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The Rapid Synthesis of High Purity [18F]Butyrophenone Neuroleptics from Nitro Precursors for PET Study

Kazunari Hashizume, Naoto Hashimoto, Hiroo Kato, David G. Cork, † and Yoshihiro Miyake Institute of Biofunctional Research c/o National Cardiovascular Center, Suita, Osaka 565

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We have completed rapid syntheses of $[^{18}F]$ butyrophenone neuroleptics ($[^{18}F]$ haloperidol and $[^{18}F]$ spiperone) from their nitro precursors in high radiochemical yields (up to 21%) by combining a one-step nitro-fluoro exchange reaction and a novel high performance liquid chromatography (HPLC) separation method. The synthesis time was ca. 95 min and both the radiochemical and chemical purities of the labeled products were over 99%.

Compounds labeled with positron emitting radionuclides have been developed as radiotracers to study human brain and cardiovascular functions with positron emission tomography (PET). Among the positron emitters, fluorine-18 (half life: 110 min) and carbon-11 (20 min) are most commonly used for radio labeling organic compounds. The longer half life of fluorine-18 labeled compounds will allow them to be delivered from a central production center in the near future. ²

Butyrophenone neuroleptics are ligands of the dopamine D2 receptor in the brain, and many of them, such as haloperidol, spiperone and N-methylspiperone, already possess a fluorine atom that can be labeled.³ Kook et al. first prepared [¹⁸F]butyrophenone neuroleptics by thermal decomposition of the corresponding diazonium fluorides,⁴ and in the 1980s nitro compounds were used as the precursors.⁵ However, these syntheses gave labeled butyrophenone neuroleptics of very low purity either because of their nature or due to complicated and lengthy multi-step procedures.

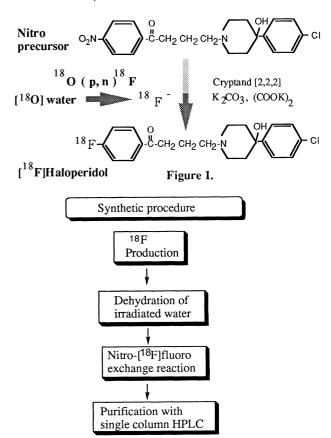
Subsequently a variety of synthetic methods have been elaborated for labeling butyrophenone neuroleptics with fluorine-18. Among them, the one-step nitro-fluoro exchange of a nitrobutyrophenone neuroleptic precursor 18 is advantageous, because one-step reaction reduces synthesis time and renders the radio synthesis apparatus simple. However, a suitable method for the purification has been difficult to develop and no report of both radiochemical purity and yield has been made.

Known synthetic methods of butyrophenone neuroleptics using multi-step reactions are too difficult to use routinely, as the synthetic apparatus becomes too complicated to be readily controlled and many machinery troubles occur.

To overcome these problems we investigated a novel synthetic method involving a one-step nitro-fluoro exchange reaction combined with a single-column HPLC purification which would allow even non-skilled persons to synthesize high purity [18F]butyrophenone neuroleptics (Figures 1 and 3).

An azimuthally-varying-field (AVF) cyclotron (Cypris HM-18, Sumitomo Heavy Industries, Ltd., Tokyo) was used to produce the positron emitting nuclide from the target [18 O]water (isotopic enrichment : $10\sim99\%$; Isotec Inc., Ohio, USA). [18 F]Fluoride was obtained by irradiating (time : $10\sim60$ min, current : $5\sim15~\mu$ A) the [18 O]water target with an 18~MeV

proton beam. Thus, 100 mCi of [18 F]fluoride was obtained by irradiation at 10 μ A for 10 min.



The first step of the synthesis involves drying-up the recovered target water. To get as high a radiochemical yield as possible, it was necessary to maximize the recovery of the target water. We were able to recover much more irradiated water (2.4 g) than previously reported ($10 \sim 100 \ \mu \, l$), ⁸ and by using a high temperature ($108 \, ^{\circ} \, C$) and reduced pressure ($15 \, mmHg$), the time for dehydration was kept to within $15 \sim 25 \, min$.

As for the operation of this step, we modified Katsifis et al.'s conditions as follows; irradiated water was recovered to a flask containing cryptand[2.2.2] (Merck-Schuchardt, Munchen, Germany) (15 \sim 25 mg), potassium oxalate (2 mg), potassium carbonate (0.03 mg) and acetonitrile (1 \sim 3.5 ml), and then evaporated to dryness. A dimethylsulfoxide (0.5 ml) solution containing the nitro precursor was added to the residue and heated to 150 \sim 170 °C. Nitro precursors were synthesized by an improved method which will be described elsewhere. No carrier [19 Flfluoride ion was added.

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Table 1.	Radiochemical	vields and	purities of	[¹⁸ F]bu	tyrophenone neuro	leptics
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Rur	Product (precursor)	Radiochemical	Radiochemical	Chemical	Reaction temp	Reaction time	Total synthesis
		yield/%	purity/%	purity/%	℃	min	time/min
1 [[¹⁸ F]haloperidol (nitrohaloperido	ol) 21	99	99	160	30	90
2 [[¹⁸ F]haloperidol (nitrohaloperido	ol) 11	99	99	160	20	80
3 [¹⁸ F]haloperidol (nitrohaloperido	ol) 9	99	99	160	10	70
4 [[¹⁸ F]haloperidol (nitrohaloperido	ol) 1	99	99	150	5	65
5 [[18F]spiperone (nitrospiperone)	19	99	99	160	20	80
6	¹⁸ F]spiperone (nitrospiperone)	1	99	99	150	5	65

nitrohaloperidol: 1-[4(4-Nitrophenyl)-4-oxobutyl]-4-(4'-chlorophenyl)-4-hydroxypiperidine nitrospiperone: 8-[4-(4-nitrophenyl)-4-oxobutyl]-1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one

We then applied our reported purification method⁹ for separating fluorobutyrophenone neuroleptics from their nitro precursors using a single HPLC column. The whole [18 F]labeling reaction mixture was injected onto the preparative HPLC column [Eluent: MeCN:10mM NaOH = 50:50 (v/v), Asahipak ODP-50 (Shoko Co. Ltd., Tokyo), ϕ 21.5 mm x 250 mm + guard column ϕ 21.5 mm x 100 mm, flow rate 10 ml/min, positron monitor: TCS-R81 (Aloka Co. Ltd., Tokyo)] to isolate the labeled compound.

Analytical HPLC [Eluent: MeCN:10mM NaOH = 55:45 (v/v), Asahipak ODP-5, ϕ 4.6 mm x 150 mm + guard column ϕ 4.6 mm x 10 mm, flow rate 0.8 ml/min, UV 241 nm, radio analyzer: RLC-700 (Aloka)] was used to check the radiochemical and chemical purities of the purified hot products, using both UV (241 nm) and radioisotope detectors. As an example, the chromatographic pattern for separation of [18F]haloperidol is shown in Figure 2.

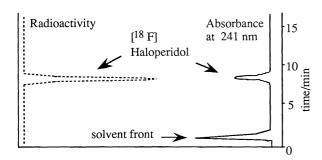


Figure 2. Analytical HPLC profile of [18 F]haloperidol. (Eluent: MeCN:10mM NaOH = 50:50 (v/v), Asahipak ODP-50, 4.6 mm \times 250 mm).

We synthesized [18F]haloperidol and [18F]spiperone from their nitro precursors as shown in Table 1. The total synthesis time was $60\sim95$ min (drying-up: $20\sim30$ min, fluorination: $5\sim30$ min: purification: 35 min). The radiochemical yields were $1\sim21\%$ [decay corrected] and both the radiochemical purity and chemical purity were 99% (no precursors were detected). The analytical values were remarkably high compared to previous products from the nitro-fluoro exchange reaction.

The simplicity of our synthetic method has allowed us to make a straightforward automated synthesis apparatus that is suitable for routine use. We are now applying this method to the synthesis of other high radiochemical purity ¹⁸F-labeled butyrophenone neuroleptics ([¹⁸F]N-methylspiperone, etc.) and other ligands for studying brain and cardiovascular functions.

Figure 3.

We believe our synthetic method will further promote the development of $^{18}\text{F-labeled}$ tracers for PET.

References and Notes

- † Present address: Molecular Chemistry Laboratory, Takeda Chemical Industries Ltd., Juso, Osaka 532.
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