Synthesis of Fluorine and Iodine Analogues of Clorglyline and Selective Inhibition of Monoamine Oxidase A

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A series of fluorine and iodine analogues of clorglyline was synthesized and evaluated for inhibitory potency and selectivity toward monoamine oxidase A (MAO-A). Among them, \( \text{N-[3-(4-dichloro-6-iodophenoxo)propyl]-N-methyl-2-propynylamine (3d), N-[3-(4-chloro-2-fluorophenoxo)propyl]-N-methyl-2-propynylamine (3f) and N-[3-(2-chloro-4-fluorophenoxo)propyl]-N-methyl-2-propynylamine (3g) were found to have high inhibitory potency and selectivity toward MAO-A comparable to those of clorglyline itself. Thus, they were considered for advanced development as radiofluorinated and radioiodinated ligands that may be useful for functional MAO-A studies in the living brain with positron emission tomography and single photon emission computer tomography.}

**Keywords** monoamine oxidase; specific inhibitor; clorglyline; fluorine analogue; iodine analogue

Monoamine oxidase (MAO) [E.C.1.4.3.4] catalyzes the oxidative deamination of endogenous neurotransmitter amines as well as exogenous amines. It has been divided into two subtypes, MAO-A and MAO-B, on the basis of substrate and inhibitor selectivity.1) Both forms appear to be important for neurotransmitter regulation and fluctuations in functional MAO activity may be associated with human diseases such as Parkinson’s disease, depression and certain psychiatric disorders.2)

The development of positron emission tomography (PET) and single photon emission computer tomography (SPECT) has made possible the studies of metabolism and physiological processes in the living human body utilizing organic molecules labeled with positron emitter or single photon emitter. For the direct and non-invasive mapping and functional studies of the MAO activity in the living brain, the carbon-11 labeled suicide inhibitors, paraglyine, clorglyline and \( \text{l-deprenyl, have been investigated as positron ligands for PET.3) Clorglyline and \text{l-deprenyl inhibit irreversibly and selectively MAO-A and MAO-B, respectively, by binding covalently to the enzyme itself.4) These }^{11} \text{C labeled inhibitors appear to be suitable as the ligands of first approach for PET studies because of their relatively easy preparation. However, the short 20min half-life time of }^{11} \text{C, among the positron emitting radionuclides, has limited the ability to obtain an understanding of relatively slow ligand kinetics. Fluorine-18 with its half-life time of 110min may be favored as a longer-lived alternative to the }^{11} \text{C for studies of the kinetic analysis with PET. For SPECT imaging and investigation of the MAO activity in the living human brain, iodine-123 possesses very suitable radiation properties, a half-life time of 13h and gamma ray energy of 159keV.}

We have explored the feasibility of the fluorinated and iodinated MAO inhibitors as alternatives to clorglyline and \( \text{l-deprenyl themselves for functional MAO studies in the brain with PET and SPECT. This paper describes the synthesis of the fluorine and iodine analogues of clorglyline. The comparative in vitro studies on the inhibitory potency and selectivity toward MAO-A and MAO-B of these non-labeled compounds were also evaluated in order to select new ligand candidates for }^{18} \text{F and }^{123} \text{I labeling.}

The fluorine and iodine analogues of clorglyline were prepared by the reactions outlined in Chart 1, based on the published procedure for clorglyline itself.3) The fluorinated- and iodinated phenol derivatives (\( \text{1a—h} \)) were converted to their corresponding phenoxypropyl bromides (\( \text{2a—h} \)). Alkylation of \( \text{N-methylpropargylamine with the phenoxypropyl bromides in the presence of potassium carbonate in acetonitrile gave the required fluorine and iodine analogues (\( \text{3a—h} \)) of clorglyline.}

The MAO inhibitory potency of the compounds was assayed fluorometrically using kynuramine as a substrate.5) The MAO-A and MAO-B activity was selectively measured by treating rat liver homogenate with l-deprenyl (MAO-B specific inhibitor) and clorglyline (MAO-A specific inhibitor), respectively.6,7) The IC_{50} values of these compounds including clorglyline for MAO-A and MAO-B are summarized in Table 1.

The 4-chloro-2-fluoro (\( \text{3f} \)) and 2-chloro-4-fluoro (\( \text{3g} \))

![Chemical structure of compounds](attachment:image)

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derivatives were found to have high inhibitory potency against MAO-A (IC50 3.6 x 10^-11 and 3.4 x 10^-11 M, respectively), fully comparable to that of clorgyline (IC50 3.0 x 10^-11 M) examined under the same conditions. However, compound 3e was found to be a relatively weak inhibitor of MAO-A (IC50 2.5 x 10^-8 M). The ratio of IC50 for MAO-B to that for MAO-A of 3f and 3g was 2.0 x 10^3 and 1.9 x 10^3, respectively, showing their high specificity for MAO-A. It thus appears that, in the fluorine analogues, one of the two chlorines on the benzene ring of clorgyline is essential for high inhibitory potency and the replacement of another chlorine with a fluorine causes unfavorable effects on the potency and selectivity toward MAO-A compared to clorgyline itself.

Among the iodine analogues, as shown in Table I, the 2,4-dichloro-6-iodo derivative (3d) retained high MAO-A inhibitory potency compared to that of clorgyline (3h) (IC50 6.3 x 10^-11 M versus 3.0 x 10^-11 M). The high ratio of IC50 for MAO-B to that for MAO-A of 3d, 5.7 x 10^3, also showed its preferential inhibition toward MAO-A. Other iodine analogues 3a—e, however, were found to be relatively weak MAO-A inhibitors. In the series of iodine analogues, in contrast to fluorine analogues, two chlorines on the benzene ring of clorgyline appear to be indispensable to retain the high potency.

In conclusion, the fluorine and iodine analogues of clorgyline 3d, 3f and 3g were found to have high inhibitory potency and selectivity for MAO-A. They were, therefore, considered to be candidates for further studies as PET and SPECT radiopharmaceuticals for functional MAO-A studies in the brain. Since the present procedure for the preparation of fluorine and iodine analogues of clorgyline involves a rather long reaction period, an alternative short time synthesis of the 1^19F and 1^21I labeled counterparts are now in progress.

Experimental
All melting points are uncorrected. Infrared (IR) spectra were recorded on a JASCO IR-700 spectrometer. Proton nuclear magnetic resonance (1^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. Mass spectra (MS) were obtained on a Hitachi M-80 instrument.

Phenol Derivatives (1a—h) Compounds 1a and 1e—h were obtained commercially and used without further purification. Compounds 1b, 1c and 1d were prepared by the reported methods.6

Preparation of Clorgyline Analogues (3a—h) A mixture of appropriate phenol derivative 1a—h (25 mmol), 1,3-dibromopropane (50 mmol) and a solution of sodium hydroxide (1.0 g) in water (4 ml) was stirred at reflux for 1.5 h. A solution of sodium hydroxide (1.0 g) was added, and the mixture was refluxed for an additional 1.5 h. After cooling, the reaction mixture was extracted with chloroform (50 ml) and washed with water (30 ml x 3). The organic layer was dried over sodium sulfate and evaporated in vacuo. Distillation gave the desired phenoxypyropyl bromide 2a—h.

To a solution of phenoxypyropyl bromide (10 mmol) in acetonitrile (30 ml) was added a solution of potassium carbonate (11 mmol) in water (3 ml) followed by N-methylpropargylamine (20 mmol) and the resulting mixture was stirred at room temperature for 24 h. The acetonitrile solution was decanted and evaporated in vacuo. The residue was taken up with ether (50 ml) and washed with water (30 ml x 3). The ether layer was dried over sodium sulfate. Removal of the solvent in vacuo gave free base, which was converted to hydrochloride salt. Recrystallization from ethanol—ether afforded the desired product.

N-[3-(4-Iodophenyl)propyl]-N-methyl-2-propynylamine Hydrochloride (3a): Yield 73%. mp 151—152°C. Anal. Calcd for C13H13INO: C, 32.9; H, 3.2; N, 3.5. Found: C, 32.9; H, 3.3; N, 3.6.

N-[3-(2-Chloro-6-iodophenyl)propyl]-N-methyl-2-propynylamine Hydrochloride (3b): Yield 66%. mp 141—142°C. Anal. Calcd for C14H13ClINO: C, 39.2; H, 3.0; N, 3.5. Found: C, 39.6; H, 4.0; N, 3.5.


N-[3-(2-Chloro-6-iodophenyl)propyl]-N-methyl-2-propynylamine Hydrochloride (3e): Yield 52%. mp 117—118°C. Anal. Calcd for C14H13ClINO: C, 60.58; H, 6.65; N, 5.44. Found: C, 60.59; H, 6.68; N, 5.50.


N-[3-(2-Fluorophenyl)propyl]-N-methyl-2-propynylamine Hydrochloride (3g): Yield 80%. mp 148—150°C. Anal. Calcd for C14H13ClINO: C, 56.60—56.64; H, 5.50; N, 4.75. Found: C, 56.62; H, 5.50; N, 4.76.
N-[3-(2-Chloro-4-fluorophenox)propyl]-N-methyl-2-propynylamine Hydrochloride (3b): Yield 74%, mp 97—98°C. Anal. Caled for C₂₅H₂₅Cl₅N: C, 53.44; H, 5.52; N, 4.79. Found: C, 53.50; H, 5.45; N, 4.86. IR (KBr): 3162, 2910, 2602, 1501, 1479, 1259, 1201 cm⁻¹. ¹H-NMR (free base, CDCl₃) δ: 1.97 (2H, quintet, J = 6.7 Hz, CH₂CH₂CH₂CH₂), 2.22 (1H, t, J = 2.4 Hz, C = CH), 2.33 (3H, s, NCH₃), 2.65 (2H, t, J = 6.7 Hz, CH₂CH₂N), 3.36 (2H, d, J = 2.4 Hz, CH₂C = CH), 4.05 (2H, t, J = 6.7 Hz, OCH₂). 6.86—7.14 (3H, m, aromatic). High-resolution MS (free base) Caled for C₂₅H₂₅Cl₅NO m/z: 371.0531. Found: 371.0520.

Assay of MAO Activity Rat liver was homogenized with 10 volumes of 0.25 M sucrose and 2 mM Tris buffer (pH 7.4) under cooling. The homogenates were centrifuged at 10000 g for 10 min to remove cell debris. The protein content was measured by the biuret method. The MAO activity was assayed fluorometrically using kynuramine as a substrate according to the reported method. Fluorescence was measured at 380 nm with excitation at 315 nm. The activities of MAO-A and MAO-B were assayed in the presence of 1 μM l-depeneryl and clorgyline, respectively.

References