Journal of Labelled Compounds and Radiopharmaceuticals—Vol. XXXVIII, No. 4

Synthesis of a Radiotracer for Studying Nicotinic Acetylcholine Receptors: (+/-)-exo-2-(2-[^{18}F]fluoro-5-pyridyl)-7-azabicyclo[2.2.1]heptane

Andrew Horti[1], Hayden T. Ravert[2], Edythe D. London[1,2,3] and Robert F. Dannals*[2]

[1] Neuroimaging and Drug Action Section
Intramural Research Program, NIDA
P. O. Box 5180
Baltimore, Maryland, U.S.A. 21224

[2] Divisions of Nuclear Medicine and Radiation Health Sciences
The Johns Hopkins Medical Institutions
615 North Wolfe Street, Room 2001
Baltimore, Maryland, U.S.A. 21205-2179

[3] Department of Pharmacology and Experimental Therapeutics
University of Maryland School of Medicine
655 North Baltimore Street
Baltimore, Maryland, U.S.A. 21201-1559

Summary

The radiochemical synthesis of (+/-)-exo-2-(2-[^{18}F]fluoro-5-pyridyl)-7-azabicyclo[2.2.1]heptane ([^{18}F]**1**) was accomplished by Kryptofix® 222 assisted nucleophilic no-carrier-added [^{18}F]fluorination of (+/-)-exo-2-(2-bromo-5-pyridyl)-7-azabicyclo[2.2.1] heptane (**3a**). The average radiochemical yield of the final product was 10% and the average specific activity was greater than >2000 mCi/μmol, calculated at end-of-synthesis. The stable fluorine ligand ([^{19}F]**1**) was prepared by Kryptofix® 222 assisted nucleophilic fluorination of (+/-)-exo-2-(2-bromo-5-pyridyl) - 7- methoxycarbonyl - 7 - azabicyclo[2.2.1]heptane (**3b**) followed by acid deprotection.

Key Words: radiotracer, epibatidine, ^{18}F, fluorination, halogen-exchange, nicotinic receptors, acetylcholine, positron emission tomography.

* Author for correspondence.

CCC 0362–4803/96/040355–11

Received 29 September 1995
Revised 30 October 1995

Introduction

The nicotinic acetylcholine receptor (nAChR) bears recognition sites for acetylcholine and alkaloids, such as nicotine, and its activation mediates a variety of physiological functions and pharmacological effects (1). Postmortem studies have revealed losses of nAChRs in brains from patients with Alzheimer's disease (2-7), suggesting that imaging of nAChRs might be useful in the study of this disorder.

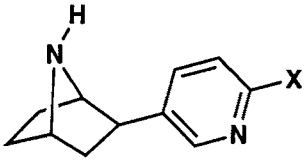
Various radioligands, such as [^{3}H]nicotine (5,8-11), [^{3}H]acetylcholine (12), [^{3}H]methylcarbamylcholine (13,14), and [^{3}H]cytisine (15) have been used to study central nAChRs *in vitro;* whereas, *in vivo* studies of nAChRs have been more limited. In mice, intravenously injected [^{3}H]nicotine bound specifically, with an anatomical distribution reflecting that of nAChRs assayed *in vitro*; however, the level of nonspecific binding was high, and the tracer was cleared rapidly from the brain (16). [^{3}H]Cytisine displayed longer retention and lower nonspecific binding in the mouse brain than [^{3}H]nicotine, but its nonspecific binding was still substantial, and there was a relatively low uptake of the tracer in brain (17).

Studies of nAChRs by positron emission tomography (PET) have been performed only with [^{11}C-methyl]nicotine. The radiochemical synthesis of racemic [^{11}C-methyl]nicotine was first described in 1979 (18), and syntheses of the resolved enantiomers of [^{11}C-methyl]nicotine were subsequently reported (19-21). [^{11}C-methyl]Nicotine has been used in studies of Rhesus monkeys and human research volunteers without neurological disease (22), and patients with Alzheimer's disease (23). The rapid clearance of [^{11}C-methyl]nicotine from the brain and its considerable nonspecific binding have been obstacles to more widespread use of the tracer to study nAChRs (24). In addition to isotopically labeled nicotine, radiofluorinated (25) and radioiodinated nicotine analogs (26) have been synthesized and have been considered for use in *in vivo* studies.

Recent findings have indicated that epibatidine ((+)-exo-2-(6-chloro-3-pyridyl)-7-azabicyclo[2.2.1]heptane, **2a**), an extract of frog skin, is an extremely promising parent structure on which to base future radiotracer development related to the nAChR. The alkaloid is a potent antinoceptive agent that possesses extremely high potency for nAChRs *in vitro* (27). *In vivo* studies with [^{3}H]epibatidine in mice showed high uptake of the tracer, a regional distribution consistent with that of nAChRs, a slow clearance from brain, and low estimates of nonspecific binding (28). Epibatidine analogs with hydrogen, iodine, or methyl substitutions in place of the chlorine at position 2 of the pyridine ring have been prepared, and each showed high selectivity and affinity for nAChR *in vitro* (27,29). The *in vivo* biodistribution of the [^{3}H]norchloro analog was similar to that of the parent compound (30). In this paper, the radiochemical synthesis of the fluoro analog of epibatidine, (+/-)-exo-2-(2-[^{18}F]fluoro-5-pyridyl)-7-azabicyclo[2.2.1] heptane ([^{18}F]**1**), is reported.

Results and Discussion

The chemical structure of (+/-)-exo-2-(2-fluoro-5-pyridyl)-7-azabicyclo[2.2.1]heptane (1) is shown in Figure 1. Since naturally occurring (+)-epibatidine and its synthetic (-)-enantiomer are reported to have similar receptor binding profiles (27), in the present study, we report our work with the racemate.



X = F (1)
X = Cl (epibatidine, 2a)
X = Br (3a)

Figure 1

Although no less than 14 total syntheses of epibatidine have been published during the past two years (see two recent reviews - 31,32) and epibatidine itself is commercially available (albeit quite expensive), it was necessary to find an efficient pathway to incorporate fluorine into the 5-pyridyl-7-azabicyclo[2.2.1]heptane structure and develop a synthesis of suitable quantities of the appropriate precursor for radiolabeling. Our strategy was based on analysis of published methods for synthesis of epibatidine and 2-fluoropyridine derivatives.

Nucleophilic fluorination of 2-substituted-pyridines has been previously described (33,34). Treatment of 2-chloropyridine with KF in dimethylsulfone at high temperature for 18 days yielded 2-fluoropyridine in poor yield (33). Halogen exchange fluorination of 2-bromopyridine with KF in the same solvent at similar temperature and times yielded 2-fluoropyridine in moderate yield (34). The literature revealed only a few examples for preparation of [^{18}F]fluoropyridine derivatives. Treatment of 6-chloronicotinic acid N,N-diethylamide with K^{18}F afforded the corresponding [^{18}F]-derivative with 40% yield (35).

2-Chloronicotine and 6-chloronicotine have been shown to be relatively inert for nucleophilic fluorination (36). However, 2-bromonicotine and 6-bromonicotine are converted to corresponding [^{18}F] or [^{19}F]fluoronicotines with cesium fluoride in DMSO (35).

In our model experiments studied by HPLC, the fluorination of 2-chloropyridine using KF/Kryptofix® 222 in DMSO at 200° C proceeded slowly at best (results not presented). It was therefore not surprising that initial attempts to use the same fluoride-chloride exchange on epibatidine itself yielded only unidentified tar-like reaction mixtures with complete decomposition of epibatidine after only 15 min at elevated temperature.

However, the fluorination of 2-bromopyridine under similar conditions yielded 80% of 2-fluoropyridine (by HPLC) after only 1 hr. Based on these

preliminary results we chose to pursue the bromo analog of epibatidine **3a** as an appropriate precursor for radiofluorination.

(+/-)-Exo-2-(2-bromo-5-pyridyl)-7-azabicyclo[2.2.1]heptane (**3a**) was initially prepared using a few milligrams of commercially available (+/-)-epibatidine (**2a**) by the halogen-exchange reaction shown in Figure 2. **3a** could also be prepared from N-methoxycarbonyl epibatidine **2b** using similar conditions.

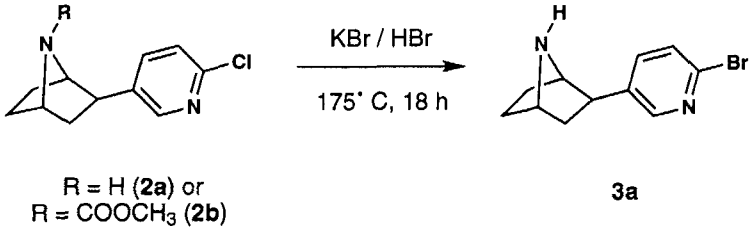


Figure 2

The synthesis of protected epibatidine **2b** was accomplished using a modification of a published procedure (37). However, when using the published solvent conditions for desulfonation with sodium amalgam (methanol, -30° C), a low yield (10%) of desulfonated intermediate product was obtained. The yield doubled when boiling t-butyl alcohol was used in the desulfonation step.

Synthesis of **3a** from N-methoxycarbonyl-7-azabicyclo[2.2.1]heptene (**4**) was also accomplished via a Heck type palladium-assisted reductive coupling (Figure 3). This reaction has been recently described for preparation of exo-aryl derivatives of

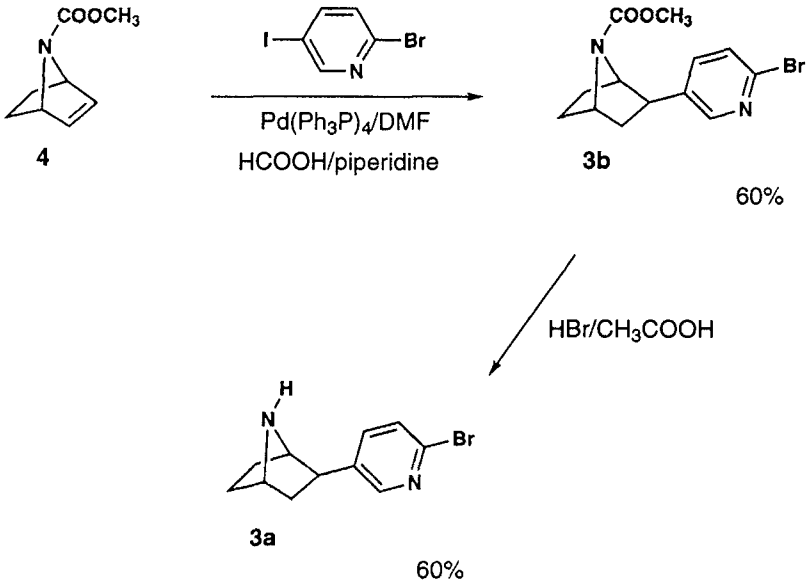


Figure 3

norbornane (38,39) and epibatidine (40). The palladium-assisted coupling was modified by using commercially available tetrakis(triphenylphosphine)palladium(0) as a catalyst (41). The olefin **4** could be prepared by either the literature procedure (42) or from N-methoxycarbonyl-7-azabicyclo[2.2.1]heptadiene-2,3-dicarboxylic acid, dimethyl ester (43) using an adaption by Regan (41) of the published electrolytic oxidative bisdecarboxylation method (44). Using this reaction sequence it has been possible to prepare hundreds of milligrams of **3a**.

Nucleophilic fluorination of **3a** with stable fluoride as KF/Kryptofix® 222 in DMSO at 160 - 200° C afforded only a mixture of decomposition products with little if any desired product. However, the fluorination of (+/-)-exo-7-methoxycarbonyl-(2-bromo-5-pyridyl)-7-azabicyclo[2.2.1]heptane (**3b**) under the same reaction conditions yielded the corresponding (+/-)-exo-7-methoxycarbonyl-(2-fluoro-5-pyridyl)-7-azabicyclo[2.2.1]heptane (**5**) in reasonable yield (15 - 26%) (see Figure 4). Deprotection of **5** yielded the desired product, [^{19}F]**1**, in 47% yield (Figure 4).

Unlike the fluorination with stable fluoride, no-carrier-added radiofluorination of (+/-)-exo-2-(2-bromo-5-pyridyl)-7-azabicyclo[2.2.1]heptane (**3a**) gave a reasonable yield of [^{18}F]**1** (approximately 10% calculated at end-of-the-synthesis) with an average time of synthesis of 50 min. The average specific of [^{18}F]**1** was greater 2000 mCi/μmol calculated at end-of-the-synthesis. [^{18}F]**1** prepared by the method described was shown to be radiochemically pure (> 99% by radioHPLC), chemically pure (> 95%), and coeluted with the authentic standard prepared as part of this research.

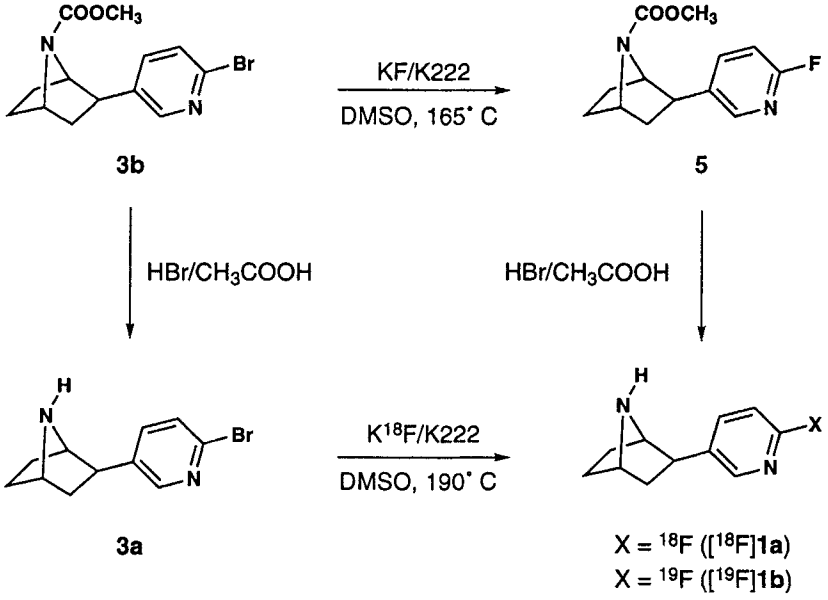


Figure 4

In summary, a simple, one-step radiosynthesis of a high specific activity radiofluorinated ligand for studying nAChRs has been developed. The synthesis is rapid and yields sufficient quantities of radioligand for future studies of these receptors using PET.

Experimental

All reagents used were ACS or HPLC grade. ^{1}H-NMR spectra were recorded on a Bruker AM 300 (300 MHz); chemical shifts (δ) were recorded in parts per million (ppm) downfield from TMS. High resolution mass-spectra was recorded on an AEI MS-30 (University of Minnesota Mass Spectra Laboratory). High performance liquid chromatographic analysis and purification were performed with two Waters 590EF HPLC pumps, an in-line fixed wavelength (254 nm) detector, and a single two inch NaI crystal radioactive detector. HPLC chromatograms were recorded by a Rainin Dynamax dual channel control/interface module connected to a Macintosh computer with appropriate program software (Dynamax - version 1.3). HPLC semipreparative purifications were completed on a Waters PrepPak μBondapak C18 HPLC cartridge. All HPLC analyses were performed on Alltech Econosil C18 column. A dose calibrator (Capintec CRC-12R) was used for all radioactivity measurements.

(+/-) - 2- - (2 - chloro - 5 - pyridyl) - 7 - methoxycarbonyl - 7-azabicyclo[2.2.1]heptane (2b). This compound was prepared in 28% yield by separation of mixture of endo- and exo-isomers of (+/-)-2-(2-chloro-5-pyridyl)-7-methoxycarbonyl-7-azabicyclo[2.2.1]heptane by semipreparative HPLC using a Waters PrepPak cartridge (25 mm x 100 mm, μPorasil, 10 μ) eluted with hexane:2-propanol (95:5) at a flow rate of 15 ml/min. The retention times of the endo and exo were 7 and 8 min, respectively. The starting endo/exo mixture was prepared using minor modifications to the published procedure (36).

MS (EI), m/z (rel. intensity), [M^+] 266.0817 (18%); calculated for $C_{13}H_{15}N_2ClO_2$: M 266.0821.

^{1}H-NMR, $CDCl_3$, δ (ppm), (multiplicity, J (Hz)): 8.24 (1H, d, 2.1, $H_{6'}$), 7.61 (1H, dd, 8.2, 2.1, $H_{4'}$), 7.25 (1H, d, 8.8, $H_{3'}$), 4.45 (1H,s), 4.22 (1H,s), 3.67 (3H, b.s), 2.90 (1H, dd, 9.0, 4.8), 2.01 (1H, m), 1.90-1.52 (5H, m)

(+/-)-exo-2-(2-bromo-5-pyridyl)-7-azabicyclo[2.2.1]heptane (3a). (+/-)-Epibatidine dihydrochloride (2a, 7.5 mg, 27 μmol, obtained from Research Biochemicals Incorporated, Natick, MA), NaBr (0.22 g), and 48% HBr (1.5 ml) were heated in a sealed vial for 18 hrs at 180° C. The reaction mixture made basic with a combination of NaOH and $NaHCO_3$ and extracted with CH_2Cl_2. The organic

extract was evaporated and the residue was redissolved in 2-propanol. The product was purified by semipreparative HPLC using a Waters PrepPak cartridge (8 mm x 100 mm, μPorasil, 10 μ) eluted with hexane:2-propanol:triethylamine (84:16:0.2) at a flow rate of 7.5 ml/min. Using these conditions, the product eluted with a retention time of 3 min. The HPLC solvent containing the product was evaporated under reduced pressure to yield **3a** (7 mg, 83%) as a transparent oil.

MS (EI), m/z (rel. intensity), [M$^+$] 252.0255/254.0247 (9.6%/9.9%); calculated for $C_{11}H_{13}N_2{}^{79}Br$ / $C_{11}H_{13}N_2{}^{81}Br$: M 252.0268/254.0248

^{1}H-NMR, $CDCl_3$, δ (ppm), (multiplicity, J (Hz)): 8.26 (1H, d, 2.5, $H_{6'}$), 7.68 (1H, dd, 8.3, 2.5, $H_{4'}$), 7.38 (1H, d, 8.3, $H_{3'}$), 3.82(1H, t, 3.7), 3.58 (1H, d, 1.8), 2.76 (1H, dd, 8.79, 5.04, H_2), 2.0-1.49 (6H, m, overlapping).

An alternative synthesis of **3a** was to stir a mixture of **3b** (128 mg, 0.4 mmol) and 45% HBr in acetic acid (2 mL) for 24 hrs at room temperature. The reaction mixture was partly neutralized with 6 N NaOH (3 mL) and initially purified using semipreparative HPLC (Waters PrepPak μBondapak C18 HPLC cartridge (25 x 100 mm); eluent CH_3CN:H_2O:CF_3COOH (15:85:0.15) at a flow rate of 10 mL/min. The product eluted with a retention time of 10 to 14 min. Following evaporation of the HPLC solvent, the residue was redissolved in 2-propanol and further purified using the semipreparative conditions described above. After semipreparative chromatography, the deprotected derivative **3a** was obtained in 60% yield (60 mg).

(+/-)-exo-2-(2-bromo-5-pyridyl)-7-methoxycarbonyl-7-azabicyclo [2.2.1]heptane (3b). A mixture of 7-methoxycarbonyl-7-azabicyclo[2.2.1] heptene (**4**, 0.5 g, 3.26 mmol), 2-bromo-5-iodopyridine (1.5 g, 5.28 mmol) (45), tetrakis(triphenylphosphine)palladium(0) (200 mg, 0.17 mmol), piperidine (1 mL), 96% formic acid (0.38 mL), and DMF (1.5 mL) was stirred in a sealed vial under argon at 70° C for 12 hrs. The reaction mixture was diluted with water and extracted with CH_2Cl_2. The extract was washed with water (3 x 25 mL) and dried over Na_2SO_4. The solvent was evaporated and CH_3CN (4 mL) was added to redissolve the residue. The reaction product **3b** was purified by preparative HPLC (Waters PrepPak μBondapak C18 HPLC cartridge (25 mm x 100 mm) (eluent CH_3CN:H_2O 45:55; flow rate 10 mL/min). Under these conditions, the product eluted with a retention time of 12 to 13 min. The product solution in mobile phase was partially evaporated on rotary-evaporator, saturated with NaCl, and extracted with CH_2Cl_2 (3 x 50 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered, and evaporated to yield **3b** as transparent oil (588 mg, 58%).

MS (EI), m/z (rel. intensity), [M$^+$] 310.0304/312.0294 (8%/9%); calculated for $C_{13}H_{15}N_2{}^{79}BrO_2$ / $C_{13}H_{15}N_2{}^{81}BrO_2$: M 310.0316/312.0296.

^{1}H-NMR, $CDCl_3$, δ (ppm), (multiplicity, J (Hz)): 8.22 (1H, d, 2.1, $H_{6'}$), 7.50 (1H, dd, 8.4, 1.9 , $H_{4'}$), 7.39 (1H, d, 8.25, $H_{3'}$), 4.45 (1H, s), 4.22 (1H, s), 3.68 (3H, s), 2.87(1H, dd, 8.88, 4.6, H_2), 2.02(1H, dd, 12.3, 9.1), 1.83-1.47 (5H, m, overlapping).

(+/-)-exo-2-(2-fluoro-5-pyridyl)-7-methoxycarbonyl-7-azabicyclo [2.2.1] heptane (5). A mixture of (+/-)-exo-2-(2-bromo-5-pyridyl)-7-methoxycarbonyl-7-azabicyclo[2.2.1]heptane (**3b**, 100 mg, 0.32 mmol), KF (900 mg, 15.7 mmol), Kryptofix® 222 (120 mg, 0.32 mmol), and anhydrous DMSO (4 mL) was stirred in a sealed vial at 160 - 170° C for 20 hrs. The product was isolated by semipreparative HPLC using Waters PrepPak μBondapak C18 cartridge (25 mm x 100 mm) eluted with CH_3CN:H_2O (45:55) at a flow rate of 12 mL/min; the retention time of the product was 8 min. The HPLC solvent containing the product was reduced in volume, saturated with Na_2SO_4, and extracted with CH_2Cl_2. The resulting CH_2Cl_2 solution was dried over Na_2SO_4 and evaporated to yield **6** (21.2 mg, 26.6%) as transparent oil.

MS, m/z (rel. intensity), [M+] 250.1127 (100%); calculated for $C_{13}H_{15}N_2FO_2$: M 250.1117.

^{1}H-NMR, $CDCl_3$ δ (ppm), (multiplicity, J (Hz)): 8.05 (1H, d, 2.1, $H_{6'}$), 7.75 (1H, dt, $J_{H4'-H3'}$ 9.12, $J_{H4'-F}$ 5.7, $J_{H4'-H6'}$ 2.5; $H_{4'}$), 6.86 (1H, dd, 8.5, 3.0, $H_{3'}$), 4.45 (1H, s), 4.22 (1H, s), 3.67 (3H, b.s.), 2.8 (1H, m), 1.4-2.0 (5H, m).

(+/-)-exo-2-(2-fluoro-5-pyridyl)-7-azabicyclo[2.2.1]heptane ([^{19}F]1). A mixture of (+/-)-exo-2-(2-fluoro-5-pyridyl)-7-methoxycarbonyl-7-azabicyclo[2.2.1] heptane, **5** (40 mg, 0.16 mmol) and 1 mL of 48% HBr in acetic acid was stirred for 12 hrs at room temperature. The reaction mixture was chilled in a dry ice/acetone bath and partly neutralized with 6 N NaOH (1.6 mL). The solution was injected onto a Waters PrepPak μBondapak C18 HPLC cartridge (25 mm x 100 mm) eluted with CH_3CN:H_2O:CH_3COOH (15:85:0.2) at a flow rate of 10 mL/min. The peak with a retention time of 6 min was collected, the HPLC solvent partially evaporated on rotary-evaporator (bath temperature < 60° C), 100 mL of CH_3CN was added and solvent was evaporated to dryness. Carbon tetrachloride (25 mL) was added to the same flask and evaporated to dryness yielded 19 mg of deprotected [^{19}F]**1** (47%). The product contained 1 equivalent of acetic acid.

MS, m/z (rel. intensity), [(M+1)$^+$] 193.1136 (%); calculated for $C_{11}H_{14}N_2F$: M+1 193.1141

^{1}H-NMR, $CDCl_3$, δ (ppm), (multiplicity, J (Hz)): 8.15 (1H, d, 1.9, $H_{6'}$), 7.95 (1H, dt, 12.2, 8.1, 2.6, $H_{4'}$), 6.88 (1H, dd, 8.5, 3.0, $H_{3'}$), 3.96 (1H, t, 3.9), 3.73 (1H, d, 3.2), 3.09 (3H, s, acetate), 2.8 (1H, m), 2.0-1.5 (5H, m)

(+/-)-exo-2-(2-[^{18}F]fluoro-5-pyridyl)-7-azabicyclo[2.2.1]heptane ([^{18}F]1). In a 10 mL Reactivial, an aqueous solution of the $^{18}F^-$ (prepared by 16 MeV proton irradiation of 98% enriched $H_2{}^{18}O$), 20 mg of Kryptofix® 222, and 6 mg K_2CO_3 was heated under a stream of argon in an oil bath at 120° C while water was azeotropically evaporated using repeated additions of dry CH_3CN. A solution of (+/-)-exo-2-(2-bromo-5-pyridyl)-7-azabicyclo[2.2.1]heptane (3a, 5 mg) in anhydrous DMSO (0.5 mL) was added into the reaction vessel. The reaction vessel was sealed and heated at 190° C for 15 min. The reaction mixture was cooled and diluted with 0.5 mL of preparative HPLC mobile phase and injected onto the Waters PrepPak μBondapak C18 HPLC cartridge (25 mm x 100 mm) eluted with CH_3CN:H_2O:CF_3COOH (15:85:0.15) at a flow rate of 12 mL/min. The radioactive peak with a retention time of 7 - 8 min corresponding to authentic 1 was collected and the solvent was removed on rotary-evaporator. The product was redissolved in saline (5 mL) and $NaHCO_3$ (0.5 mL, 8.4%) was added.

An aliquot of the final solution of known volume and radioactivity was applied to an analytical reverse-phase HPLC column (Alltech Econosil C18 10μ 250 mm x 4.6 mm). A mobile phase of CH_3CN:H_2O:CF_3COOH (12.5:87.5:0.15) at a flow rate of 3 mL/min was used to elute the radioligand, which had a retention time of 4 min. The area of the UV absorbance peak measured at 254 nm corresponding to carrier product was measured and compared to a standard curve relating mass to UV absorbance. The radiochemical product also coeluted with a sample of authentic [^{19}F]1.

Acknowledgements

The authors would like to thank Dr. Andrew Regan of the Department of Chemistry at the University of Manchester, England for his helpful discussions involving the synthesis of epibatidine. The authors also wish to thank Drs. William B. Mathews and John L. Musachio for their helpful discussions, and Mr. Robert C. Smoot for his assistance with the radiochemical syntheses.

References

1. Aceto M.D. and Martin B.R. - Med. Res. Rev. 2: 43 (1982)
2. Araujo D.M., Lapchak P.A., Robitaille Y., Gauthier S., and Quirion R.J. - Neurochem. 50: 1914 (1988)
3. Kellar K.J., Whitehouse P.J., Martino-Barrows A.M., Marcus K., and Price D.L. - Brain Res. 436: 62 (1987)
4. Nordberg A. and Winblad B. - Neurosci. Lett. 72: 115 (1986)
5. Shimohama S., Taniguchi T., Fujiwara M., and Kameyama M. - J. Neurochem. 45: 604 (1985)

6. Whitehouse P.J., Martino A.M., Antuono P.G., Lowenstein P.R., Coyle J.T., Price D.L., and Kellar K.J. - Brian Res. 371: 146 (1986)
7. London E.D., Ball M.J., and Waller S.B. - Neurochem. Res. 14: 745 (1989)
8. Abood L.G., Reynolds D.T., and Bidlack J.M. - Life Sci. 27: 1307 (1980)
9. Romano C. and Goldstein A. - Science 210: 647 (1980)
10. Clarke P.B.S., Pert C.B., and Pert A. - Brain Res. 323: 390 (1984)
11. London E.D., Waller S.B., and Wamsley J.K. - Neurosci. Lett. 53: 179 (1985)
12. Schwartz R.D., McGee R. Jr., and Kellar K.J. - Mol. Pharmacol. 22: 56 (1982)
13. Boksa P. and Quirion R. - Eur. J. Pharmacol 139: 323 (1987)
14. Takayama H., Majewska M.D., and London E.D. - J. Pharmacol. Exp. Ther. 253: 1083 (1989)
15. Pabreza L.A., Dhawan S., and Kellar K.J. - Mol. Pharmacol. 39: 9 (1991)
16. Broussolle E.P., Wong D.F., Fanelli R.J., and London E.D. - Life Sci. 44: 1123 (1989)
17. Flesher J.E., Scheffel U., London E.D., and Frost J.J. - Life Sci. 54: 1883 (1994)
18. Berger G., Maziere M., Knipper R., Prenant C., and Comar D. - Int. J. Appl. Radiat. Isot. 30: 393 (1979)
19. Långström B., Antoni G., Halldin C., Svard H., and Bergson G. - Chemica Scripta 20: 46 (1982)
20. Halldin C., Någren K., Swahn C.-G., Långström B., and Nybäck H. - Nucl. Med. Biol. 19: 871 (1992)
21. Saji H., Magata Y., Yamada Y., Tajima K., Yonekura Y., Konishi J., Ohmomo Y., and Yokoyama A. - Chem. Pharm. Bull. 40: 734 (1992)
22. Nybäck H., Nordberg A., Långström B., Halldin C., Hartvig P, Ahlin A., Swahn C.-G., and Sedvall G. - Progress in Brain Research, Vol. 79, Elsevier Science Publishers, pp. 313-319 (1989).
23. Nordberg A., Lundqvist H., Hartvig P., Lilja A., and Långström B.- Alzheimer Dis. Assoc. Disord. 9: 21 (1995)
24. Nybäck H., Halldin C., Ahlin A., Curvall M., and Eriksson L. - Psychopharmacol. 115: 31 (1994).
25. Ballinger J.R., Bowen B.M., Firnau G., Garnett E.S., and Teare F.W. - Int. J. Appl. Radiat. Isot. 35: 1125 (1984)
26. Chan S.M., Basmadjian G.P., Marten D.F., Sadek S.A., Magarian R.A., and Grunder J.R. - J. Label. Compd. Radiopharm. 23: 647 (1986)
27. Badio B. and Daly J.W. - Mol. Pharm. 45: 563 (1994)
28. London E.D., Scheffel U., Kimes A.S., and Kellar K.J. - Eur. J. Pharm. 278: R1 (1995)
29. Corey E.J., Loh T.-P., Achyutha R.S., Daley D.C., and Sarshar S. - J. Org. Chem. 58: 5600 (1993)

30. Scheffel U., Carroll F.I., Kepler J.A., Taylor G.F., Stathis M., London E.D., and Kuhar M.J. - J. Nucl. Med. 36: 253P (1995)
31. Broka C.A. - Med. Chem. Res. 4: 449 (1994)
32. Dehmlow E.V. - J. prakt. Chem. 337: 167 (1995)
33. Hammer J., Link W.J., Jurjevich A., and Vigo T.L. - Recueil 81: 1058 (1962)
34. Finger G., Starr L.D., Dickerson D.R., Gutowsky H.S., and Hammer J. - J. Org. Chem. 28: 1666 (1963)
35. Kilbourn M.R. - Fluorine-18 Labeling of Radiopharmaceuticals. National Academy Press, Washington, D.C. (1990)
36. Ballinger J.R., Bowen B.M., Firnau G., Garnett E.S., and Teare F.W. - Int. J. Appl. Radiat. Isot. 35: 1125(1984)
37. Huang D.F. and Shen T.Y. - Tet. Lett. 34: 4477 (1993)
38. Larock R.C. and Johnson P.L. - J. Chem. Soc., Chem. Comm. 1368 (1989)
39. Arcadi A., Marinelli F., Bernocchi E., and Cacchi S. - J. Organomet. Chem. 368: 249 (1989)
40. Clayton S.C. and Regan A.C. - Tet. Lett. 34: 7493 (1993)
41. Regan A.C. - Personal communication.
42. Altenbach H.-J., Constant D., Martin H.-D., Mayer B., Müller M., and Vogel E. - Chem. Ber. 124: 791 (1991)
43. Bansal R.C., McCulloch A.W., McInnes A.G. - Can. J. Chem. 47: 2391 (1969)
44. Marchand A.P. and Allen R.W. - J. Org. Chem. 41: 2551 (1975)
45. Hama Y., Nobuhara Y., Aso Y., Otsubo T., and Ogura F. - Bull. Chem. Soc. Jpn. 61: 1683 (1988)