(3-*N*-[^{11}C]Methyl)Spiperone, A Ligand Binding to Dopamine Receptors: Radiochemical Synthesis and Biodistribution Studies in Mice

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Carbon-11-labeled 3-*N*-methylspiperone, a positron-emitting dopamine-receptor antagonist with potential for use in positron emission tomography studies of human neurotransmitter receptors, was synthesized from $^{11}CO_2$ in 40 min, with a radiochemical yield of ~20–40%. The specific activity of the (3-*N*-[^{11}C]methyl)-spiperone was determined by ultraviolet spectroscopy to be approximately 270 mCi/μmol at the end of synthesis. In in vitro binding experiments, the K_i for 3-*N*-methylspiperone was found to be approximately 250 p*M* (against H-3 spiperone). The brain-to-blood ratios in normal ICR mice were 2.8 or greater at the times studied, and the striatum-to-cerebellum ratio at 60 min after injection was 20:1.

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Some diseases of the nervous system are believed to be associated with disturbed synaptic transmission at the biochemical level. Evidence to support this hypothesis comes from monitoring the cerebrospinal fluid, plasma, or urinary levels of metabolites of neurotransmitters, or from measuring the number, location, and affinity of neurotransmitter receptors by ligand-binding techniques. Abnormalities of dopamine receptor have been reported in several neuropsychiatric disorders, such as Huntington's chorea (*1*), Parkinson's disease (*2*), schizophrenia (*3–8*), and tardive dyskinesia (*9–11*).

Over the past several years, there has been considerable interest in the development of radiotracers for use with scintigraphic techniques for the external detection and quantification of receptor sites in man (*12–18*). Spiperone (I, Fig. 1) is a butyrophenone neuroleptic with an extremely high affinity for dopamine receptors. We have synthesized an analog of spiperone, 3-*N*-methylspiperone (II, Fig. 1), labeled with carbon-11 by methyl-for-hydrogen substitution, and studied its biodistribution in ICR mice and its binding affinity for dopamine receptors in the brain.

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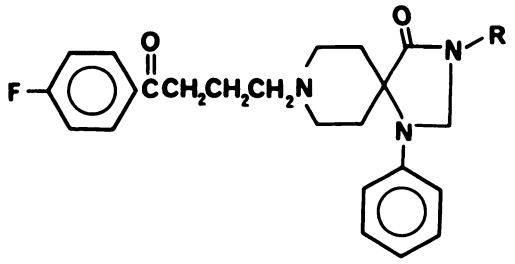
MATERIALS AND METHODS

The procedures for the synthesis of 3-*N*-methylspiperone, and the radiosynthesis of (3-*N*-[^{11}C]methyl)-spiperone are described below. Elemental analyses were performed; ir, and uv spectra were recorded. Proton magnetic resonance (PMR) spectra were obtained on an 80-MHz spectrometer* and are reported relative to TMS.

Preparation of 3-*N*-methylspiperone (II, Fig. 1). Spiperone (*19*) (1.0 g, 2.5 mmol) was dissolved in 50 ml of freshly distilled, anhydrous tetrahydrofuran (THF). A stoichiometric amount of NaH, as a 60% Nujol slurry, was weighed onto a sinter glass funnel, washed with anhydrous THF under a stream of nitrogen, and quickly added to the solution of spiperone. Methyl iodide (356 mg, 2.5 mmol) was immediately added by syringe. The mixture was vigorously stirred for 120 min, then evaporated under reduced pressure to an amber oil. The oil was triturated with 20 ml of water three times, separated, and dissolved in ether/ethanol (2:1, v/v). The solution was filtered and evaporated.



I. Spiperone R = H
II. 3-N-Methylspiperone R = CH_3

FIG. 1. Chemical structures of spiperone (I) and 3-*N*-methylspiperone (II).

Trituration of the residue with boiling cyclohexane gave white crystals of both starting material and product; upon cooling the cyclohexane, however, a crystalline product was obtained. Successive recrystallizations from cyclohexane gave 450 mg of 3-*N*-methylspiperone (43% of theoretical yield), mp 135–137° (uncorrected).

Elemental analysis (calculated for $C_{24}H_{28}FN_3O_2$):
Calcd: C: 70.40 H: 6.89 N: 10.26
Found: C: 70.45 H: 6.89 N: 10.25

IR (in Nujol mull): 1700 cm^{-1} (imidazolone C=O), 1664 cm^{-1} (ketone C=O).

PMR ($CDCl_3$). δ 1.79–2.20 (m, 4H); 2.40–3.20 (series of overlapping multiplets, 13H, incorporating 3H singlet at 3.02 ppm); 4.68 (s, 2H); 6.83–7.23 (m, 7H); 7.95 (q, 2H).

Preparation of α-methyl-γ-chloro-*p*-fluorobutyrophenone (V, Fig. 2). A solution of 4-chloro-2-methylbutyryl chloride (*20*) in fluorobenzene (4.0 g, 0.256 mole) was added to a mixture of $AlCl_3$ (4.20 g, 0.031 mole) in fluorobenzene (30 ml; total amount of fluorobenzene 37.0 g, 0.385 mole) at 20°C. The mixture was allowed to stir for 30 min, then poured onto ice. The organic layer was diluted with ether, separated, and dried over $MgSO_4$. The volatiles were removed under reduced pressure, yielding 5 g of a yellow oil. Bulb-to-bulb distillation of a 2.9-g sample yielded 2.72 g of a clear colorless oil: $bp^{(3mm)}$ 120°C; ir (film): 1670 cm^{-1} C=O; PMR ($CDCl_3$) δ: 1.29 (d, 3H); 1.90 (m, 1H); 2.30 (m, 1H); 3.4–3.9 (m, 3H); 6.99–7.30 (m, 2H); 7.90–8.16 (m, 2H).

Elemental analysis (calculated for $C_{11}H_{12}ClFO$):

Calcd:	C: 61.55	H: 5.63	Cl: 16.52
Found:	C: 61.36	H: 5.62	Cl: 16.62

Preparation of α-methylspiperone (III, Fig. 3). A mixture of V (740 mg, 3.45 mmol), recrystallized 1-phenyl-1,3,8-triazaspiro[4.5]decane-4-one (1000 mg, 4.32 mmol), Na_2CO_3 (500 mg), and a few crystals of KI were refluxed for 60 hr in 4-methyl-2-pentanone (60 ml). The mixture was diluted with water and the organic layer was separated and dried over $MgSO_4$. The solvent was removed under reduced pressure, leaving 1.66 g of a viscous brown residue. The material was purified using short-path chromatography (silica, $CHCl_3$/MeOH, 96:4) to yield 630 mg (44.6%) of product, mp 150–3°C. The material was recrystallized from CH_2Cl_2/pentane. IR (KBr): 1690 cm^{-1} (imidazalone C=O), 1670 cm^{-1} (ketone, C=O). PMR ($CDCl_3$) δ: 1.19 (d, 3H); 1.40–3.00 (series of overlapping multiplets, 12H); 3.56 (m, 1H); 4.71 (s, 2H); 6.82–7.43 (m, 8H); 7.94–8.12 (m, 2H).

Elemental analysis (calculated for $C_{24}H_{28}FN_3O_2$):

Calcd:	C: 70.40	H: 6.89	N: 10.26
Found:	C: 70.18	H: 7.00	N: 10.19

Preparation of (3-*N*[^{11}C]methyl)spiperone. Spiperone (*19*) (1–3 mg, ~5 μmol) was dissolved in methylene chloride (1 ml) and then cooled in an ethyl alcohol/dry ice bath. Carbon-11 dioxide was produced in a biomedical cyclotron by the $^{14}N(p,\alpha)$ ^{11}C reaction. From the $[^{11}C]CO_2$, carbon-11-labeled methyl iodide was prepared by the procedure of Langström (*21*), and this was bubbled in a nitrogen carrier gas (30 ml/min) through the cooled spiperone solution. An aqueous solution of tetrabutylammonium hydroxide (0.2 ml, 0.4 *M*) was added to the reaction vial and the mixture was sonicated in a 65°C water bath for 6 min. Heptyl iodide (0.2 ml, 1 mmol) was added, and the sonication was continued for an additional 4 min.

The reaction solution was cooled to room temperature and the phases allowed to separate. The organic phase was removed, added to 78% methanol/22% 0.1 *M* ammonium formate (1 ml), and evaporated to dryness under reduced pressure. The residue was redissolved in 78% methanol/22% 0.1 *M* ammonium formate (1.5 ml), applied to a high-performance liquid chromatographic column†, and eluted with the same solvent at a flow rate of 4 ml/min. The major radioactive peak, which eluted at 6.1 min, was collected and evaporated to dryness under reduced pressure. Under the same high performance liquid chromatography (HPLC) conditions, spiperone elutes at 5.7 min and heptyl derivatized spiperone elutes after 15 min.

The residue was dissolved in sterile, normal saline (3 ml) and filtered through a sterile, 0.22-μ filter into a sterile, pyrogen-free evacuated vial containing sterile bicarbonate solution (3 ml). The pH of the final solution for injection was ~7.5. Total synthesis time from carbon-11 dioxide is 40 min, with a radiochemical yield of 20–40%.

HPLC analysis. Method A. C-18 analytical column eluted with 78% methanol/22% 0.1 *M* ammonium formate at a flow rate of 2 ml/min. The retention times for spiperone, 3-*N*-methylspiperone, and heptyl derivatized spiperone were 2.22, 2.30, and 17.5 min, respectively.

Method B. C-18 analytical column‡ eluted with 55%

methanol/45% 0.1 *M* ammonium formate at a flow rate of 2.7 ml/min. The retention times for spiperone, 3-*N*-methylspiperone and α-methylspiperone were 5.4, 7.0, and 8.3 min, respectively.

Determination of specific activity. A measured aliquot of the final solution for injection was removed and assayed for total radioactivity in a dose calibrator. A small portion of this aliquot was applied to a high-performance liquid chromatographic column[§] and eluted with 78% methanol/22% 0.1 *M* ammonium formate following HPLC Method A. The area of the ultraviolet absorbance peak at 254 nm was determined by an automated integrating recorder[¶] and compared with a standard curve relating mass to ultraviolet absorbance.

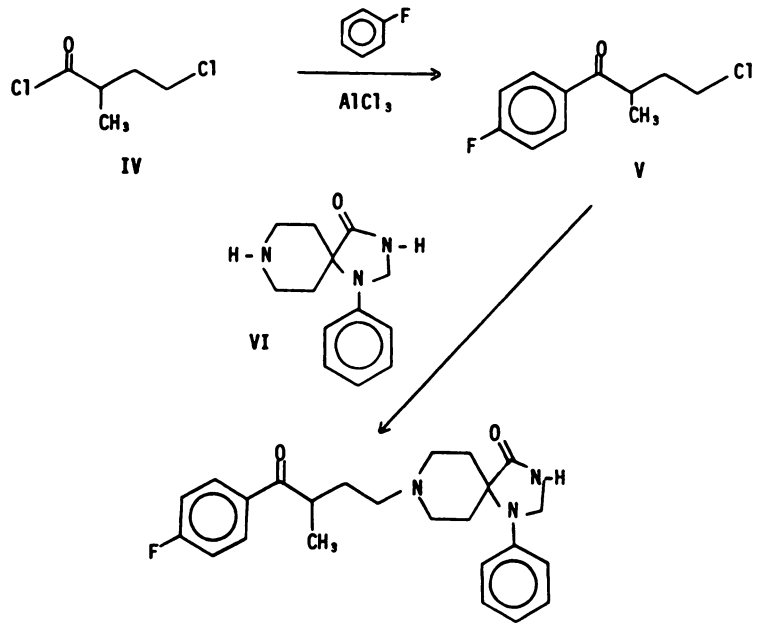
Determination of binding affinity. Competitive in vitro binding assays for the displacement of H-3 spiperone from isolated dopamine receptors (obtained from the corpus striatum of male Sprague Dawley rats) were performed according to literature procedures (*23*). Each determination was performed in triplicate. Nonspecific binding is defined as the total binding in the presence of $10^{-6}M$ (+)-butaclamol, and specific binding is defined as the difference in total binding between the presence and absence of (+)-butaclamol.

Tissue distribution in normal ICR white mice. The tissue distribution of (3-*N*[^{11}C]methyl)spiperone was determined as a function of time in ICR mice. Normal mice weighing 25–35 g at the time of the study were divided into groups of six and killed by cervical dislocation at intervals of 15, 30, and 60 min following the i.v. administration of ~25 μCi of the radiolabeled compound in ~0.1 ml of saline/bicarbonate solution. Samples of blood, heart, lungs, kidneys, liver, spleen, stomach, G.I. tract, muscle, and brain were removed and counted in an automated gamma counter. The corpus striatum and cerebellum were removed from a separate group of mice killed at 60 min after injection, and counted separately (*22*). The percent injected dose per organ and per gram wet tissue were calculated by comparison with a standard dilution of the injected dose, after correction for radioactive decay.

RESULTS AND DISCUSSION

Competitive in vitro binding assays for the displacement of H-3 spiperone from isolated rat dopamine receptor preparations have been useful in selecting analogs of spiperone for radiolabeling and in vivo studies (*23*). In the in vitro binding experiments, the K_i for 3-*N*-methylspiperone was determined to be 250 p*M* (against H-3 spiperone), whereas the K_D of spiperone under the same conditions was about 190 p*M*; thus, the methyl-for-hydrogen substitution results in only a small decrease in the binding affinity for dopamine receptors relative to the parent compound, spiperone.

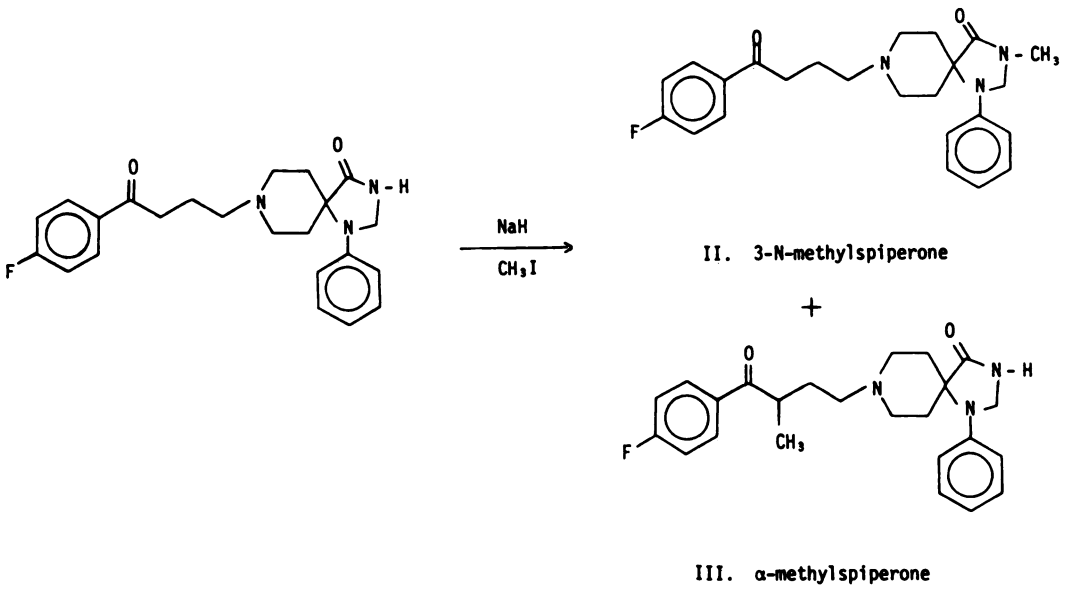
When one considers the limited number of precursors available and the short half-life of C-11, the known routes for the synthesis of spiperone and 3-*N*-methyl-



III. α-methylspiperone

Scheme 2

FIG. 2. Reaction Scheme 2.



Scheme 1

FIG. 3. Reaction Scheme 1.

spiperone (*19*) were not suitable for the incorporation of this nuclide. Therefore, the synthesis we have reported here was used to introduce C-11 rapidly into the molecule by methylation of the amide nitrogen with C-11 methyl iodide.

Authentic 3-*N*-methylspiperone was prepared by treating spiperone with a stoichiometric amount of sodium hydride and methyl iodide in tetrahydrofuran, as outlined in Scheme 1, Fig. 2. Proton magnetic resonance (PMR) analysis of the crude reaction mixture suggested that some C-alkylation may have occurred alpha to the ketone carbonyl to yield α-methylspiperone (**III**, Scheme 1). Pure 3-*N*-methylspiperone was obtained in 43% yield by repeated recrystallization of the crude product from cyclohexane.

Since some C-alkylation might also be expected to occur under the conditions used to prepare (3-*N*[^{11}C]-methyl)spiperone, it was necessary to prepare authentic α-methylspiperone by an unambiguous route for use as an HPLC standard. This procedure is shown in Scheme 2 (Fig. 3). The required ketone (α-methyl-γ-chloro-*p*-fluorobutyrophenone, V) was synthesized by Friedel-Crafts acylation of fluorobenzene with 4-chloro-2-methylbutyrylchloride (IV). PMR analysis indicated that the desired para-acylated material was obtained. Ketone V was used to alkylate 1-phenyl-1,3,8-triazaspiro[4,5]decane-4-one to yield the desired α-methylspiperone (**III**). PMR analysis easily distinguished between **II** and **III**, with the *N*-methyl resonance of **II** appearing at δ 3.02 and the C-methyl of III appearing as a doublet at δ 1.19, as expected.

(3-*N*[^{11}C]methyl)spiperone was prepared by *N*-alkylation of spiperone with carbon-11-labeled methyl iodide in a reaction analogous to the synthesis of cold 3-*N*-methylspiperone. The carbon-11 methyl iodide was prepared from carbon-11 dioxide according to procedures of Langström (*21*). An average of 75% of the cyclotron-produced carbon dioxide was converted into labeled methyl iodide, which was efficiently trapped in the cooled methylene chloride solution containing the spiperone to be labeled. After the addition of an aqueous solution of tetrabutylammonium hydroxide, the reaction mixture, consisting of two separate phases, was sonicated for 6 min in warm water. The sonication produced complete mixing of the phases.

Heptyliodide was then added to convert unreacted spiperone to a more lipophilic compound, presumably 3-*N*-heptylspiperone, and sonication continued for an additional 4 min. Thus the HPLC purification was simplified by synthesizing a byproduct that was more lipophilic and eluted with a longer retention volume than the desired product. The fraction of the eluant containing the labeled 3-*N*-methylspiperone was collected and evaporated to dryness, dissolved in a mixture of sterile saline/bicarbonate, and assayed for sterility, apyrogenicity (*25*), and radiochemical purity.

Due to the short half-life of C-11 and the need to know the mass of carrier containing byproducts and starting materials before the in vivo distribution studies, it was necessary to develop a fast, reliable method for determining the specific activity of the final product and the presence of any contaminants. We used analytical HPLC and an automated integrating recorder because of its speed and reproducibility. With this system we determined the specific activity of the (3-*N*[^{11}C]-methyl)spiperone in the final injectable solution within

TABLE 1. BIODISTRIBUTION OF (3-*N*[^{11}C]-METHYL)SPIPERONE IN NORMAL ICR MICE (MEAN PERCENT DOSE PER ORGAN ± s.d.*)

Organ	15 min	30 min	60 min
Brain	1.09 ± 0.21	1.13 ± 0.13	0.69 ± 0.22
Heart	0.29 ± 0.07	0.27 ± 0.04	0.12 ± 0.04
Lungs	1.76 ± 0.25	1.27 ± 0.12	0.53 ± 0.23
Liver	12.13 ± 2.12	9.98 ± 0.41	5.61 ± 1.80
Kidneys	3.56 ± 0.63	3.94 ± 0.77	1.79 ± 0.60
Spleen	0.50 ± 0.14	0.54 ± 0.13	0.20 ± 0.05
Stomach	3.25 ± 0.68	3.18 ± 1.06	1.62 ± 0.76
GI tract	10.0 ± 6.2	20.5 ± 5.2	13.5 ± 3.7
Carcass	43.9 ± 5.6	32.8 ± 7.8	20.2 ± 5.3

* Six mice studied at each time period.

TABLE 2. BIODISTRIBUTION OF (3-*N*[^{11}C]-METHYL)SPIPERONE IN NORMAL ICR MICE (MEAN PERCENT DOSE PER GRAM ± s.d.*)

Organ	15 min	30 min	60 min
Blood	0.78 ± 0.13	0.85 ± 0.96	0.47 ± 0.22
Brain	2.44 ± 0.28	2.50 ± 0.43	1.32 ± 0.37
Heart	2.20 ± 0.41	1.80 ± 0.23	0.76 ± 0.23
Lungs	6.93 ± 1.70	4.63 ± 1.09	2.06 ± 0.96
Liver	7.74 ± 0.91	6.53 ± 0.91	3.55 ± 1.06
Kidneys	7.07 ± 1.70	6.63 ± 0.84	3.46 ± 1.03
Spleen	5.05 ± 1.83	5.17 ± 1.16	1.56 ± 0.52
Muscle	1.36 ± 0.16	1.37 ± 0.09	0.72 ± 0.18

* Six mice studied at each time period.

4 min. The average specific activity of 72 consecutive preparations that we have studied was 270 mCi/μmole at end of synthesis (E.O.S.) (1080 mCi/μmole at end of bombardment). Both the analytical and preparative columns resolve 3-*N*-methylspiperone and spiperone to baseline.

Routine verification of the purity of the (3-*N*[^{11}C]-methyl)spiperone, using the analytical HPLC Method A, indicated that the final product was free of contamination by unreacted spiperone. A second analytical system (Method B) was used to analyze for α-methylspiperone. A sample of (3-*N*[^{11}C]methyl)spiperone was allowed to decay, then analyzed using Method B. With this system α-methylspiperone (retention time: 8.3 min) and 3-*N*-methylspiperone (retention time: 7.0 min) were easily resolved. The results of the analysis showed no detectable α-methylspiperone, indicating that the (3-*N*[^{11}C]methyl)spiperone could not contain more than 2% (α-[^{11}C]methyl)spiperone.

Tables 1 and 2 show the results of the biodistribution of (3-*N*[^{11}C]methyl)spiperone in normal ICR white mice. The studies were performed with radiolabeled material from several separate preparations at an average specific activity of 150 mCi/μmole (E.O.S.). A constant injected dose per mouse of 10 μg/kg body weight was maintained throughout the distribution study. The liver and kidneys were the organs of highest accumulation. The uptake in the whole brain reached a maximum of 1.13% dose/organ at 30 min; blood levels also reached a maximum at that time. The slight rise in blood activity at 30 min was not statistically significant.

The results of regional biodistribution studies of two specific portions of the brain (striatum and cerebellum) at 60 min after injection show that the percent injected dose per gram in the striatum was 4.89 ± 1.43 and the striatum-to-cerebellum ratio, based on percent dose per gram of each organ, was 20.1. The brain-to-blood ratios were 3.1, 2.9, and 2.8 at 15, 30, and 60 min after injection, respectively.

Recently Zanzonico et al. summarized and reviewed the striatal and cerebellar concentrations under conditions of maximal specific binding for several different radiolabeled neuroleptics (*15*). In their summary, striatum-to-cerebellum ratios ranged from 1.9 to 8.8 for four different drugs studied in various species by 11 different investigators. In the same study, the brain-to-blood concentration ratios for several radiolabeled neuroleptics were also compared. These ratios ranged from 0.67 to 51. The ratios obtained with (3-*N*[^{11}C]methyl)spiperone compare very favorably with this previous study. The striatum-to-cerebellum ratio, calculated from the distribution data for mice killed at 60 min after i.v. injection, was 20.1, and the brain-to-blood ratio was 2.8 at 60 min and 2.9 at 30 min after injection. Since the striatum has very high concentrations of dopamine receptors whereas the cerebellum has very low levels (*24,26–28*), the high striatum-to-cerebellum ratio of this compound suggests preferential labeling of dopamine receptors in vivo.

This ratio is higher than that reported for spiperone, a finding that is surprising since spiperone has a slightly higher binding affinity for dopamine receptors than 3-*N*-methylspiperone. This finding may be related to the fact that 3-*N*-methylspiperone is slightly more lipophilic than spiperone, as indicated by its increased retention on reverse-phase liquid chromatography. Thus one would expect it to diffuse more rapidly into the brain, resulting in exposure of the receptors to a higher concentration of the neuroleptic.

Recently (*30*) a preliminary report has appeared describing the use of this compound for imaging dopamine receptors in the brains of baboons and a human. Based on that work and the results presented here, (3-*N*[^{11}C]methyl)spiperone shows great potential as a radiotracer for imaging dopamine receptors in vivo.

FOOTNOTES

* IBM FT NR-80 80 mHz spectrometer.
† EM Prep-10 LiChrosorb RP-18, 1 cm × 25 cm, Rainin Scientific, Woburn, MA.
‡ Waters Associates NOVA-PAK, Milford, MA.
§ Waters Associates C-18 μBondapak, 3.9 mm x 30 cm, Miford, MA.
¶ Hewlett Packard 3390 Integrator.

ACKNOWLEDGMENTS

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Erratum

Please note page corrections for the following entries to the Table of Contents, Volume 25, Number 8, August 1984, p. 7A:

ADJUNCTIVE MEDICAL KNOWLEDGE
The Significance of Chromosomal Aberrations in Indium-111-Labeled Lymphocytes
Mathew L. Thakur and John G. McAfee 922
TEACHING EDITORIAL
Scatter Correction for SPECT
Bernard E. Oppenheim 928