Curves for the Inhibition of MAO-A (■) and MAO-B (●) in Mouse Brain by **2d**

Mice were injected intravenously with graded doses ($0.1\text{--}200 \mu\text{mol/kg}$) of **2d** 1 h before sacrifice. The brains were excised and homogenized. MAO-A and MAO-B activities in the brain homogenates were measured *ex vivo* using kynuramine as a substrate in the presence of *L*-deprenyl or cloglyline as described under Experimental. Data represent mean $\pm$ S.D. of four animals as percent of the control values.

MAO-B activities in the homogenates were selectively measured *ex vivo*. As shown in Fig. 3, there was an almost exclusive inhibition of MAO-B activity in the brain. The ED_{50} value for MAO-B inhibition was calculated as $14 \mu\text{mol/kg}$ from these results. On the contrary, MAO-A activity in the brain was only slightly affected up to the high dose of $200 \mu\text{mol/kg}$, where it was reduced by about 15% compared to the control activity. These results confirmed that **2d** had a very potent and specific inhibitory effect on MAO-B *in vivo* as well as *in vitro*.

The time course of inhibitory effect and recovery of MAO-B activity in the mouse brain was investigated after a single administration of $50 \mu\text{mol/kg}$ of **2d**. As shown in Fig. 4, the MAO-B activity was nearly 30% of the control activity at 0.5–4 h, about 60% at 12 h, and the enzyme activity completely returned to the control value 24 h after injection. Thus, the reversibility of the brain MAO-B inhibition by **2d** was shown directly from these experiments.

The clinical use of the long-acting irreversible MAO inhibitors was obstructed by their marked hepatotoxic and hypertensive effects.¹¹⁾ In contrast, the new generation of reversible and short-acting MAO inhibitor is expected to be more tolerable and easier to dose.⁶⁾ Short duration of action is also suitable for the use of the labeled compound as a radiopharmaceutical, because the acquisition of the

Fig. 4. Time Course of the Recovery of MAO-B Activity in Mouse Brain after Administration of **2d**

Mice were injected intravenously with 50 $\mu\text{mol/kg}$ of **2d**. The animals were sacrificed at various times after administration and their brains were removed and homogenized. MAO-B activity in the brain homogenates was measured *ex vivo* using kynuramine as a substrate in the presence of clorgyline as described under Experimental. Data represent mean $\pm$ S.D. of four animals as percent of the control activity.

in vivo images or diagnosis using a radiopharmaceutical is generally accomplished within an hour. Moreover, this characteristic seems to be very effective in reducing the radiation dose and it is also preferable for repeated studies.

Radioiodinated **2d**, ^{125}I labeled **2d**, has been synthesized from its corresponding tributylstannyl precursor by radioiododestannylation reaction using sodium [^{125}I]iodide and hydrogen peroxide with high yield and high site specificity as well as high specific radioactivity. Further studies of this new agent are now in progress.

In conclusion, among the iodinated Ro 16-6491 derivatives prepared, **2d** was found to have high inhibitory potency and selectivity against MAO-B. The type of MAO-B inhibition by **2d** was non-competitive. Strong and selective MAO-B inhibition by **2d** was also confirmed *in vivo*. Moreover, the reversibility of the brain MAO-B inhibition by **2d** was demonstrated. These characteristics seem to be suitable for the use of the radioiodinated **2d** as a radiopharmaceutical. In conjunction with the effective preparation of the radioiodinated counterpart, **2d** was considered to be a candidate for further studies as a SPECT radiopharmaceutical for functional MAO-B studies in the living brain.

Experimental

All melting points are uncorrected. Infrared (IR) spectra were recorded on a JASCO IR-700 spectrometer. Proton nuclear magnetic resonance ($^1\text{H-NMR}$) spectra were recorded on a Varian Gemini-200 (200 MHz) spectrometer and the chemical shifts are reported in ppm downfield from an internal tetramethylsilane standard. High-resolution mass spectra (HRMS) were obtained on a Hitachi M-80 instrument.

Benzoic Acid Derivatives (1a–e) Compounds **1a**, **1b** and **1e** were obtained commercially and used without further purification. Compounds **1c**¹² and **1d**¹³ were prepared by the reported methods.

***N*-(2-Aminoethyl)-3-iodobenzamide Hydrochloride (2a)** A mixture of 3-iodobenzoic acid (**1a**) (5.0 g, 20 mmol) and thionyl chloride (20 ml) was refluxed for 2 h. After removing the excess thionyl chloride *in vacuo*, the residue was dissolved in anhydrous chloroform (20 ml), which was added dropwise to a solution of *N*-acetylenediamine (2.2 g, 22 mmol) and triethylamine (2.2 g, 22 mmol) in anhydrous chloroform (50 ml) under cooling. The reaction mixture was stirred at an ambient temperature for 2 h and then evaporated *in vacuo*. The crude *N*-(2-acetylaminoethyl)-3-iodobenzamide was dissolved in a mixture of ethanol (40 ml) and 2 *N* hydrochloric acid (60 ml), which was then refluxed for 15 h. After removal of the volatile components *in vacuo*, the residue was recrystallized from methanol–ether to give **2a** (2.90 g, 44%). mp 244–246 °C. *Anal.* Calcd for $\text{C}_9\text{H}_{12}\text{ClIN}_2\text{O}$: C, 33.10; H, 3.70; N, 8.58. Found: C, 32.81; H, 3.73; N, 8.63. IR (KBr): 3252, 2910, 1647, 1548, 1451, 1317, 1169 cm^{-1} .

$^1\text{H-NMR}$ ($\text{DMSO-}d_6$) δ : 2.98 (2H, t, $J=6.0$ Hz, CH_2NH_3^+), 3.52 (2H, q, $J=6.0$ Hz, NHCH_2), 7.29 (1H, t, $J=7.8$ Hz, aromatic), 7.89–7.96 (2H, m, aromatics), 8.18 (3H, br, NH_3^+), 8.27 (1H, t, $J=1.5$ Hz, aromatic), 8.87 (1H, br, NH). CI-HRMS (free base) Calcd for $\text{C}_9\text{H}_{12}\text{IN}_2\text{O}$ (MH^+) m/z : 290.9993. Found: 290.9985.

The following compounds, **2b–e**, were prepared in a similar manner to that of **2a** from the corresponding substituted benzoic acid derivatives, **1b–e**.

***N*-(2-Aminoethyl)-4-iodobenzamide Hydrochloride (2b)** Yield 64%. mp 260–262 °C. *Anal.* Calcd for $\text{C}_9\text{H}_{12}\text{ClIN}_2\text{O}$: C, 33.10; H, 3.70; N, 8.58. Found: C, 32.93; H, 3.70; N, 8.63. IR (KBr): 3266, 3016, 1642, 1543, 1476, 1318, 1168 cm^{-1} . $^1\text{H-NMR}$ ($\text{DMSO-}d_6$) δ : 2.98 (2H, t, $J=6.0$ Hz, CH_2NH_3^+), 3.52 (2H, q, $J=6.0$ Hz, NHCH_2), 7.71 (2H, d, $J=8.4$ Hz, aromatics), 7.87 (2H, d, $J=8.4$ Hz, aromatics), 8.12 (3H, br, NH_3^+), 8.86 (1H, br, NH). CI-HRMS (free base) Calcd for $\text{C}_9\text{H}_{12}\text{IN}_2\text{O}$ (MH^+) m/z : 290.9993. Found: 291.0010.

***N*-(2-Aminoethyl)-4-chloro-2-iodobenzamide Hydrochloride (2c)** Yield 46%. mp 204–206 °C. *Anal.* Calcd for $\text{C}_9\text{H}_{11}\text{Cl}_2\text{IN}_2\text{O}$: C, 29.94; H, 3.07; N, 7.76. Found: C, 30.17; H, 3.12; N, 7.73. IR (KBr): 3256, 3010, 1647, 1546, 1465, 1316, 1161 cm^{-1} . $^1\text{H-NMR}$ ($\text{DMSO-}d_6$) δ : 2.96 (2H, t, $J=6.2$ Hz, CH_2NH_3^+), 3.50 (2H, q, $J=6.2$ Hz, NHCH_2), 7.53 (2H, s, aromatics), 7.96 (1H, s, aromatic), 8.34 (3H, br, NH_3^+), 8.72 (1H, br, NH). CI-HRMS (free base) Calcd for $\text{C}_9\text{H}_{11}\text{ClIN}_2\text{O}$ (MH^+) m/z : 324.9603. Found: 324.9567.

***N*-(2-Aminoethyl)-2-chloro-4-iodobenzamide Hydrochloride (2d)** Yield 48%. mp 238–240 °C. *Anal.* Calcd for $\text{C}_9\text{H}_{11}\text{Cl}_2\text{IN}_2\text{O}$: C, 29.94; H, 3.07; N, 7.76. Found: C, 29.98; H, 3.10; N, 7.74. IR (KBr): 3264, 3040, 1649, 1535, 1465, 1316, 1165 cm^{-1} . $^1\text{H-NMR}$ ($\text{DMSO-}d_6$) δ : 2.95 (2H, t, $J=6.2$ Hz, CH_2NH_3^+), 3.49 (2H, q, $J=6.2$ Hz, NHCH_2), 7.39 (1H, d, $J=8.0$ Hz, aromatic), 7.80 (1H, dd, $J=8.0$, 1.4 Hz, aromatic), 7.93 (1H, d, $J=1.4$ Hz, aromatic), 8.15 (3H, br, NH_3^+), 8.73 (1H, br, NH). CI-HRMS (free base) Calcd for $\text{C}_9\text{H}_{11}\text{ClIN}_2\text{O}$ (MH^+) m/z : 324.9603. Found: 324.9612.

***N*-(2-Aminoethyl)-4-chlorobenzamide Hydrochloride (Ro 16-6491, 2e)** Yield 50%. mp 213–215 °C. (lit.¹⁴) mp 211–213 °C. *Anal.* Calcd for $\text{C}_9\text{H}_{12}\text{Cl}_2\text{N}_2\text{O}$: C, 45.98; H, 5.14; N, 11.91. Found: C, 45.90; H, 5.12; N, 11.91. IR (KBr): 3266, 2912, 1646, 1546, 1486, 1318 1166 cm^{-1} . $^1\text{H-NMR}$ ($\text{DMSO-}d_6$) δ : 3.00 (2H, t, $J=6.0$ Hz, CH_2NH_3^+), 3.55 (2H, q, $J=6.0$ Hz, NHCH_2), 7.55 (2H, d, $J=8.4$ Hz, aromatics), 7.98 (2H, d, $J=8.4$ Hz, aromatics), 8.23 (3H, br, NH_3^+), 8.96 (1H, br, NH). CI-HRMS (free base) Calcd for $\text{C}_9\text{H}_{12}\text{ClIN}_2\text{O}$ (MH^+) m/z : 199.0638. Found: 199.0623.

Assay of MAO Activity The livers of male Wistar rats weighing 200–250 g were homogenized with 10 volumes of ice-cold 0.25 M sucrose and 10 mM sodium phosphate buffer (pH 7.4). The homogenates were centrifuged at 1000 *g* for 10 min at 4 °C to remove cell debris. The supernatants were taken and their protein content was adjusted to 10 mg/ml and stored at –20 °C until used. The protein content was determined according to the biuret method.

MAO-A and MAO-B activities in the homogenates were selectively measured using kynuramine as a substrate and clorgyline or *l*-deprenyl as specific MAO-A or MAO-B inhibitors, respectively, according to the modified fluorometric procedure.¹⁰ Briefly, a reaction mixture containing 0.25 ml of homogenate (2.5 mg protein) and 1 μM of *l*-deprenyl hydrochloride (Research Biochemicals Inc.) (for MAO-A assay) or clorgyline hydrochloride (Research Biochemicals Inc.) (for MAO-B assay) in a total volume of 0.75 ml of 30 mM sodium phosphate buffer (pH 7.4) was preincubated at 37 °C for 20 min. Then, varying amounts of the test compound in 0.5 ml of an aqueous solution were added to the mixture and incubated at 37 °C for another 20 min. The reaction was started by the addition of 0.25 ml of 10 mM kynuramine dihydrobromide (Sigma Chemical Co.) solution and incubation was continued at 37 °C. After 30 min, the reaction was terminated by the addition of 0.5 ml of 10% zinc sulfate solution. The reaction mixture was centrifuged at 1000 *g* for 10 min. One milliliter of the supernatant was mixed with 2 ml of 1 *N* NaOH, then the fluorescence was measured at 390 nm with an excitation at 320 nm.

Dose-Dependent Inhibition of MAO Activity in Mouse Brain by 2d Male ddY mice weighing 20–25 g were used. Groups of four mice were injected intravenously through a lateral tail vein with graded doses (0.1–200 $\mu\text{mol/kg}$) of **2d** in 0.1 ml saline 1 h before sacrifice. Their brains were excised and homogenized with 5 volumes of an ice-cold Krebs–Ringer buffer (118 mM NaCl, 4.8 mM KCl, 25 mM NaHCO_3 , 1.2 mM KH_2PO_4 , 1.3 mM CaCl_2 , 1.2 mM MgSO_4 , and 10 mM glucose, pH 7.4–7.6). The homogenates were centrifuged at 1000 *g* for 10 min at 4 °C. The protein content of the supernatant was adjusted to 2.5 mg/ml. MAO-A and MAO-B activities in these brain homogenates were selectively measured *ex vivo* as described

above. Data were expressed as percent of the control values.

Time Course of Recovery of MAO-B Activity in Mouse Brain Groups of four male ddY mice (20–25 g) were injected intravenously through a lateral tail vein with 50 $\mu\text{mol/kg}$ of **2d** in 0.1 ml saline. The animals were sacrificed at various times after administration. The brains were removed and homogenized with 5 volumes of the ice-cold Krebs–Ringer buffer. The homogenates were centrifuged at 1000 g for 10 min at 4°C. The protein content of the supernatant was adjusted to 2.5 mg/ml. Then, the MAO-B activity in the brain homogenates was determined *ex vivo* as described above. Data were expressed as percent of the control activity.

References

- 1) a) D. L. Murphy, *Biochem. Pharmacol.*, **27**, 1889 (1978); b) C. J. Fowler, L. Orelund, and B. A. Callingham, *J. Pharm. Pharmacol.*, **33**, 341 (1981); c) C. J. Fowler and S. B. Ross, *Med. Res. Rev.*, **4**, 323 (1984).
- 2) a) R. R. Rando, *Science*, **185**, 320 (1974); b) J. Nagy and J. I. Salach, *Arch. Biochem. Biophys.*, **208**, 388 (1981).
- 3) a) C. T. Walsh, *Ann. Rev. Biochem.*, **53**, 493 (1984); b) L. E. Richards and A. Burger, *Progress Drug Research*, **30**, 205 (1986).
- 4) a) R. R. MacGregor, C. Halldin, J. S. Fowler, A. P. Wolf, C. D. Arnett, B. Langstrom, and D. Alexoff, *Biochem. Pharmacol.*, **34**, 3207 (1985); b) J. S. Fowler, R. R. MacGregor, A. P. Wolf, C. D. Arnett, S. L. Dewey, D. Schlyer, D. Christman, J. Logan, M. Smith, H. Sachs, S. M. Aquilonius, P. Bjurling, C. Halldin, P. Hartvig, K. L. Leenders, H. Lundqvist, L. Orelund, C. G. Stalnacke, and B. Langstrom, *Science*, **235**, 481 (1987); c) C. D. Arnett, J. S. Fowler, R. R. MacGregor, D. J. Schlyer, A. P. Wolf, B. Langstrom, and C. Halldin, *J. Neurochem.*, **49**, 522 (1987).
- 5) a) Y. Ohmomo, M. Hirata, K. Murakami, Y. Magata, C. Tanaka, and A. Yokoyama, *Chem. Pharm. Bull.*, **39**, 1038 (1991); b) *Idem*, *ibid.*, **39**, 3343 (1991).
- 6) K. F. Tipton, P. Dostert, and M. Strolin-Benedetti (eds.), "Monoamine Oxidase and Disease," Academic Press, New York, 1984.
- 7) a) R. Kettler, H. H. Keller, E. P. Bonetti, P. C. Wyss, and M. Da Prada, *J. Neurochem.*, **44** (Suppl.), S94 (1985); b) H. H. Keller, R. Kettler, G. Keller, and M. Da Prada, *Naunyn-Schmiedeberg's Arch. Pharmacol.*, **335**, 12 (1987).
- 8) M. Da Prada, R. Kettler, H. H. Keller, E. P. Bonetti, and R. Imhof, "Advances in Neurology," Vol. 45, Raven Press, New York, 1986, pp. 175–178.
- 9) a) A. M. Cesura, M. D. Galva, R. Imhof, and M. Da Prada, *J. Neurochem.*, **48**, 170 (1987); b) A. M. Cesura, R. Imhof, B. Takacs, M. D. Galva, G. B. Picotti, and M. Da Prada, *ibid.*, **50**, 1037 (1988); c) A. M. Cesura, R. Imhof, D. Muggli-Maniglio, G. B. Picotti, and M. Da Prada, *Biochem. Pharmacol.*, **39**, 216 (1990).
- 10) a) M. Kraml, *Biochem. Pharmacol.*, **14**, 1683 (1965); b) T. Yokoyama, N. Iwata, and T. Kobayashi, *Jpn. J. Pharmacol.*, **44**, 421 (1987); c) M. Naoi, Y. Hirata, and T. Nagatsu, *J. Neurochem.*, **48**, 709 (1987); d) M. Yamazaki, Y. Satoh, Y. Maebayashi, and Y. Horie, *Chem. Pharm. Bull.*, **36**, 670 (1988).
- 11) a) J. Rabkin, F. Quitkin, W. Harrison, E. Tricamo, and P. McGrath, *J. Clin. Psychopharmacol.*, **4**, 270 (1984); b) K. White and G. Simpson, *Integr. Psychiatry*, **3**, 34 (1985).
- 12) K. Plez, I. Ernest, E. Adoleroova, J. Metysova, and M. Protiva, *Collect. Czech. Chem. Commun.*, **33**, 1852 (1968).
- 13) I. G. Farbenind, Brit. Patent 353537 (1930) [*Chem. Abstr.*, **26**, 5311 (1932)].
- 14) M. Da Prada, J. Renato, E. Kyburz, and P. C. Wyss, Ger. Patent 3407654 (1984) [*Chem. Abstr.*, **102**, 45640z (1985)].