Comparison of [^{18}F]Fluoropropylating Agents for ^{18}F-Radiolabeling of Amines

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It has been demonstrated that [^{18}F]fluoroalkylating agents are useful prosthetic groups for radiofluorination of amines which are contained in many positron emission tomography (PET) radiopharmaceuticals. These agents can be synthesized from disubstituted alkanes, in which the disubstituted propanes are shown to give higher radiochemical yield than the corresponding methanes and ethanes upon radiofluorination.[1-3] Although some [^{18}F]fluoropropylating agents have been investigated, chemical purity of the resulting *N*-[^{18}F]-fluoroalkylamines has not been significantly examined.[1,3]

We therefore compared and analyzed the most commonly used [^{18}F]fluoropropylating agents with respect to precursor availability, labeling conditions and the chemical purity of the *N*-alkylated product, 1-(3-[^{18}F]fluoropropyl)-4-phenylpiperazine ([^{18}F]**1**). 1-Phenylpiperazine (**2**) was selected as an amine for [^{18}F]fluoropropylation, since many neuropharmaceuticals contain phenylpiperazine moieties.[4-6]

Experimental Section

General procedure for synthesis of n.c.a. [^{18}F]fluoropropylating agents. Fluorine-18 was prepared from [^{18}O]-H_2O by the ^{18}O(p,n)^{18}F reaction as previously described.[7] The [^{18}F]fluoride ion was directly added to a Vacutainer® containing *n*Bu_4NOH (40% aq., 3.8 μL, 5.7 μmol). The solution was then evaporated to dryness at 90 °C (oil bath) under a gentle stream of N_2 with CH_3CN (200 μL × 2). The radioactivity was resolubilized in CH_3CN (200 μL) and transferred to a reaction vial containing the precursor (3-bromopropyl triflate, 1 μL, 6 μmol; 1,3-diiodopropane, 2.3 mg, 7.8 μmol; 1,3-propyl bismesylate, 1.4 mg, 6 μmol). The reaction mixture was then heated at 90 °C for an appropriate time period (3-bromopropyl triflate, 2 min; 1,3-diiodopropane, 6 min; 1,3-propyl bismesylate, 6 min). After the ^{18}F-labeling of the 3-bromopropyl triflate, hydrolysis of the unreacted triflate was carried out by treating the reaction mixture with water (30 μL) at 150 °C for 3 min.[8] In the case of 1,3-diiodopropane as the precursor, the [^{18}F]fluorinated product was distilled (110 °C, N_2 flow), and this procedure took 2.5 min.[9] The other [^{18}F]fluoropropylating agents were used for the following *N*-alkylation reaction without isolation.

Radiochemical synthesis of 1-(3-[^{18}F]fluoropropyl)-4-phenylpiperazine ([^{18}F]1). To [^{18}F]fluoropropylating agents were added **2** (2 μL, 12.4 μmol) and Et_3N (5 μL, 35.9 μmol). The reaction mixture was heated at 150 °C for 30 min, cooled down and passed through a short plug filled sequentially with a piece of cotton, 2 cm of silica gel and 2 cm of Na_2SO_4 using a 9 : 1 mixture of CH_2Cl_2 and methanol. The solvents were removed in a water bath under a gentle stream of N_2. The residue was redissolved in CH_2Cl_2 and injected onto a semipreparative HPLC column which was eluted at a flow rate of 4 mL/min with a 98.5 : 1.5 mixture of CH_2Cl_2 : MeOH (1% NH_4OH). The desired product was eluted at 15-18 min. In the synthesis using 3-[^{18}F]fluoropropyl mesylate, hydrolysis was performed after the *N*-alkylation in the presence of 1 N NaOH (30 μL) at 100 °C for 3 min, and the mixture was then taken up with ethyl acetate, extracted with water and passed through a short plug filled with 7 cm of Na_2SO_4. Control reactions were also carried out without the hydrolysis procedure in the syntheses using 3-[^{18}F]fluoropropyl bromide and 3-[^{18}F]fluoropropyl mesylate. The total reaction and purification time was 90 min, and decay-corrected overall radiochemical yields were 10-15% and 8-10% when 3-bromopropyl triflate and 1,3-diiodopropane were used as the precursors, respectively whereas the yield was higher (15-20%) for 1,3-propyl bismesylate. Authenticity of the [^{18}F]**1** was confirmed by coinjection with unlabeled standard, 1-(3-fluoropropyl)-4-phenylpiperazine.

Chemical purity of the [^{18}F]**1** was determined by HPLC. A standard curve was constructed by using the compound **1** with different concentrations *vs.* UV absorbance at 254 nm. The area of the UV absorbance peak close to or coeluted with the [^{18}F]**1** was measured and compared with the standard curve.

Results and Discussion

Three [^{18}F]fluoropropylating agents were prepared from the corresponding precursors and *n*Bu_4N[^{18}F]F in acetonitrile, and used for the *N*-alkylation of the amine **2**. The precursors used for the preparation of 3-[^{18}F]fluoropropyl iodide, 3-[^{18}F]fluoropropyl bromide and 3-[^{18}F]fluoropropyl mesylate include 1,3-diiodopropane,[9] 3-bromopropyl triflate[8,10] and 1,3-propyl bismesylate[3]. The first precursor is commercially available, whereas the latter two are readily prepared from 3-bromopropanol and 1,3-propanediol, respectively. The 3-bromopropyl triflate, which is not UV active and not easily stainable, was purified using a Kugelrohr distillation apparatus and unstable on a long-term storage. In contrast,

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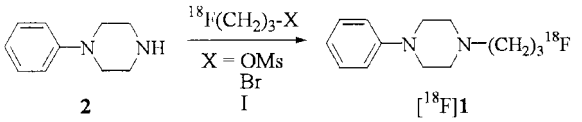

2 [^{18}F]**1**

Scheme 1. Radiochemical synthesis of the [^{18}F]**1** using three different fluoropropylating agents.

1,3-propyl bismesylate is visualized by UV illumination. [^{18}F]Fluorination reactions were carried out according to the literature with some modifications.[3,8,9] 3-[^{18}F]Fluoropropyl mesylate was prepared from 1,3-propyl bismesylate in 74-85% yield (n=3) which was the highest compared with the other two agents. 3-[^{18}F]fluoropropyl iodide in 26-45% (n=3) after distillation and 3-[^{18}F]fluoropropyl bromide in 55-70% yield (n=3).

The [^{18}F]fluoropropylating agents were not isolated except the 3-[^{18}F]fluoropropyl iodide that was purified by distillation, and the N-alkylation reactions of the amine **2** were followed (Scheme 1). In the case of 3-[^{18}F]fluoropropyl bromide, hydrolysis was carried out prior to N-alkylation, which converts the unreacted 3-bromopropyl triflate into the corresponding alcohol and thus prevents the formation of side products coeluted with the desired product.[8] In a same vein, hydrolysis was carried out after the N-alkylation of **2** with 3-[^{18}F]fluoropropyl mesylate to convert a possible side product, 1-(3-methanesulfonyloxypropyl)-4-phenylpiperazine into the cor- responding alcohol. This hydrolysis procedure with NaOH caused defluorination from the product by 6% and greater fraction of [^{18}F]fluoride (26%) was generated under harsh conditions (150 °C, 5 min).

Chemical purity of the [^{18}F]**1** was determined by HPLC (Figure 1). The area of the UV peak corresponding to the [^{18}F]**1** prepared from 3-[^{18}F]fluoropropyl iodide was smaller than those of the N-alkylated products prepared from 3-[^{18}F]fluoropropyl bromide and 3-[^{18}F]fluoropropyl mesylate by a factor of 12 and 4, respectively (Figure 1. A *vs.* B and

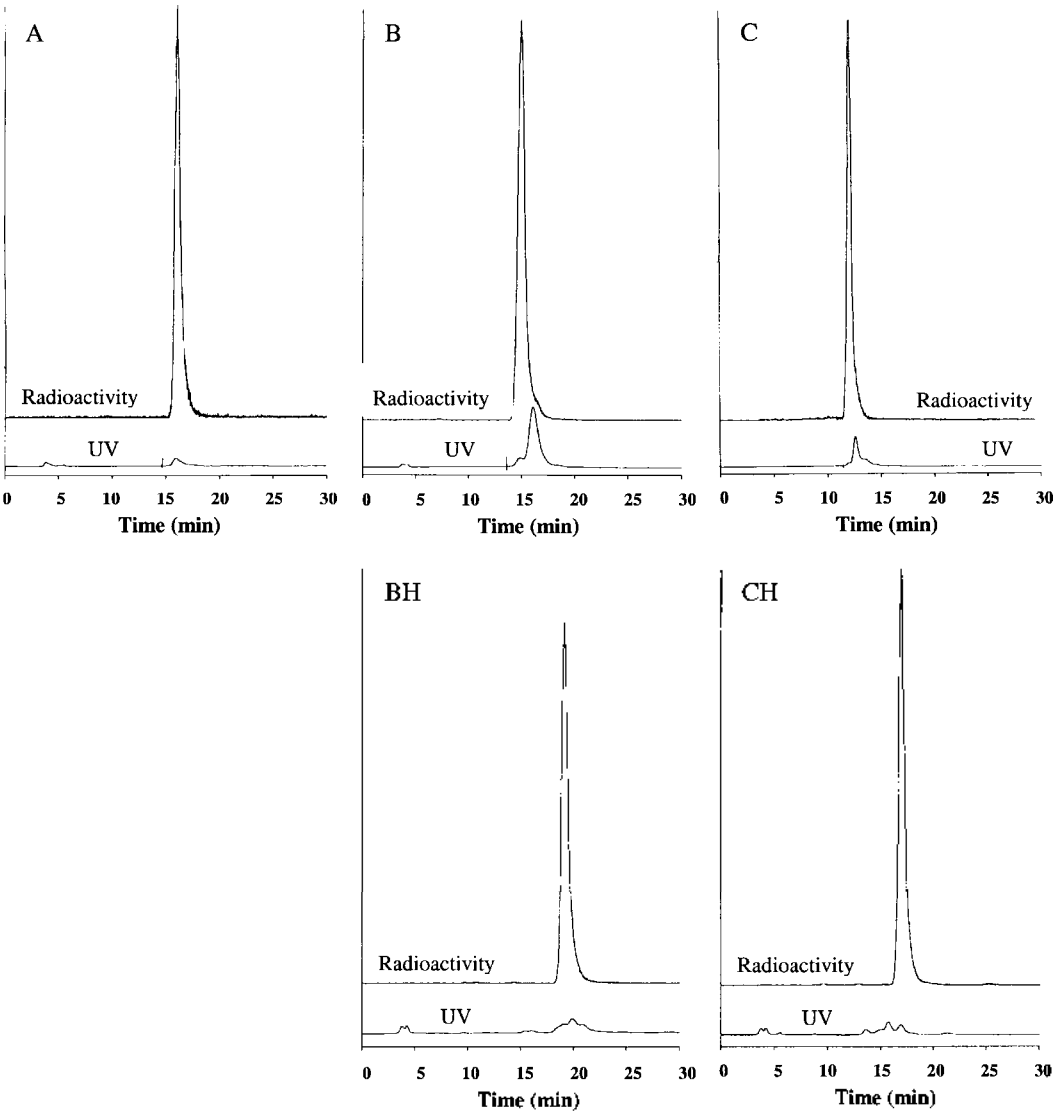

Figure 1. HPLC chromatograms of the [^{18}F]**1** prepared from N-alkylation of **2** with [^{18}F]fluoropropylating agents: 3-[^{18}F]fluoropropyl iodide (A), 3-[^{18}F]fluoropropyl bromide without (B) and with hydrolysis (BH), and 3-[^{18}F]fluoropropyl mesylate without (C) and with hydrolysis (CH). Retention times varied on different days, however, the product was identified by coelution with the unlabeled standard **1**.

C). However, the hydrolysis procedures using H_2O and NaOH markedly reduced the UV peak area of the [^{18}F]**1** prepared from 3-[^{18}F]fluoropropyl bromide and 3-[^{18}F]fluoropropyl mesylate by a factor of 6 and 4, respectively (Figure 1, B *vs.* BH and C *vs.* CH). As a result, the UV peak area of the [^{18}F]**1** prepared from 3-[^{18}F]fluoropropyl mesylate after the hydrolysis was comparable to that of 3-[^{18}F]fluoropropyl iodide (Figure 1, A *vs.* CH). Although distillation after the preparation of 3-[^{18}F]fluoropropyl iodide needs to be carried out, the precursor, 1,3-diiodopropane is commercially available, and the hydrolysis procedure is unnecessary. In contrast, the precursor of 3-[^{18}F]fluoropropyl mesylate needs to be prepared from 1,3-propanediol, and the hydrolysis is required after the *N*-alkylation. Besides, a little amount of defluorination (6%) is accompanied during the hydrolysis procedure. Although 1,3-propyl bistosylate has been reported to give 3-[^{18}F]fluoropropyl tosylate in higher yield than the corresponding bismesylate, the chemical purity of the resulting *N*-alkylated product is expected to be similar. Therefore, this study showed that the 3-[^{18}F]fluoropropyl iodide is superior to the other two [^{18}F]fluoropropylating agents.

Conclusion

The [^{18}F]fluoropropylating agents were prepared from 1,3-diiodopropane, 3-bromopropyl triflate and 1,3-propyl bismesylate. Among these agents, 3-[^{18}F]fluoropropyl iodide prepared from 1,3-diiodopropane is the most desirable with respect to precursor availability, labeling conditions and chemical purity of the *N*-alkylated product of the amine **2**, although the radiofluorination yield was lower than the others. This study showed that the 3-[^{18}F]fluoropropyl iodide can be widely used for the preparation of high chemical purity radiopharmaceuticals containing a [^{18}F]fluoropropyl group.

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References

1. Shiue, C. -Y.; Bai, L. -Q.; Teng, R. -R.; Wolf, A. P. *J. Labelled Cpd. Radiopharm.* **1987**, *24*, 55.
2. Coenen, H. H.; Colosimo, M.; Schüller, M.; Stöcklin, G. *J. Labelled Cpd. Radiopharm.* **1986**, *23*, 587.
3. Block, D.; Coenen, H. H.; Stöcklin, G. *J. Labelled Cpd. Radiopharm.* **1987**, *24*, 1029.
4. Babich, J. W.; Graham, W. A.; Fischman, A. J. *Br. J. Cancer* **1996**, *74*, 917.
5. Bagdy, G.; Szemeredi, K.; Kanyicska, B.; Murphy, D. L. *J. Pharmacol. Exp. Therap.* **1989**, *250*, 72.
6. Maj, J.; Lewandowska, A. *Pol. J. Pharmacol. Pharm.* **1980**, *32*, 495.
7. Kilbourn, M. R.; Hood, J. T.; Welch, M. J. *Int. J. Appl. Radiat. Isot.* **1984**, *35*, 599.
8. Oh, S. J.; Choe, Y. S.; Chi, D. Y.; Kim, S. E.; Choi, Y.; Lee, K. H.; Ha, H. J.; Kim, B. -T. *Appl. Radiat. Isot.* **1999**, *51*, 293.
9. Goodman, M. M.; Keil, R.; Shoup, T. M.; Eshima, D.; Eshima, L.; Kilts, C.; Votaw, J.; Camp, V. M.; Votaw, D.; Smith, E.; Kung, M. -P.; Malveaux, E.; Watts, R.; Huerkamp, M.; Wu, D.; Garcia, E.; Hoffman, J. M. *J. Nucl. Med.* **1997**, *38*, 119.
10. Chi, D. Y.; Kilbourn, M. R.; Katzenellenbogen, J. A.; Brodack, J. W.; Welch, M. J. *Int. J. Appl. Radiat. Isot.* **1986**, *37*, 1173.