Syntheses and Specific Activity Determinations of No-Carrier-Added Fluorine-18-Labeled Neuroleptic Drugs

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A general method for the syntheses of no-carrier-added (NCA) ^{18}F-labeled butyrophenone neuroleptics—benperidol, haloperidol, spiroperidol, and pipamperone is described. These ^{18}F-labeled neuroleptic drugs are synthesized by a multistep synthesis in an overall radiochemical yield of 10–20% at end of bombardment (EOB) in a synthesis time of 90 min from EOB. The sequence involves the synthesis of NCA *p*-[^{18}F]fluorobenzonitrile from NCA [^{18}F]-fluoride and *p*-nitrobenzonitrile using the nucleophilic aromatic substitution reaction (^{18}F for NO_2). *p*-[^{18}F]Fluorobenzonitrile is rapidly converted to γ-chloro-*p*-[^{18}F]fluorobutyrophenone which is alkylated with appropriate amines to give NCA ^{18}F-labeled benperidol, haloperidol, spiroperidol, and pipamperone. The final product is purified by preparative high performance liquid chromatography (HPLC). The ^{18}F solution used in the synthesis as determined by ion chromatography contains 15.3 ± 9.0 nmol of stable fluoride. The specific activities of the resulting butyrophenone neuroleptics were determined to be 3 Ci/μmol (at EOB) (range 1–6 Ci/μmol) as determined by radioreceptor assay and HPLC assay.

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The development of positron emission transaxial tomography (PETT) methods for studying neurotransmitter receptors in the living brain is critically dependent on the choice of a radioligand which not only binds to receptor in a specific and verifiable way, but also has a half-life appropriate for the required kinetic measurements. The butyrophenone neuroleptics, known antagonists of the dopamine receptor which also cross the blood-brain barrier, have been proposed as candidate structures for labeling based on studies with hydrogen-3-(^{3}H) -labeled compounds (*1*). One of these, spiroperidol, has been suggested as the ideal candidate for labeling and the parent molecule has been labeled with carbon-11 (^{11}C) and fluorine-18(^{18}F) (*2–5*), and analogs of spiroperidol have also been labeled with bromine-77 (^{77}Br) and ^{11}C (*6–8*). Studies by several groups with [^{18}F] haloperidol and [^{18}F]spiroperidol of low specific activity present conflicting results as to the suitability of these radioligands for studying the dopamine receptor (*3,9–13*). In addition, there is some question as to whether or not the results of experiments with ^{3}H-labeled ligands can be used to guide the selection of priority structures for labeling with ^{18}F (*10*). These problems emphasize the need for a more general method for the synthesis of practical quantities of no-carrier-added (NCA) [^{18}F]butyrophenone neuroleptic drugs so that an objective PETT study intercomparing them in terms of brain kinetics, specificity of binding to dopamine receptor rich areas, and physiological and biochemical fate in brain tissue and plasma can be made.

The development of a general route to NCA ^{18}F-labeled butyrophenone neuroleptic drugs based on the nucleophilic aromatic substitution reaction (*14,15*) is described (*16*). Practical yields in excess of 20 mCi are

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readily obtained. Specific activities of the products are also reported.

MATERIALS AND METHODS

Cesium carbonate was purchased* and dimethylsulfoxide (DMSO), a Gold Label reagent, was obtained.† DMSO was dried over a 4Å molecular sieve. Used without purification were *p*-nitrobenzonitrile, 1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one, 4-(*p*-chlorophenyl)-4-hydroxypiperidine, and 4-(2-keto-1-benzimidazolinyl)piperidine.† Cyclopropyl lithium and 4-piperidine-4-piperidinecarboxamide were synthesized by the known methods (*17,18*). Benperidol, spiroperidol, pipamperone,‡ and haloperidol§ were gifts.

Thin-layer chromatographic analyses (TLC) were performed on plastic-backed TLC plates (Merck) with either CH_3CN:MeOH (4:1), CH_2Cl_2:MeOH (90:10), or $CHCl_3$:MeOH:H_2O (30:9:1) as solvent. HPLC analyses were carried out with a Perkin-Elmer Series 3B liquid chromatograph equipped with a radioactivity monitor (Berthold Model LB503). An IBM C_{18} column (4.5 × 250 mm) was used with MeOH:0.01 *M* $(NH_4)_2HPO_4$ (70:30) as the solvent with a flow rate of 2 ml/min. For the preparative separations an IBM C18 column (10 × 250 mm) was used with a flow rate of 6 ml/min.

General procedure for the syntheses of NCA ^{18}F-labeled butyrophenone neuroleptics

No-carrier-added aqueous [^{18}F]fluoride (0.5 ml) prepared by the $^{18}O(p,n)^{18}F$ reaction (*19*) on a small volume enriched water (95–99% ^{18}O) target (*20,21*) was added to a solution of 1.8 mg of Cs_2CO_3 in 0.1 ml of water in an open platinum or pyrex vessel. The water was removed using a stream of nitrogen at 140° and coevaporated to dryness after adding CH_3CN (2 × 0.5 ml). To the dried Cs[^{18}F] was added a solution of 2 mg of *p*-nitrobenzonitrile in 0.2 ml DMSO. This solution was heated at 140° for 10 min, 2 ml of water was added and the mixture transferred onto a SEP-PAK (C_{18}) cartridge¶ which had been prewashed with 3 ml of methanol followed by 4 ml of water. The SEP-PAK was washed with 4 ml of water and 0.5 ml of pentane and the washing was discarded. The product (*p*-[^{18}F]fluorobenzonitrile) was eluted with 5 ml of pentane which was filtered through anhydrous K_2CO_3. A solution of 0.5 ml of 1 *M* cyclopropyl lithium in ether was added to the pentane solution followed by 2 ml of a methanol:HCl solution (methanol:conc HCl, 1:1). The mixture was heated at 110° in an open vessel and after the pentane had evaporated, it was heated for an additional 7 min. Three milliliters of water were added and the SEP-PAK extraction procedure described in the first step was repeated. The appropriate amine (5 mg) and KI (5–10 mg) was added to the dry pentane, a heating bath (140°) was applied and, when the volume of the pentane was reduced to ~0.2 ml, 0.5 ml of a 1:10 solution of DMF:THF was added and the mixture was heated for 10 min after THF had evaporated. One milliliter of $CHCl_3$ and 0.5 ml of water were added to the residue. The $CHCl_3$ layer was removed, dried, and applied to a flash silica gel column (0.75 × 10 cm) (*22*) which was eluted with appropriate solvents. The product eluted from the silica gel column was evaporated to dryness, dissolved in 1 ml of MeOH:H_2O (1:1), applied to a preparative C_{18} high performance liquid chromatography (HPLC) column and eluted with MeOH:0.01 *M* $(NH_4)_2HPO_4$ (70:30) with a flow of 6 ml/min. Retention times for spiroperidol, benperidol, haloperidol, and pipamperone were 7.7, 6.5, 8.5, and 6.0 min, respectively. The eluate from HPLC was evaporated. The product was dissolved in saline and the solution passed through a Millipore filter (0.22 μm) for animal studies. The radiochemical yields of ^{18}F-labeled butyrophenone neuroleptics synthesized by this method was ~10–20% (based on [$^{18}F^-$] solubilized in DMSO which was ~60%) in a synthesis time of ~90 min from EOB. Specific activity was determined by HPLC to be 3 Ci/μmol (range 1–6 Ci/μmol) (EOB) and by radioreceptor assay to be 3 Ci/μmol (EOB) (range 0.7–7.3 Ci/μmol) (see description below). Radiochemical purity was >98% as determined by radioTLC in two solvent systems and by HPLC using both a normal phase silica gel column eluting with CH_2Cl_2:MeOH (80:20) and a reverse phase C_{18} column eluting with MeOH:0.01 *M* $(NH_4)_2HPO_4$. No other radioactive peaks were observed on TLC or HPLC and all of the radioactivity was observed to coelute with authentic butyrophenone neuroleptics which were coinjected (or cospotted) with samples of the ^{18}F-labeled products.

The solvent used to elute compounds from a flash silica gel column varies with each compound. For spiroperidol and haloperidol, the column was first eluted with 35 ml of CH_3CN:MeOH (4:1), the washing discarded, and the product was then eluted with 25 ml of CH_3CN:MeOH (2:1). For benperidol, the column was eluted with 20 ml of CH_3CN:MeOH (4:1), the washing discarded, and the product was eluted with 10 ml of solvent. For pipamperone, the column was eluted with 25 ml of CH_3CN:MeOH (2:1), the washing discarded, and the product was eluted with 20 ml of CH_3CN:MeOH (1:2).

Stable fluoride analyses of enriched water samples before and after irradiation

Enriched water (0.5 ml, 95–99% ^{18}O)** was irradiated in the small volume titanium water target (15 μA × 90 min) and the target contents delivered through 90 ft of polyethylene tubing into a reaction vessel in the chemistry laboratory. An aliquot (0.010 ml) from each run was analyzed for fluoride by ion chromatography (Dionex; HPIC-AS-3 anion exchange column; 0.002*M*

$NaHCO_3$; conductivity detector) (*23*). Eight runs were analyzed for fluoride over a 5 mo period. Samples of unirradiated $H_2{}^{18}O$ were also analyzed.

Average fluoride content from eight irradiated $H_2{}^{18}O$ samples was 15.3 ± 9.0 nmol/0.5 ml. For a 600 mCi run, this represents a specific activity of 95–25 Ci/μmol (^{19}F:^{18}F ~ 18–68:1). Samples (0.5 ml) of $H_2{}^{18}O$ before irradiation were found to contain 1–4 nmol of stable fluoride.

Specific activity determination of [^{18}F]spiroperidol by radioreceptor assay

The specific activity of [^{18}F]spiroperidol was determined by radioreceptor assay as described previously (*2*). Assay of four separate runs of [^{18}F]spiroperidol gave an effective specific activity of 3 Ci/μmol (range 0.7–7.3 Ci/μmol) at end of bombardment (EOB).

Specific activity determination of [^{18}F]spiroperidol by high performance liquid chromatography

A standard curve for each of the four butyrophenones was obtained by using unlabeled compounds with different concentrations. About 10% of the purified ^{18}F-labeled butyrophenone neuroleptics from the HPLC eluate for each synthesis was saved for specific activity determination. This solution was evaporated to dryness under N_2. The residue was dissolved in $CHCl_3$ and aliquots of this solution were counted and injected onto a normal phase amino HPLC column and eluted with 3 ml/min of $CHCl_3$ for mass determination. Retention times for benperidol, haloperidol, and spiroperidol were 3.7, 2.0, and 2.7 min, respectively. Specific activity was averaged 3 Ci/μmol (range 1–6 Ci/μmol) at EOB. A small amount of unidentified uv absorbing material was frequently present and poorly resolved from the ^{18}F-labeled butyrophenone neuroleptics and represents 1–10 nmol (corrected to the total sample volume, and assuming that this unidentified material has an extinction coefficient equal to that of spiroperidol, ϵ = 23,000) (*2*).

DISCUSSION

A number of different radionuclides (^{11}C, ^{18}F, ^{75}Br, ^{77}Br) have been used as radiolabels for dopamine receptor ligands (*24–26*). Carbon-11 ($t_{1/2}$ = 20.4 min) has been used to label spiroperidol itself (*2*) and a derivative of spiroperidol in which the amide hydrogen atom is replaced by $^{11}CH_3$ (*8*). Both of these tracers exhibit a high degree of specific binding (*8,27*) and in the case of [^{11}C]spiroperidol itself, a double injection serial study protocol was developed to allow control and intervention studies to be carried out in the same experimental subject (baboons) within a 3 hr time frame using PETT (*28*). With ^{11}C-labeled radiotracers, however, studies are limited to ~90 min postinjection. The availability of neuroleptics labeled with ^{18}F, a nuclide with longer half-life, offers the possibility of observing the dynamics of radioligand-receptor interactions for periods of several hours and facilitates the intercomparison of important kinetic parameters such as the half-life of dissociation of ligand from the receptor.

Until very recently, only two routes to ^{18}F-labeled aryl fluorides were known. These were the Schiemann reaction (*29,30*) and the triazene decomposition reaction (*31–33*). Both of these reactions have been investigated as routes to ^{18}F-labeled butyrophenones such as spiroperidol and haloperidol (*3,24–26*). Both methods, however, give low yields and while the triazene decomposition reaction gives a NCA product, the Schiemann reaction gives a product with low specific activity. Recently, a modification of the triazene method using trichloroacetonitrile as a solvent has been reported to give [^{18}F]spiroperidol up to 4%, although no details were given (*33*).

In searching for new methods applicable to tracer synthesis with ^{18}F, we studied nucleophilic aromatic substitution as a viable pathway. Initial mechanistic and synthetic studies explored the ^{18}F for ^{19}F exchange reaction leading to labeled arenes (*34,35*). This exchange method led to labeled neuroleptics of relatively low specific activity (*3–5*). The substitution of the nitro

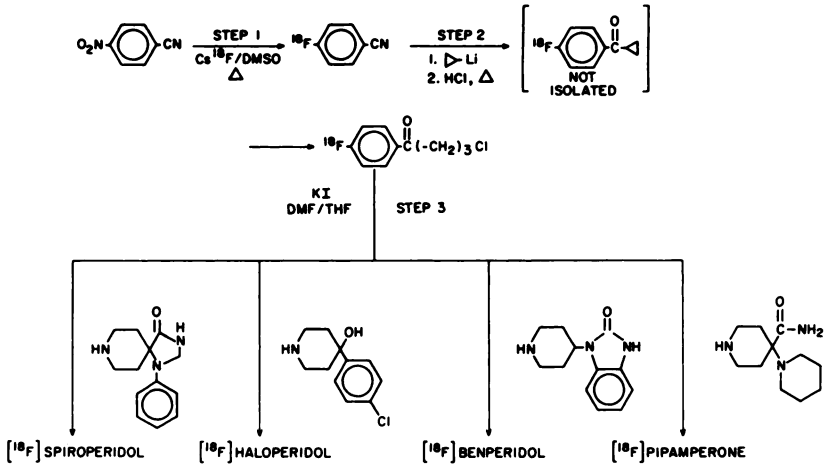

FIGURE 1
Syntheses NCA ^{18}F-labeled butyrophenone neuroleptics

group in suitable precursors can however lead to a NCA product. Conditions for this reaction were studied (*14,15*) and applied to the preparation of the four neuroleptics described in this paper. The synthesis shown in Fig. 1 can be used to prepare adequate quantities of NCA ^{18}F labeled butyrophenones of sufficiently high specific activity (range 1–6 Ci/μmol) to avoid saturation of receptor sites and/or toxic or pharmacologic effects (*36*). The sequence (Fig. 1) takes advantage of (a) the availability of large quantities of NCA [^{18}F]fluoride from a small volume water target utilizing the $^{18}O(p,n)^{18}F$ reaction, (b) the reaction of [^{18}F]fluoride with *p*-nitrobenzonitrile to yield *p*-[^{18}F]fluorobenzonitrile in high yield and high radiochemical purity, (c) the rapid reaction of cyclopropyl lithium with *p*-[^{18}F]fluorobenzonitrile to produce *p*-[^{18}F]fluorophenyl cyclopropyl ketone, (d) the rapid conversion of *p*-[^{18}F]fluorophenyl cyclopropyl ketone to γ-chloro-*p*-[^{18}F]fluorobutyrophenone and, (e) the rapid alkylation reaction of γ-chloro-*p*-[^{18}F]fluorobutyrophenone with commercially available amines to produce NCA ^{18}F-labeled butyrophenone neuroleptic drugs benperidol, haloperidol, spiroperidol, and pipamperone in similar yields. The addition of cyclopropyl lithium to *p*-[^{18}F]fluorobenzonitrile, the workup and hydrolysis to γ-chloro-*p*-[^{18}F]fluorobutyrophenone are all carried out in a single reaction vessel without isolation of the intermediate cyclopropyl ketone. The conversion of 4-fluorophenyl cyclopropyl ketone to the butyrophenone has precedence and was used in the synthesis of ^{14}C-labeled haloperidol and trifluperidol (*37*). Another advantage of the sequence is that cyclopropyl lithium does not react with *p*-nitrobenzonitrile to produce *p*-nitrophenyl cyclopropyl ketone, a potential chemical contaminant which could be carried through the reaction sequence to produce a nitro analog of the butyrophenone neuroleptics. The conditions for the alkylation reaction are modeled after the work of Soudijn et al. (*38*) who demonstrated that side reactions could be reduced by carrying out alkylations in the melt or in a small quantity of high boiling solvent. In this step, the reformation of *p*-[^{18}F]fluorophenyl cyclopropyl ketone competes with the alkylation reaction, reducing the yield of desired product. All intermediates and products in this synthesis were isolated and identified by nuclear magnetic resonance and by comparing HPLC retention times with authentic samples during the development phase of the synthesis in which carrier quantities were used. For the development of the NCA synthesis, all intermediates and products were identified by adding authentic carrier as a standard and comparing thin layer chromatography and HPLC retention times. Purification of the final product is accomplished by flash chromatography followed by preparative reverse phase HPLC to remove the unreacted amine, unidentified uv absorbing materials, γ-chloro-*p*-[^{18}F]fluorobutyrophenone and [^{18}F]fluorophenyl cyclopropyl ketone. Typical yields for each step are given in Table 1.

TABLE 1
Yield Data for Synthesis of NCA ^{18}F-Labeled Butyrophenone Neuroleptics

Step	Time (min)	Yield* (%)
1	20	40–50† (70–80)‡
2	25	75–85
3	35	30–50
HPLC purification	15	70–80
Millipore filtration		

* Percentage of activity isolated in the product, corrected for decay.
† Based on total ^{18}F produced.
‡ Based on solubilized Cs[^{18}F] in DMSO.

During the initial development work on this synthesis, a number of observations were made regarding the reactivity of the ^{18}F from the water target. For example, there was a decrease in the yield of the nucleophilic aromatic substitution step with longer irradiation times. Although the reason for this was not determined, it was found that the use of the high concentrations of Cs_2CO_3 reported in the experimental section largely overcome this problem. It was also observed that the Cs[^{18}F] could not be completely solubilized in DMSO (without adding substrate), and therefore the yields we report here are based on the DMSO soluble [$^{18}F^-$]. Whether this insolubility is due to different forms of [$^{18}F^-$] or insolubility of the Cs[^{18}F] in the presence of excess Cs_2CO_3 is currently being investigated. In preliminary studies, it was found that by readdition of DMSO along with substrate to the DMSO insoluble [$^{18}F^-$], the nucleophilic aromatic substitution reaction was also observed, although in lower yield than with DMSO soluble $^{18}F^-$. Since these reactions are always carried out in a single vessel without preliminary solubilization of Cs^{18}F in DMSO, it is possible that solution occurs during the nucleophilic aromatic substitution step thereby allowing more of the $^{18}F^-$ to be available for reaction than the amount of "DMSO soluble" material would predict. In related experiments, we found that the choice of reaction vessel material also influences the extent of solubility of [$^{18}F^-$] in the absence of added Cs_2CO_3 and that the [$^{18}F^-$] solubilization from a pyrex vessel is significantly greater than that from a platinum vessel. Although the initial syntheses reported in this paper were carried out in a platinum crucible (*4*), more recent studies were carried out in a pyrex vessel, more conveniently, and with no decrease in yield. Because of their potential impact on yield, each of these factors—length of irradiation time, Cs[^{18}F] solubility, and vessel material—is being studied in detail.

The maximum specific activity of the radiopharma-

ceutical depends on the specific activity of the [^{18}F]-fluoride ion used in the synthesis. This in turn depends on the total ^{19}F introduced from the $H_2{}^{18}O$ and from the ^{19}F present as a low level contaminant in the cesium carbonate. Fluorine-19 contaminant introduced from the water target was in the range of 6–24 nmol with another 1–4 nmol derived from the cesium carbonate. Thus, 600 mCi of ^{18}F with a mass of 28 nmol of ^{19}F represents a specific activity of 21 Ci/μmol EOB (11 Ci/μmol, EOS). This represents a ^{19}F:^{18}F ratio of 81:1 (EOB). The specific activity of the ^{18}F-labeled butyrophenones prepared according to this new method was determined by radioreceptor assay and HPLC analysis to range from 1–7 Ci/μmol at EOB (0.6–4 Ci/μmol, EOS) representing a ^{19}F:^{18}F ratio in the range of 1700–240:1. The specific activity as measured by radioreceptor assay represents the effective specific activity and its value would be sensitive to the presence of materials which are receptor active. The HPLC measurement of specific activity would be influenced by the presence of uv absorbing materials not removed during purification. In the case of the ^{18}F-labeled butyrophenones reported here, the lower value for the specific activity as measured by HPLC and radioreceptor assay reflects this small amount of uv absorbing materials.

The importance and utility of measuring the precursor specific activity is noted here since this value provides an upper limit in terms of product specific activity. Studies are presently underway to further reduce or eliminate ^{19}F contamination in critical reagents and to devise synthetic methods which utilize substrates which are highly amenable to rapid purification.

In summary, this new synthetic method provides access into a series of NCA ^{18}F-labeled butyrophenone neuroleptics. Comparative brain uptake and kinetics of spiroperidol, haloperidol, and benperidol synthesized by this method have been measured in baboons using PETT (*36*). The results of these and other studies in progress are being used to guide in the objective selection of a radioligand which has the optimum brain uptake, specific binding, and metabolic stability therefore providing the basis for quantitative PETT measurements at low radiation risk.

FOOTNOTES

* Johnson, Matthey and Co.

† Aldrich Chemical Co.

‡ Janssen Pharmaceutica, Inc.

§ McNeil Laboratories.

¶ The C_{18} SEP-PAK cartridges were obtained from Waters Associate

** Mound Laboratory.

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