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Synthesis of [^{18}F]Flunarizine

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Flunarizine, a calcium channel antagonist of the piperazine class, has been labeled with the positron-emitter ^{18}F. 4-[^{18}F]Fluoro-4′-fluorobenzhydryl chloride was prepared in three steps from no-carrier-added [^{18}F]fluoride ion, and used in the alkylation of *N*-cinnamylpiperazine to give [^{18}F]flunarizine in 13% radiochemical yield (from [^{18}F]fluoride).

Introduction

Flunarizine [1-(bis-4-fluorophenyl)methyl)-4-(3-phenylpropenyl)piperazine) is a clinically used calcium channel blocker of the piperazine class (Holmes *et al.*, 1984; Todd and Benfield, 1989). Flunarizine, and other calcium channel antagonists, are of recent interest in treatment of neurological disorders such as epilepsy and migraine (Greenberg, 1987). A large number of benzhydryl substituted piperazines, including cinnarizine (1-diphenylmethyl-4-(3-phenylpropenyl)piperazine) and flunarizine, have been prepared and evaluated as calcium channel antagonists (Janssen, 1960, 1970), and this remains an active area of pharmaceutical research (Ohtaka and Tsukamoto, 1987; Gubert *et al.*, 1987). Flunarizine affects dopamine metabolism in rat brain (Fadda *et al.*, 1989), and flunarizine and cinnarizine have been described as worsening the effects of Parkinson's disease in some clinical populations (Masso *et al.*, 1987; Lugaresi *et al.*, 1987). Flunarizine has been recently described as an inhibitor of bachrotoxin-B binding to sodium channels (Pauwels *et al.*, 1989). Finally, flunarizine is also structurally similar to a class of dialkylpiperazines, exemplified by GBR 12909 (1-[2-(bis(4-fluorophenyl)methoxy)ethyl]-4-(3-phenylpropyl)piperazine), which are in clinical studies as dopamine reuptake antagonists (Sogaard *et al.*, 1988) and in ^{18}F labeled form as possible radiotracers for studies using positron emission tomography (PET) (Kilbourn *et al.*, 1989).

In order to study the *in vivo* biodistribution of flunarizine, its possible effects on the dopamine system and in particular its effects on the dopamine uptake system, and the metabolism of ^{18}F labeled bis(4-fluorophenyl)methyl groups, we have prepared flunarizine in no-carrier-added ^{18}F labeled form.

Experimental

Materials and methods

[^{18}F]Fluoride ion was prepared by irradiation of [^{18}O] water in an all-silver cyclotron target (Mulholland *et al.*, 1989). Lithium aluminum hydride (LAH) and thionyl chloride were obtained from Aldrich Chem. Co., *N*-cinnamyl piperazine from Adams Chem. Co., and flunarizine from Sigma Chem. Co. 4-Fluoro-4′-(trimethylammonium)-benzophenone trifluoromethanesulfonate was prepared by literature methods (Haka *et al.*, 1989; Haka and Kilbourn, 1990). TLC analyses were done using plastic backed silica gel (EM Science 5735) and aluminum oxide (Type E neutral; EM Science 5581) plates. HPLC analysis was done using a Phenomenex C_{18} column, 0.45 × 115 cm, eluted with 60:40 acetonitrile:0.065 M NH_4OAc, 1.0 mL/min flow: detection by u.v. (254 nm) and radioactivity (Beckman Model 170 flow radioactivity detector).

4-[^{18}F]Fluoro-4′-fluorobenzhydryl chloride (1). This benzylic chloride was prepared by published methods (Haka *et al.*, 1989; Haka and Kilbourn, 1990). In brief, 4-[^{18}F]fluoro-4′-fluorobenzophenone was prepared by [^{18}F]fluoride ion substitution of 4-fluoro-4′-(trimethyl-ammonium)benzophenone trifluoromethanesulfonate (DMSO, 155°C, 25 min). The 4-[^{18}F]fluoro-4′-fluorobenzophenone was not isolated but immediately reduced to 4-[^{18}F]fluoro-4′-fluorobenzhydrol ($LiAlH_4$, DMSO, 1 min, 0–5°C). The alcohol was isolated by C_{18} Sep-Pak and converted to the desired chloride by treatment with thionyl chloride (neat, 100°C, 20 min). TLC (7/3 hexane/ethylacetate), R_f **1** = 0.43, R_f alcohol = 0.16. Overall yield of the 4-[^{18}F]fluoro-4′-fluorobenzhydryl chloride **1** was 40% (uncorrected) in a synthesis time of 60 min.

[^{18}F]Flunarizine. To a solution of **1** in 200 μL DMSO was added 3 mg of *N*-cinnamylpiperazine. The solution was heated (100°C) for 30 min, cooled, and diluted with 5 mL of 2N HCl. The aqueous solution was twice extracted with 5 mL portions of diethyl ether to remove unreacted [^{18}F]benzhydryl chloride. The aqueous solution was then neutralized with $NaHCO_3$ and extracted with diethyl ether. The ether layer was dried (Na_2SO_4), evaporated, and the residue dissolved in dichloromethane. Silica gel flash chromatography (silica gel Sep-Pak, 2% methanol in dichloromethane in 5 mL portions) was used to isolate the [^{18}F]flunarizine. Yield was 33% (uncorrected, 45 min synthesis) starting from the [^{18}F]benzhydryl chloride, and 13% (uncorrected, 105 min synthesis) from resolubolized [^{18}F]fluoride ion. Radiochemical purity was 99% as determined in three TLC systems: (1) silica gel, 10% CH_3OH/CH_2Cl_2 R_f flunarizine = 0.55, R_f chloride = 0.69, R_f *N*-cinnamylpiperazine = 0.05; (2) alumina, 70:30 pentane:diethyl ether, R_f flunarizine = 0.32, R_f chloride = 0.73, R_f cinnamylpiperazine = 0.13; (3) silica gel, 7/3 hexane/ethylacetate R_f flunarizine = 0.20, R_f chloride = 0.43, R_f cinnamylpiperazine = 0.01. No chemical impurities were observed by u.v. or iodine visualization of the TLC plate. HPLC analysis showed a single radioactive product (radiochemical purity 97%: R_t = 14.15 min) which coeluted with authentic flunarizine. Estimates of specific activity by HPLC (comparison to standard injections of flunarizine) were in excess of 2000 Ci/mmol. In some preparations small amounts of a chemical impurity identified as *N*-cinnamylpiperazine were observed.

Results and Discussion

The synthesis of [^{18}F]flunarizine (Fig. 1) is quite straightforward, and utilizes a precursor, 4-[^{18}F]fluoro-4′-fluorobenzhydryl chloride (**1**), which we have previously used in the synthesis of [^{18}F]GBR 12909, a dopamine uptake antagonist (Haka and Kilbourn, 1990). Alkylation of the piperazine nitrogen with this reactive halide is simple. The amine products are then separated from the neutral, unreacted [^{18}F]benzhydryl chloride by acid–base extractions, and the product is separated from unreacted *N*-cinnamyl-piperazine using flash chromatography with a small column of silica gel. In most cases the product was obtained in adequate chemical purity (no or little contamination with *N*-cinnamyl-piperazine) and the product was suitable for animal experimentation. For consistent high purity preparations, however, the inclusion of a HPLC purification step might be advisable. The product [^{18}F]flunarizine is obtained in 13% overall yield starting from resolubolized [^{18}F]fluoride ion, with an overall synthesis time of less than one half-life of ^{18}F. Neither the yields or the synthesis time have been optimized.

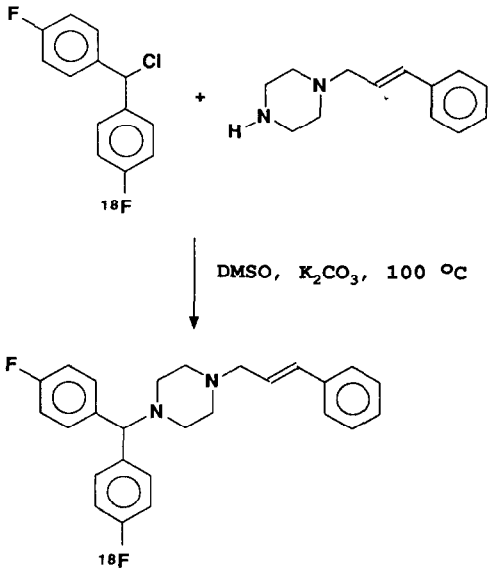

Fig. 1

The specific activity of the product has been estimated to be in excess of 2000 Ci/mmol, consistent with a synthesis beginning with no-carrier-added [^{18}F]fluoride ion and similar to that obtained for [^{18}F]GBR 12909 (also prepared from the intermediate benzhydryl chloride **1**) and [^{18}F]GBR 13119 (Haka *et al.*, 1989).

By the identical route, using 4-[^{18}F]fluorobenzhydryl chloride (Haka *et al.*, 1989) as intermediate, we have previously prepared [^{18}F]fluorocinnarizine (1-(4-[^{18}F]fluorophenyl)(phenyl)-methyl-4-(3-phenylpropenyl)piperazine) and examined its *in vivo* brain distribution in mice (Kilbourn, 1989). Those studies showed low brain extraction of [^{18}F]fluorocinnarizine and no specificity for the dopaminergic brain regions. Similar studies of the biodistribution of [^{18}F]flunarizine, possible effects of dopamine reuptake blockers, and metabolic products are underway.

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