High Yield Synthesis of High Purity [^{18}F]-Labelled Aromatic Compounds by Aryl F-for-X Halogen Exchange Reactions

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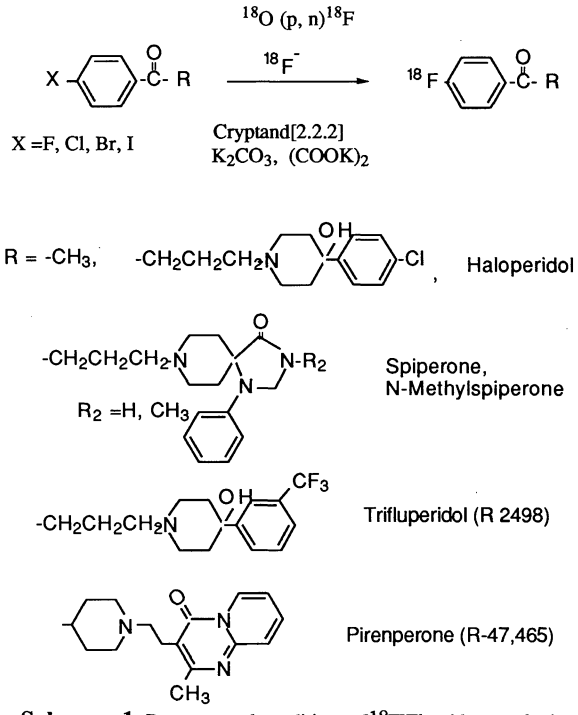
The relative efficacy of aromatic fluorine-for-halogen (F-X) exchange reactions was found to be F-F > F-Cl > F-Br > F-I in a [^{18}F]fluoride-cryptand-oxalate system using 4'-halo-acetophenones (F, Cl, Br and I), key intermediates for many ^{18}F-radiopharmaceuticals. Efficient ^{18}F-labelling reaction and a new chromatographic separation method has enabled the potential of F-for-X exchange (X=Cl and F) to be realized for the high yield synthesis of high purity [^{18}F]-neuroleptics.

Exchange reactions of aromatic halogens with fluorine are well known and widely used as a method of fluorination.[1] The exchanges are designated F-X. Although the relative efficacy of F-X (X=Cl, Br, I) aryl exchange reactions may be in the order of F-Cl > F-Br > F-I in ^{19}F-fluoride reaction systems where an S_{NAr} mechanism with an associative rate determining step is expected, the results for ^{18}F-fluoride systems (X=F, Cl, Br, I) have failed to agree with this order.[2-4] Indeed, there appeared different order of reactivity depending on the literatures and there was no systematic study on the relative reactivity of all four halo-precursors (X=F, Cl, Br and I) with ^{18}F-fluoride. The only isotope of fluorine that can be used to study the F-F exchange is F-18, which is a positron emitter ($t_{1/2}$=110 min) that is used in ever increasing applications for positron emission tomography (PET). Our studies on the synthesis of ^{18}F-labelled compounds offer the chance and reason to investigate the F-X halogen exchange reaction systematically.

The scattered data reported on F-X exchange reactions using ^{18}F suggest that the relative reactivity is F-F > F-I > F-Br > F-Cl.[4] Although the F-F exchange should be the fastest reaction, this exchange has not been interested in synthesis of ^{18}F-labeled PET radiopharmaceuticals by reasons of its low radiochemical yield[5,6] and the inherent carrier-added nature of the product. The F-Cl exchange reactions are often unsuitable for ^{18}F fluorination,[3] because of, 1) the low yields of the reactions compared to other exchange reactions, e.g. the exchanges of aromatic nitro group and trimethyl ammmonium salt with ^{18}F (^{18}F-NO_2, ^{18}F-Me_3N), as well as 2) the lack of a complete separation method of the labeled compounds and precursors for the F-Cl exchange.

In this regard, the reactivity of the four halo-substituted precursors for the production of 4'-[^{18}F]fluoroacetophenone, a key intermediate for the synthesis of various neuroleptics,[7] was investigated (Table 1). The order of decreasing radiochemical yield (decay corrected) can be clearly seen to be F-F > F-Cl > F-Br > F-I, which is in accordance with the decreasing electronegativity of the starting halide substituent and an S_{NAr} mechanism involving an associative rate determining step, and contrary to the order of the leaving ability. Furthermore, the radiochemical yield of F-F isotopic exchange was found to be excellent, much higher than that of the F-Cl exchange which was similar to the yield of the commonly employed F-NO_2 and F-Me_3N exchanges (Table 1, entries 5 and 6). These results prompted us to reinvestigate the use of the ^{18}F-for-^{19}F exchange for labelling PET neuroleptic ligands that require high specific activity.



Scheme 1. Reagents and conditions: [^{18}F]Fluoride was obtained by irradiating (5-180 min, 15-20 μA) [^{18}O]water (10-99%) with 18 MeV protons [nuclear reaction: ^{18}O (p, n) ^{18}F] generated with a Thomas type cyclotron (Cypris HM-18, Sumitomo Heavy Industries Ltd., Tokyo). The whole irradiated water (2.4 g) was recovered in a glassy carbon vessel containing cryptand[2.2.2.] (Merck) (5-15 mg), potassium oxalate (2 mg), potassium carbonate (0.03 mg) and dry acetonitrile (0.5-1.5 ml), and then evaporated to dryness at 108 ℃ under a low pressure (< 15 mmHg) in 10-15 min. A dimethylsulfoxide (0.5 ml; distilled before use) solution containing the precursor (0.05 mmol) was added to the residue and the mixture heated at 160 ℃ for 20 min. Total synthesis time was 70-95 min. No carrier [^{19}F]fluoride ion was added.

The radiochemical yields that were obtained for brain dopamine D2 receptor ligands ([^{18}F]haloperidol, [^{18}F]spiperone, [^{18}F]N-methylspiperone and [^{18}F]trifluperidol) and an antagonist of the 5-HT2 receptor ([^{18}F]pirenperone) from ^{19}F-precursors, were remarkably high, 45-72%, (Table 2), comparable to that for [^{18}F]4'-fluoroacetophenone, and much higher than previously reported the results ([^{18}F]haloperidol; 1 to 10% from ^{19}F-precursor[5], [^{18}F]haloperidol and [^{18}F]spiperone; 1 to 21% from the corresponding nitro-precursor[8]). Chemical purities of the products were also extremely high (Table 2). It can be estimated

Table 1. Radiochemical yields of [^{18}F]fluoroacetophenone using halo-precursor with [^{18}F]fluoride

Entry	Leaving group (X)	Radiochemical yield (%)	Radiochemical purity(%)	Chemical purity (%)
1	F	75	99	99
2	Cl	28	99	99
3	Br	6	99	99
4	I	2	99	99
5	NO_2	34	99	99
6	$(CH_3)_3N$	34	99	-

Radiochemical yield: Corrected to end of bombardment.

that high specific activity of 100-200 mCi/mmole is obtainable by the F-F exchange under our conditions, because small amounts of precursor (0.25-50 mmol) can be used and high yields of ^{18}F (2-3 Ci) can be obtained. Trifluperidol (R 2498) could be labeled with [^{18}F]fluoride in spite of the inhibiting influence of coexisting chloride ion (Table 2, entry 5).

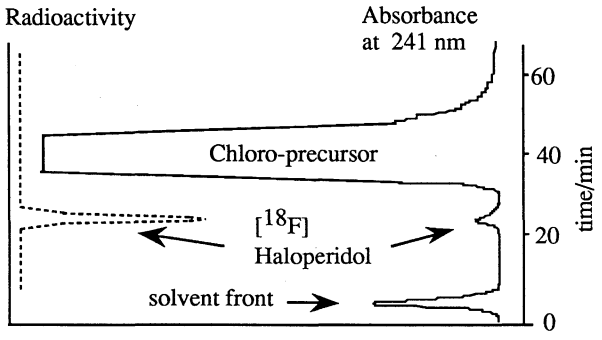


Figure 1. Preparative HPLC profile of [^{18}F]haloperidol. (Eluent : MeCN:10 mM NaOH = 55 : 45 (v/v), Asahipak ODP-5, 21.5 mm x 100 mm + 21.5 mm x 300 mm, flow rate 10 ml/min).

Our results on the relative efficacy of the four halogen exchange reactions also encouraged us to reinvestigate the F-Cl exchange for the preparation of very high purity [^{18}F]haloperidol (Table 2, entry 2). Using the chloro-precursor in the same reaction system, together with our recently developed highly selective chromatographic separation method,[9] we were able to obtain extremely high radiochemical and chemical purities (no precursor was detected). The labelled products are separated from their Cl-precursors more easily than the nitro precursors. Figure 1 shows the typical HPLC pattern obtained, and the analytical values were remarkably high compared to previous reports for halogen exchange reactions.

We believe that the present results are due to several factors, including the nature of the cryptand-oxalate fluorinating system and the use of, 1) a glassy carbon reaction vessel, 2) a fairly low pressure (< 15 mmHg) for the reagent-drying step and 3) our highly selective HPLC system. For comparison, a different fluorinating system (tetrabutylammonium [^{18}F]fluoride), using the conditions of Farrokhzad[5] or Pascari,[3] gave only a low yield (9%) of [^{18}F]-labelled product from the chloro-precursor. Our results also indicate how it will be possible to produce several curies of ^{18}F-labelled radiopharmaceuticals and, with an

Table 2. Radiochemical yields of [^{18}F]neuloleptics using [^{18}F]fluoride

Entry	Precursor	Radiochemical yield (%)	Radiochemical purity (%)	Chemical purity (%)
1	haloperidol	61	99	99
2	chlorohaloperidol	21	99	99
3	N-methylspiperone	47	99	99
4	spiperone	45	99	99
5	trifluperidol, hydrochloride	3	99	99
6	pirenperone	72	99	99

chlorohaloperidol: 1-[4(4-Chlorophenyl)-4-oxobutyl]-4-(4'-chlorophenyl)-4-hydroxypiperidine.

appropriate delivery network, supply several PET-centers from a central production laboratory. We propose that the improved ^{18}F-production and labelling methodology will allow the F-F and F-Cl exchange reactions to be widely recognized as the reactions of choice for [^{18}F]labeling aromatic compounds. The halide precursors are more stable than the nitro analogues at the high temperatures required for nucleophilic aromatic fluorination, and to obtain chloro compounds is generally easiest among the halide precursors.

Further studies on the wide applicability of this halogen exchange method (F-F and F-Cl) to the synthesis of radiofluorinated tracers are now in progress.

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