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Research Article

Radiosynthesis of 2-*exo*-(2′-[^{18}F]Fluoro-3′-(4-fluorophenyl)-pyridin-5′-yl)-7-azabicyclo[2.2.1]heptane ([^{18}F]F_2PhEP), a potent epibatidine-based radioligand for nicotinic acetylcholine receptor PET imaging

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Summary

2-*exo*-(2′-Fluoro-3′-(4-fluorophenyl)-pyridin-5′-yl)-7-azabicyclo[2.2.1]heptane (F_2PhEP), a novel, epibatidine-based, α4β2-selective nicotinic acetylcholine receptor antagonist of low toxicity, as well as the corresponding *N*-Boc-protected chloro- and bromo derivatives as precursors for labelling with fluorine-18 were synthesized from 7-*tert*-butoxycarbonyl-7-azabicyclo[2.2.1]hept-2-ene in 13, 19 and 8% overall yield, respectively. [^{18}F]F_2PhEP was prepared in 8–9% overall yield (non-decay-corrected) using 1 mg of the bromo derivative in the following two-step radiochemical process: (1) no-carrier-added nucleophilic *hetero*aromatic *ortho*-radiofluorination with the activated K[^{18}F]F-Kryptofix$^{®}_{222}$ complex in DMSO using microwave activation at 250 W for 90 s, followed by (2) quantitative TFA-induced removal of the *N*-Boc protective group. Radiochemically pure (>95%) [^{18}F]F_2PhEP (1.48–1.66 GBq, 74–148 GBq/μmol) was obtained after semi-preparative HPLC (Symmetry® C18, eluent aqueous 0.05 M NaH_2PO_4 CH_3CN: 78/22 (v:v)) in 75–80 min starting from an 18.5 GBq aliquot of a cyclotron-produced [^{18}F]fluoride production batch. Copyright © 2006 John Wiley & Sons, Ltd.

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Key Words: fluorine-18; F_2PhEP; epibatidine analogue; nAChR

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Introduction

Several central nervous system related disorders, including Alzheimer's and Parkinson's disease, schizophrenia, anxiety and depression, seem to implicate the cholinergic system and in particular the nicotinic acetylcholine receptors (nAChRs).[1,2] Based on the predominance, within the mammalian brain of the α4 and β2 subtypes, considerable efforts have been spent in recent years on the design and development of α4β2-selective, positron-emitting, radioligands as *in vivo* Positron Emission Tomography (PET) imaging and diagnostic tools. Among those labelled with fluorine-18, one of the most attractive positron-emitting radioisotopes for radiopharmaceutical chemistry (half-life: 109.8 minutes), 2-[^{18}F]F-A-85380[3–8] (Figure 1) is the only PET probe currently used in humans for quantitative brain imaging of the nAChRs. 2-[^{18}F]F-A-85380 shows reasonable affinity and selectivity for this subtype[9–12] and has already been extensively validated in non-human primate studies.[13–17] It also displays a safe profile – low toxicity,[12,18] no mutagenicity[12,18] and acceptable effective dose equivalent to the patient in dosimetric studies [12,19,20] – for its use in humans.[21,22] On the other hand, 2-[^{18}F]F-A-85380 is a relatively strong-hydrophilic derivative displaying rather slow brain kinetics. This results in long scanning times, often exceeding 3 hours, which could be a limitation in routine use. Another drawback of this radioligand is its non-displacable binding (up to 30–40% in regions showing high nAChRs densities, such as the thalamus).[13]

In the course of the development of this azetidinyl-based radioligand, structurally related analogues of the alkaloid (-)-epibatidine have also been designed (Figure 1), labelled with fluorine-18 and evaluated *in vivo* for their potential to image nAChRs with PET. Within this series, [^{18}F]FEP, a compound in which the chlorine atom of epibatidine has been replaced by a [^{18}F]fluorine-atom,[23–26] showed a brain distribution and *in vivo*

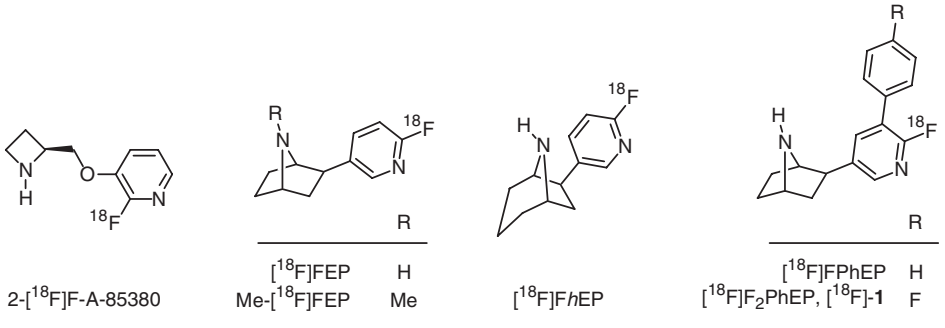

Figure 1. 2-[^{18}F]F-A-85380 and the epibatidine based [^{18}F]FEP, Me-[^{18}F]FEP, [^{18}F]F*h*EP, [^{18}F]FPhEP including the target tracer of the present work [^{18}F]F$_2$PhEP ([^{18}F]-1)

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pharmacological characteristics in non-human primates that were exceptionally promising,[27–32] but its toxicity prohibited its use in humans.[33] Other analogues such as its *N*-methyl derivative ([^{18}F]Me-FEP)[31] and an 8-azabicyclo[3.2.1]octane derivative ([^{18}F]F*h*EP)[34–36] have also been reported and are currently under evaluation.

Recently, a novel series of 3′-phenyl-epibatidine and 3′-phenyl-deschloroepibatidine derivatives was described.[37,38] The reported compounds not only possess subnanomolar affinity and high selectivity[39] for brain α4β2-nAChRs, but also were described as functional antagonists of low toxicity. Within this series, a first derivative, coded FPhEP (Ki of 0.24 nM against [^{3}H]epibatidine[38]) has already been labelled with fluorine-18 (Figure 1) and its potential for *in vivo* PET-imaging nAChRs was recently evaluated.[40] Another candidate is F_2PhEP (**1**, namely 2-*exo*-(2′-fluoro-3′-(4-fluorophenyl)-pyridin-5′-yl)-7-azabicyclo[2.2.1]heptane, Figure 1), a derivative showing higher affinity for brain α4β2-nAChRs with a Ki of 0.029 nM against [^{3}H]epibatidine[38,39] and equally offering an opportunity for fluorine-18-labelling by nucleophilic *ortho-hetero*aromatic substitution.[41–43]

Discussion

Chemistry

The syntheses of F_2PhEP (**1**) as the target reference compound, the corresponding *N*-Boc-protected chloro- and bromo derivatives (**7a** and **7b**) as precursors for labelling with fluorine-18 as well as the intermediate *N*-Boc-F_2PhEP (**7c**) are outlined in schemes 1 and 2. F_2PhEP (**1**) was obtained in six steps and in 13% overall yield from *N*-Boc protected 7-azanorbornene (**2**, synthesized in four steps from commercially available *N*-Boc-pyrrole in 49% according to Dolci *et al.*[26]). The corresponding *N*-Boc-protected chloro-bromo- and fluoro derivatives (**7a–c**) were obtained in five steps from **2**, in 19, 8 and 14% overall yield, respectively.

Briefly, reductive palladium-catalysed Heck-type coupling of the *N*-Boc-azanorbornene **2** with 2-amino-5-iodopyridine (**3**, synthesized in one step from commercially available 2-aminopyridine in 72% overall yield according to Dolci *et al.*[26]) using palladium acetate as catalyst in acetonitrile, containing tetrabutylammonium chloride and potassium formate, at 100°C for 2 days gave the corresponding pyridinyl-7-azabicyclo[2.2.1]heptane **4** in 69% yield (Scheme 1). Bromination of **4** using bromine and triethylamine in a mixture of dichloromethane and acetic acid at room temperature for 16 hours provided the 3′-bromopyridine **5** in 79% yield. Palladium-catalysed Suzuki-type coupling of **5** with 4-fluorophenylboronic acid using palladium acetate as catalyst in dimethoxyethane, containing tri-(2-tolyl)phosphine and sodium carbonate, at 80°C for 1.5 hours gave the 3′-phenylpyridine **6** in 90% yield.

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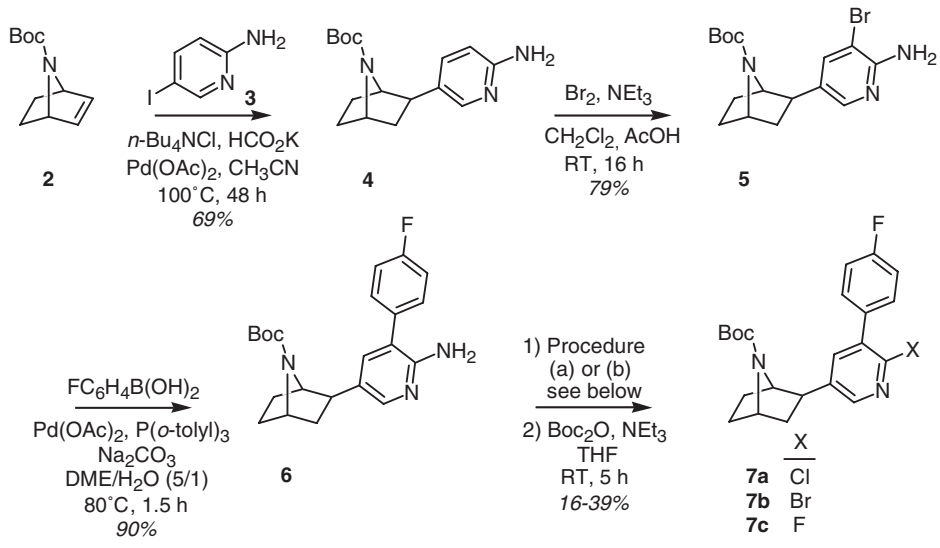

Scheme 1. Synthesis of *N*-Boc-F_2PhEP (7c) and the corresponding precursors for labelling with fluorine-18, the chloro- and bromo derivatives 7a and 7b

Chlorination of **6** (with concomitant loss of *N*-Boc) with sodium nitrite in hydrochloric acid in the presence of copper(I) chloride at 0°C for 40 minutes, followed by direct treatment with di-*tert*-butyl dicarbonate (Boc_2O) in THF containing triethylamine at room temperature for 5 hours gave the *N*-Boc-protected 2′-chloro derivative **7a** in 39% yield (Scheme 1). A similar reaction using hydrobromic acid and copper(I) bromide gave the *N*-Boc-protected 2′-bromo derivative **7b** in 16% yield. Fluorination of **6** (with also concomitant loss of *N*-Boc) with sodium nitrite in 70% HF/pyridine (at room temperature for 45 minutes, followed by heating at 100°C for another 1 hour) gave F_2PhEP (**1**), which was found difficult to isolate at this stage. The crude reaction mixture was then treated with Boc_2O (using conditions similar to those described above) to give the *N*-Boc-protected 2′-fluoro derivative **7c** in 28% yield (Scheme 1).

Finally, *N*-Boc-removal was performed with trifluoroacetic acid (TFA) in dichloromethane (1/5 v:v) at room temperature for 10 minutes and cleanly gave F_2PhEP (**1**) in 96% yield (Scheme 2).

Radiochemistry

The two-step radiosynthesis of [^{18}F]F_2PhEP ([^{18}F]-**1**) is outlined in Scheme 3. The chloro- and the bromo derivative (**7a** and **7b**, respectively) were evaluated

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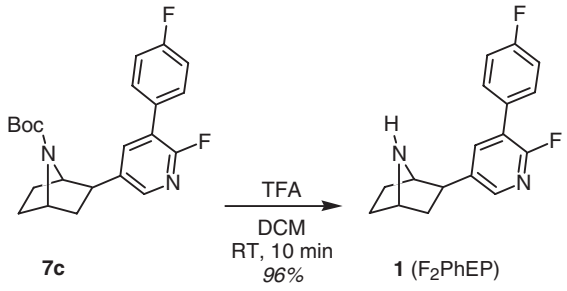
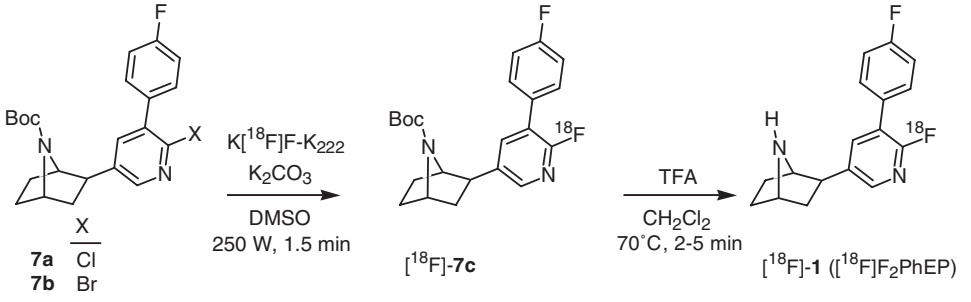


Scheme 2. Synthesis of F_2PhEP (1) as reference compound



Scheme 3. Two-step radiosynthesis of [^{18}F]F_2PhEP ([^{18}F]-1)

for their effectiveness as labelling precursors using nucleophilic *hetero*aromatic fluorinations.[41–43]

Introduction of the cyclotron-produced fluorine-18 as no-carrier-added naked [^{18}F]fluoride anion was performed in dimethyl sulphoxide (DMSO) using microwave activation at 250 W utilizing the activated K[^{18}F]F-Kryptofix®222 complex[44,45] as the radiofluorinating reactant (Kryptofix®222 (K_{222}): 4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo[8.8.8]hexacosane). Briefly, a DMSO solution (600 µl) containing 1.0 mg of the chloro- (**7a**, 2.48 µmol) or bromo (**7b**, 2.23 µmol) precursor for labelling were transferred to 30–60 mCi of the dried K[^{18}F]F-K_{222} complex (see experimental part) in a reaction vial (Vacutainer® tube). The unsealed tube was then placed in a dedicated microwave oven at 250 W for 30–90 s. The radiochemical yields of fluorine-18 incorporation were calculated from the TLC-radiochromatogram and defined as the ratio of [^{18}F]-**7c** over total fluorine-18 activity. Both the chloro- and bromo precursors (**7a,b**) were reactive, with incorporation yields slightly increasing with the reaction time (up to 40% for 90 s). Compared to our previously reported model studies,[41–43] the incorporation yields were lower and the bromo derivative **7b** gave only slightly higher yields than the chloro derivative **7a**. An explanation may be the presence of the additional bulky phenyl ring at the 3′-position, revealing a steric hindrance component in these

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*hetero*aromatic nucleophilic radiofluorinations in the pyridine series. Removal of the *N*-Boc-protective group was performed in a mixture of TFA and dichloromethane (1/50 (v:v)) at room temperature for 2–5 min, quantitatively yielding the amine [^{18}F]-**1**. HPLC purification of [^{18}F]F_2PhEP ([^{18}F]-**1**) was performed on a semi-preparative Symmetry® C18 column, using a mixture of aqueous 0.05 M NaH_2PO_4 and CH_3CN (78/22 (v:v)) as the eluent. In order to obtain >95% radiochemically pure [^{18}F]F_2PhEP, the bromo precursor **7b** was once again preferred to the chloro derivative **7a**, simplifying the HPLC purification by allowing a better separation of [^{18}F]-**1** (R_t: 14.0 min) from the corresponding *N*-Boc-deprotected bromo derivative (R_t: 17.8 min) compared to the *N*-Boc-deprotected chloro derivative (R_t: 16.5 min).

Typically, 40–45 mCi of HPLC-purified [^{18}F]F_2PhEP ([^{18}F]-**1**, 1.48–1.66 GBq) were obtained with a specific radioactivity of 2–4 Ci/μmol (74–148 GBq/μmol) using **7b** as precursor for labelling (1 mg and microwave activation at 250 W for 90 s) in 75–80 min starting from a 500 mCi (18.5 GBq) aliquot of a cyclotron-produced [^{18}F]fluoride production batch (12–18% non-decay-corrected overall yield).

Formulation of [^{18}F]F_2PhEP ([^{18}F]-**1**) as *i.v.* injectable solution was performed using a home-made Sep-pak®Plus C18 device. The HPLC-collected fraction containing the radiotracer was diluted with water and the resulting solution was passed through a C18 Sep-pak® cartridge. The cartridge was then washed with water, partially dried with nitrogen and finally eluted with ethanol followed by physiological saline. The solution was then sterile-filtered and diluted with physiological saline to an ethanol concentration below 10%. The radiotracer preparation was a clear and colourless solution with a measured pH between 5 and 7. As demonstrated by analytical HPLC analysis, the radiotracer preparation was found to be >95% chemically and radiochemically pure and the preparation was shown to be free of non-radioactive precursor and was chemically and radiochemically stable for at least 120 min. These results were in compliance with our in-house quality control/assurance specifications.

Conclusion

The novel $\alpha_4\beta_2$-selective, nicotinic antagonist 2-*exo*-(2′-fluoro-3′(4-fluorophenyl)-pyridin-5′-yl)-7-azabicyclo[2.2.1]heptane (F_2PhEP, **1**) as well as the corresponding *N*-Boc-protected chloro- and bromo derivatives (**7a**,**b**) as precursors for labelling with fluorine-18 were synthesized from 7-*tert*-butoxycarbonyl-7-azabicyclo[2.2.1]hept-2-ene in 13, 19 and 8% overall yield, respectively. [^{18}F]F_2PhEP ([^{18}F]-**1**) was prepared in 8–9% overall yield (non-decay-corrected) using 1 mg of the bromo derivative **7b** and the following two-step radiochemical process: (1) no-carrier-added nucleophilic *hetero*aromatic *ortho*-radiofluorination with the activated K[^{18}F]F-Kryptofix®$_{222}$

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complex in DMSO using microwave activation at 250 W for 90 s, followed by (2) quantitative TFA-induced removal of the *N*-Boc protective group. The potential of [^{18}F]F_2PhEP ([^{18}F]-**1**) for *in vivo* imaging neuronal nicotinic acetylcholine receptors with PET is currently evaluated in non-human primates.

Experimental

General

Chemicals, flash chromatography and TLC analysis. Chemicals were purchased from Aldrich-, Fluka- or Sigma France and were used without further purification. Flash chromatographies were conducted on silica gel (0.63–0.200 mm, VWR) columns. TLCs were run on pre-coated plates of silica gel $60F_{254}$ (Merck). The compounds were localized (1) when possible at 254 nm using a UV-lamp and/or (2) by dipping the TLC-plates in a 1% ethanolic ninhydrin solution and heating on a hot plate. Radioactive spots were detected using a Berthold TraceMaster 20 automatic TLC linear analyser.

HPLC analysis. [HPLC A]: Equipment: system equipped with a Waters 600 Pump and Waters 600 Controller, a Shimadzu SPD10-AVP UV-multi-wavelength detector and a miniature ionization chamber probe; column: semipreparative, Symmetry® C18, Waters (300×7.8 mm); porosity: 7 µm; eluent aqueous 0.05 M NaH_2PO_4/CH_3CN: 78:22 (v/v); flow rate: 6 ml/min; temperature: RT; absorbance detection at $\lambda = 254$ nm. [HPLC B]: Equipment: Waters Alliance 2690 (or a Waters binary HPLC pump 1525) equipped with a UV spectrophotometer (Photodiode Array Detector, Waters 996) and a Berthold LB509 radioactivity detector; column: analytical Symmetry-M® C-18, Waters (50×4.6 mm); porosity: 3.5 µm; conditions: isocratic elution with solvA/solvB: 40/60 (v/v) [solvent A: H_2O containing Low-UV PIC® B7 reagent (composition (% by weight): methanol (18–22%), heptane sulfonic acid – sodium salts (4–6%), phosphate buffer solution (3–7%), water (65–75%), pH 3, Waters), 20 ml for 1000 ml; solvent B: H_2O/CH_3CN: 50:50 (v/v) containing Low-UV PIC® B7 reagent (20 ml for 1000 ml)]; flow rate: 2.0 ml/min; temperature: 30°C; UV detection at λ: 247 nm.

Spectroscopic analysis. NMR spectra were recorded on a Bruker AMX (300 MHz) or a Bruker Avance (400 MHz) apparatus, using the hydrogenated residue of the deuteriated solvents (CD_2Cl_2, $\delta = 5.32$ ppm; DMSO-d_6, $\delta = 2.50$ ppm) and/or TMS as internal standards for ^{1}H-NMR as well as the deuteriated solvents (CD_2Cl_2, $\delta = 53.8$ ppm; DMSO-d_6, $\delta = 39.5$ ppm) and/or TMS as internal standards for ^{13}C-NMR. The chemical shifts are reported in ppm, downfield from TMS (s, d, t, dd, b for singlet, doublet, triplet, doublet of doublet and broad, respectively). The mass spectra (MS), DCI/NH_4^+, were measured on a Quantum TCQ Discovery spectrometer.

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Radioisotope production. No-carrier-added aqueous [^{18}F]fluoride ion was produced *via* the [^{18}O(p,n)^{18}F] nuclear reaction by irradiation of a 2 ml [^{18}O]water (> 97%-enriched, CortecNet, Paris, France) target on a IBA Cyclone-18/9 cyclotron (18 MeV proton beam) and was transferred to the appropriate hot cell. *Target hardware*: commercial, 2-ml, two-port, stainless steel target holder equipped with a domed-end niobium cylinder insert. *Target to hot cell liquid-transfer system*: 60 m PTFE line (0.8 mm internal diameter; 1/16 inch external diameter), 2.0 bar He drive pressure, transfer time 3–6 min. Typical production of [^{18}F]Fluoride at the end of bombardment for a 20 μA, 30 min (10 μA h) irradiation: 750–800 mCi (27.7–29.6 GBq).

Miscellaneous. Radiosyntheses using fluorine-18, including the HPLC purifications, were performed in a 7.5-cm-lead shielded cell using a computer assisted Zymate robot system (Zymark corporation, USA). Microwave activation was performed with a MicroWell 10 oven (2.45 GHz), Labwell AB, Sweden.

Chemistry

7-tert-Butoxycarbonyl-2-exo-(2′-aminopyridin-5′-yl)-7-azabicyclo[2.2.1] heptane **(4)**. To a stirred solution of 7-*tert*-butoxycarbonyl-7-azabicyclo[2.2.1] hept-2-ene[26] (**2**, 3.0 g, 15.4 mmol, MW: 195.26), 2-amino-5-iodopyridine[26] (**3**, 6.76 g, 30.7 mmol, 2 equivalent, MW: 220.01), *n*-Bu_4NCl (1.07 g, 3.8 mmol, 0.25 equivalent, MW: 277.92), HCO_2K (2.58 g, 30.7 mmol, 2 equivalent, MW: 84.12) in CH_3CN (60 ml) under argon was added $Pd(OAc)_2$ (345 mg, 1.5 mmol, 0.1 equivalent, MW: 224.49). After stirring the mixture for 2 days at 100°C under argon, it was poured into aqueous 9% ammonia and extracted 3 times with EtOAc. The combined organic extracts were dried with $MgSO_4$ and concentrated. The residue was chromatographed on silica gel using CH_2Cl_2/MeOH, the latter containing 0.5% of 28% ammonia, (98/02 to 90/10) as eluent to provide **4** (3.1 g, 69%) as a brown solid. R_f: 0.3 (CH_2Cl_2/MeOH: 95/05, the latter containing 0.5% of 28% ammonia). ^{1}H NMR: (CD_2Cl_2, 298 K): δ: 7.84 (d, *J*: 2.4 Hz, 1H); 7.36 (dd, *J*: 8.5 and 2.4 Hz, 1H); 6.49 (d, *J*: 8.5 Hz, 1H); 4.68 (b, 2H); 4.28 (b s, 1H); 4.04 (b s, 1H); 2.78 (dd, *J*: 8.5 and 4.9 Hz, 1H); 1.88 (dd, *J*: 12.2 and 9.1 Hz, 1H); 1.75–1.49 (b, 5H); 1.40 (s, 9H). ^{13}C NMR: (CD_2Cl_2, 298 K): 157.7 [C]; 155.3 [C]; 146.2 [CH]; 136.5 [CH]; 130.8 [C]; 108.7 [CH]; 79.3 [C]; 62.5 [CH]; 56.3 [CH]; 45.0 [CH]; 40.2 [CH_2]; 29.7 [CH_2]; 28.7 [CH_2]; 28.2 [3 CH_3]. MS $C_{16}H_{23}N_3O_2$: 290 [M + H^+].

7-tert-Butoxycarbonyl-2-exo-(2′-amino-3′-bromopyridin-5′-yl)-7-azabicyclo [2.2.1] heptane **(5)**. To a stirred solution of **4** (155 mg, 0.54 mmol, MW: 289.37) in CH_2Cl_2 (2 ml) and AcOH (1.2 ml) at 0°C under argon was subsequently added bromine (41 μl, 0.8 mmol, 1.5 equivalent, d: 3.119, MW: 159.82) and NEt_3 (41 μl, d: 0.726, 0.3 mmol). After stirring for 16 h, the

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mixture was poured into aqueous 9% ammonia (30 ml) and extracted 3 times with $CHCl_3$. The combined organic extracts were dried with $MgSO_4$ and concentrated. The residue was chromatographed on silica gel using CH_2Cl_2/MeOH, the latter containing 0.5% of 28% ammonia, (98/02 to 90/10) as eluent to provide **5** (155 mg, 79%) as a brown oil. R_f: 0.5 (CH_2Cl_2/MeOH: 95/05, the latter containing 0.5% of 28% ammonia). ^{1}H NMR: (CD_2Cl_2, 298 K): δ: 7.85 (d, $J < 2.0$ Hz, 1H); 7.66 (d, $J < 2.0$ Hz, 1H); 4.76 (b, 2H); 4.30 (bs, 1H); 4.07 (bs, 1H); 2.75 (dd, J: 9.2 and 4.9 Hz, 1H); 1.92 (dd, J: 12.8 and 9.2 Hz, 1H); 1.82–1.48 (b, 5H); 1.42 (s, 9H). ^{13}C NMR: (CD_2Cl_2, 298 K): δ: 154.4 [C]; 145.5 [CH]; 139.4 [C]; 139.4 [CH]; 133.4 [C]; 104.8 [C]; 79.7 [C]; 62.5 [CH]; 56.5 [CH]; 44.8 [CH]; 40.5 [CH_2]; 30.0 [CH_2]; 29.0 [CH_2]; 28.4 [3 CH_3]. MS $C_{16}H_{22}BrN_3O_2$: 370 [M + H^+]; 368 [M + H^+].

7-tert-Butoxycarbonyl-2-exo-(2′-amino-3′-(4-fluorophenyl)pyridin-5′-yl)-7-azabicyclo[2.2.1] heptane **(6)**. To a stirred solution of **5** (1.28 g, 3.5 mmol, MW: 365.47) in water (2.6 ml) and DME (12.8 ml) were subsequently added $Pd(OAc)_2$ (79 mg, 0.35 mmol, 0.1 equivalent, MW: 224.49), P(*o*-tolyl)$_3$ (213 mg, 0.70 mmol, 0.2 equivalent, MW: 304.38), sodium carbonate (742 mg, 7.0 mmol, 2 equivalent, MW: 105.99) and 4-fluorophenylboronic acid (683 mg, 5.6 mmol, 1.6 equivalent, MW: 139.92). After stirring for 1.5 h under argon, the reaction mixture was poured into saturated aqueous $NaHCO_3$ and extracted 3 times with EtOAc. The combined organic extracts were dried with $MgSO_4$ and concentrated. The residue was chromatographed on silica gel using heptane/EtOAc (60/40 to 30/70) to provide **6** (1.21 g, 90%) as a brown solid. R_f: 0.2 (heptane/EtOAc: 50/50). ^{1}H NMR: (300 MHz – CD_2Cl_2, 298 K): δ: 7.89 (d, J: 2.4 Hz, 1H); 7.42 (bdd, J: 8.5 and 5.5 Hz, 2H); 7.31 (d, J: 2.4 Hz, 1H); 7.14 (bt, J: 8.5 Hz, 2H); 4.45 (b, 2H); 4.28 (bt, 1H); 4.10 (bd, 1H); 2.78 (dd, J: 9.2 and 4.9 Hz, 1H); 1.93 (dd, J: 12.2 and 8.5, 1H); 1.84-1.44 (b, 5H); 1.35 (s, 9H). ^{13}C NMR: (300 MHz – CD_2Cl_2, 298 K): δ: 162.7 [d, J: 247 Hz, C]; 155.1 [C]; 155.0 [C]; 146.1 [CH]; 137.0 [CH]; 134.9 [C]; 132.1 [C]; 130.9 [d, J: 10 Hz, 2 CH]; 120.9 [C]; 116.1 [d, J: 20 Hz, 2 CH]; 79.5 [C]; 62.6 [CH]; 56.3 [CH]; 45.3 [CH]; 40.5 [CH_2]; 30.0 [CH_2]; 29.1 [CH_2]; 28.4 [3 CH_3]. MS $C_{22}H_{26}FN_3O_2$: 384 [M + H^+].

7-tert-Butoxycarbonyl-2-exo-(2′-chloro-3′-(4-fluorophenyl)-pyridin-5′-yl)-7-azabicyclo[2.2.1] heptane **(7a)**. To a solution of **6** (130 mg, 0.34 mmol, MW: 383.46) in concentrated aqueous HCl (2 ml) at 0°C was added sodium nitrite (469 mg, 6.8 mmol, 20 equivalent, MW: 69.00) in water (1 ml). After 10 min, copper(I) chloride (471 mg, 4.76 mmol, 14 equivalent, MW: 98.99) in concentrated aqueous HCl (1 ml) was added. After 30 min, at 0°C, the mixture was poured into aqueous 14% ammonia and extracted 3 times with EtOAc. The combined organic layers were dried with $MgSO_4$ and

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concentrated. The residue was treated with di-*tert*-butyldicarbonate (89 mg, 0.41 mmol, 1.2 equivalent, MW: 218.25) and NEt_3 (57 µl, 0.41 mmol, 1.2 equivalent, d: 0.726, MW: 101.19) in THF (2 ml). After 5 h, the solvent was evaporated and the oily residue was chromatographed on silica gel using heptane/EtOAc (90/10 to 80/20) as eluent to provide **7a** (53 mg, 39%) as a pale-white oil. R_f: 0.6 (heptane/EtOAc: 50/50). ^{1}H NMR: (300 MHz – CD_2Cl_2, 298 K): δ: 8.25 (d, *J*: 2.4 Hz, 1H); 7.65 (d, *J*: 2.4 Hz, 1H); 7.44 (bdd, *J*: 8.5 and 4.9 Hz, 2H); 7.15 (bt, *J*: 8.5 Hz, 2H); 4.34 (bt, 1H); 4.20 (bd, *J*: 3.7 Hz, 1H); 2.93 (dd, *J*: 8.5 and 4.9 Hz, 1H); 2.02 (dd, *J*: 12.2 and 9.1 Hz, 1H); 1.89–1.48 (b, 5H); 1.37 (s, 9H). ^{13}C NMR: (300 MHz – CD_2Cl_2, 298 K): δ: 163.1 [d, *J*: 249 Hz, C]; 155.1 [C]; 147.8 [CH]; 147.6 [C]; 141.2 [C]; 138.6 [CH], 135.7 [C], 134.2 [d, *J*: 5 Hz, C]; 131.6 [d, *J*: 10 Hz, 2 CH]; 115.5 [d, *J*: 22 Hz, 2 CH]; 79.8 [C]; 62.3 [CH]; 56.3 [CH]; 45.2 [CH]; 40.6 [CH_2]; 30.0 [CH_2]; 29.1 [CH_2]; 28.3 [3 CH_3]. MS $C_{22}H_{24}ClFN_2O_2$: 405 [M + H^+]; 403 [M + H^+].

7-tert-Butoxycarbonyl-2-exo-(2′-bromo-3′-(4-fluorophenyl)-pyridin-5′-yl)-7-azabicyclo [2.2.1]heptane **(7b)**. To a solution of **6** (95 mg, 0.25 mmol, MW: 383.46) in concentrated aqueous HBr (2 ml) at 0°C was added sodium nitrite (342 mg, 4.95 mmol, 20 equivalent, MW: 69.00) in water (1 ml). After 10 min, copper(I) bromide (343 mg, 3.47 mmol, 14 equivalent, MW: 98.99) in concentrated aqueous HBr (1 ml) was added. After 30 min, at 0°C, the mixture was poured into aqueous 14% ammonia and extracted 3 times with EtOAc. The combined organic layers were dried with $MgSO_4$ and concentrated. The residue was treated with di-*tert*-butyldicarbonate (65 mg, 0.3 mmol, 1.2 equivalent, MW: 218.25) and NEt_3 (42 µl, 0.3 mmol, 1.2 equivalent, d: 0.726, MW: 101.19) in THF (2 ml). After 5 h, the solvent was evaporated and the oily residue was chromatographed on silica gel using heptane/EtOAc (90/10 to 80/20) as eluent to provide **7b** (18 mg, 16%) as a yellow oil. R_f: 0.6 (heptane/EtOAc: 50/50). ^{1}H NMR: (300 MHz – CD_2Cl_2, 298 K): δ: 8.23 (d, *J*: 1.8 Hz, 1 H); 7.59 (d, *J*: 2.4 Hz, 1 H); 7.41 (btd, *J*: 8.5 and 5.5 Hz, 2 H); 7.14 (bt, *J*: 9.2 Hz, 2 H); 4.33 (b, 1 H); 4.19 (bs, 1 H); 2.91 (dd, *J*: 8.5 and 4.3 Hz, 1 H); 2.02 (dd, *J*: 12.2 and 9.2 Hz, 1 H); 1.88–1.48 (b, 5 H); 1.36 (s, 9 H). ^{13}C NMR: (300 MHz – CD_2Cl_2, 298 K): δ: 163.1 [d, *J*: 248 Hz, C]; 155.1 [C]; 148.3 [CH]; 141.5 [C]; 140.0 [C]; 138.5 [C], 138.2 [CH], 135.7 [d, *J*: 3 Hz, C]; 131.6 [d, *J*: 8 Hz, 2 CH]; 115.5 [d, *J*: 22 Hz, 2 CH]; 79.9 [C]; 62.3 [CH]; 56.3 [CH]; 45.2 [CH]; 40.6 [CH_2]; 30.1 [CH_2]; 29.1 [CH_2]; 28.3 [3 CH_3]. MS $C_{22}H_{24}BrFN_2O_2$: 449 [M + H^+]; 447 [M + H^+].

7-tert-Butoxycarbonyl-2-exo-(2′-fluoro-3′-(4-fluorophenyl)-pyridin-5′-yl)-7-azabicyclo[2.2.1] heptane **(7c)**. A solution of **6** (465 mg, 1.21 mmol, MW: 383.46) in concentrated 70% hydrofluoric acid/pyridine (3.0 ml) was prepared. Sodium nitrite (335 mg, 4.85 mmol, 4 equivalent, MW: 69.00) in water (1 ml)

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was added at 0°C and the reaction mixture was stirred for 45 min at room temperature followed by heating at 100°C for 1 h. The mixture was filtered and the filtrate was poured into 50 ml of 14% aqueous ammonia and extracted 3 times with EtOAc. The combined organic layers were dried with $MgSO_4$ and concentrated. The residue was treated with di-*tert*-butyldicarbonate (318 mg, 1.46 mmol, 1.2 equivalent, MW: 218.25) and NEt_3 (0.2 ml, 1.46 mmol, 1.2 equivalent, d: 0.726, MW: 101.19) in THF (5 ml). After 5 h, the solvent was evaporated and the oily residue was chromatographed on silica gel using heptane/EtOAc (80/20 to 60/40) as eluent to provide **7c** (130 mg, 28%) as a yellow oil. R_f: 0.7 (heptane/EtOAc: 50/50). ^{1}H NMR: (300 MHz – CD_2Cl_2, 298 K): δ: 8.02 (bt, 1H); 7.85 (dd, *J*: 9.8 and 2.4 Hz, 1H); 7.55 (bt, *J*: 7.3 Hz, 2H); 7.16 (bt, *J*: 8.5 Hz, 2H); 4.35 (bt, 1H); 4.20 (bs, 1H); 2.95 (dd, *J*: 8.5 and 4.3 Hz, 1H); 2.03 (dd, *J*: 12.2 and 9.2 Hz, 1H); 1.88–1.49 (b, 5H); 1.40 (s, 3H). ^{13}C NMR: (400 MHz – CD_2Cl_2, 298 K): δ: 163.2 [d, *J*: 248 Hz, C]; 159.4 [d, *J*: 237 Hz, C]; 155.2 [C]; 145.2 [d, *J*: 15 Hz, CH]; 140.6 [d, *J*: 5 Hz, C]; 139.6 [d, *J*: 4 Hz, C], 131.0 [dd, *J*: 8 and 4 Hz, 2 CH]; 130.8 [dd, *J*: 5 and 3 Hz, C]; 122.5 [d, *J*: 29 Hz, C]; 115.9 [d, *J*: 21 Hz, 2 CH]; 79.8 [C]; 62.5 [CH]; 56.4 [CH]; 45.1 [CH]; 40.9 [CH_2]; 30.0 [CH_2]; 29.1 [CH_2]; 28.4 [CH_3]. MS $C_{22}H_{24}N_2F_2O_2$: 387 [M + H^+].

2-exo-(2′-Fluoro-3′-(4-fluorophenyl)-pyridin-5′-yl)-7-azabicyclo[2.2.1]heptane (1, F_2PhEP). A solution of **7c** (130 mg, 0.34 mmol, MW: 386.44) in CH_2Cl_2 (5 ml) was treated with TFA (1 ml). After 5 h at room temperature, the mixture was poured into 14% aqueous ammonia and extracted 3 times with CH_2Cl_2. The combined organic layers were dried with $MgSO_4$ and concentrated giving **1** (92 mg, 96%) as a yellow oil. R_f: 0.3 (CH_2Cl_2/MeOH: 95/05 the latter containing 0.5% of 28% ammonia). R_t (HPLC A): 14.0 min. R_t (HPLC B): 1.55 min. ^{1}H NMR: (300 MHz – CD_2Cl_2, 298 K): δ: 8.06 (bt, 1H); 8.01 (dd, *J*: 9.8 and 2.4 Hz, 1H); 7.55 (bt, *J*: 5.5 Hz, 2H); 7.15 (bt, *J*: 9.1 Hz, 2H); 3.74 (bt, 1H); 3.53 (bs, 1H); 2.79 (dd, *J*: 8.5 and 4.3 Hz, 1H); 1.89 (dd, *J*: 12.2 and 9.2 Hz, 1H); 1.83–1.59 (b, 5H). ^{13}C NMR: (300 MHz – CD_2Cl_2, 298 K): δ: 163.0 [d, *J*: 247 Hz, C]; 159.1 [d, *J*: 234 Hz, C]; 145.3 [d, *J*: 15 Hz, CH]; 141.6 [d, *J*: 5 Hz, C]; 140.2 [CH], 131.0 [d, *J*: 7 Hz, 2 CH]; 130.9 [C]; 122.2 [d, *J*: 29 Hz, C]; 115.9 [d, *J*: 22 Hz, 2 CH]; 63.4 [CH]; 56.8 [CH]; 44.8 [CH]; 41.0 [CH_2]; 31.8 [CH_2]; 30.7 [CH_2]. MS $C_{17}H_{16}N_2F_2$: 287 [M + H^+].

Radiochemistry

K[^{18}F]F-K_{222}-complex. In order to recover and recycle the [^{18}O]water target, the 2 ml of aqueous [^{18}F]fluoride from the target holder were passed through an anion exchange resin (Sep-pak® Light Waters Accell™ Plus QMA cartridge (initially in the chloride form, then washed with aqueous 1 M $NaHCO_3$ (2 ml) and rinsed with water (20 ml) and CH_3CN (10 ml)) by helium

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pressure (1.5–2.0 bar). Helium was blown through the column to maximally extract the last traces of [^{18}O]water. See Dolci *et al.*[26] for more practical details. The [^{18}F]fluoride ion was then eluted from the resin, using 1.0 ml of a 4.5 mg/ml aqueous K_2CO_3 solution, into a Vacutainer® tube containing 12.0–15.0 mg of Kryptofix®222 (K_{222}: 4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo[8.8.8]hexacosane). The resulting solution was then gently concentrated to dryness at 145–150°C under a nitrogen stream for 10 min to give no-carrier-added K[^{18}F]F-K_{222} complex as a white semi-solid residue. If desired, the [^{18}F]fluoride ion production batch on the cartridge may also be divided into 2 to 12 aliquots in order to perform parallel syntheses. To do this, the [^{18}F]fluoride ion is eluted from the resin, using 1.0 ml of a 4.5 mg/ml aqueous K_2CO_3 solution, into an empty Vacutainer® tube. In order to distribute equally this activity over *n* tubes (Vacutainer® tube, $n = 2$–12), the quantity of K_2CO_3 was firstly adjusted to *n* times 4.5 mg with a 50.0 mg/ml aqueous K_2CO_3 solution and secondly, the total volume of the solution was adjusted to 2.0 ml with water. This new aqueous [^{18}F]fluoride solution was then equally distributed over the *n* tubes each containing 12.0–15.0 mg of Kryptofix®222. Finally, the volume of each fraction was adjusted to 1.0 ml with water. The resulting solutions were then independently gently concentrated to dryness at 160–165°C under a nitrogen stream for 10 min to give no-carrier-added K[^{18}F]F-K_{222} complex as a white semi-solid residue.

2-exo-(2′-[^{18}F]Fluoro-3′-(4-fluorophenyl)-pyridin-5′-yl)-7-azabicyclo[2.2.1] heptane ([^{18}F]-1, [^{18}F]F_2PhEP). (A) Procedure (optimized conditions) using 7-tert-butoxycarbonyl-2-exo-(2′-chloro-3′-(4-fluorophenyl)-pyridin-5′-yl)-7-azabicyclo[2.2.1] heptane (7a) as precursor for labelling: DMSO (600 µl) containing 1.0 mg of the chloro derivative **7a** (2.48 µmol) as precursor for labelling were directly added into the Vacutainer® tube containing the dried K[^{18}F]F-K_{222} complex. The tube (not sealed) was thoroughly vortexed (15 s) and then placed in a dedicated microwave oven (at 250 W, for 1.5 min) without stirring the contents. The reaction vessel was then cooled using an ice-water bath and the remaining radioactivity was measured (93–97% of the radioactivity initially added to the vessel was still present). The resulting, frequently dark-coloured reaction mixture was then analysed by radio-TLC. The reaction yield was calculated from the TLC-radiochromatogram and defined as the ratio of radioactivity area of [^{18}F]-**7c** over total fluorine-18 radioactivity area (SiO_2-TLC: eluent: EtOAc/heptane: 50/50, R_f: [^{18}F] –**7c**: 0.7 and R_f: [^{18}F]fluoride ion: 0.0). The above reaction mixture was diluted with 1 ml of water and transferred onto a C18 Sep-pak® cartridge (PrepSep™ R-C18, Fisher Scientific, which had been pre-activated with 2 ml of EtOH and then rinsed with 10 ml of water). The tube was rinsed twice with 1 ml of water, which was also transferred and added to the diluted reaction mixture on the

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cartridge (2–3% of the total radioactivity amount engaged in the fluorination process was lost in the reaction tube). The whole was then passed through the cartridge, which was then washed with 3 ml of water and partially dried for 0.5 min by applying a nitrogen stream. The 2-[^{18}F]fluoropyridine [^{18}F]-**7c** was eluted from the cartridge with 3 ml of CH_2Cl_2 into a 5 ml reaction vial containing 0.1 ml of TFA. Two 1 ml aliquots of CH_2Cl_2 were used to wash the cartridge for maximal transfer of [^{18}F]-**7c** (10–15% of the total radioactivity amount engaged in the fluorination process was left on the cartridge). The incorporation yield was also estimated after the C18 Sep-pak cartridge elution by the CH_2Cl_2 – over total eluted radioactivity (DMSO/H_2O + CH_2Cl_2) ratio. The resulting CH_2Cl_2/TFA solution (50/1, v/v) was concentrated to dryness (at 65–75°C under a gentle nitrogen stream for 4–6 min). The reaction yield (*N*-Boc deprotection) was calculated from the TLC-radiochromatogram (SiO_2-TLC, (A) eluent: EtOAc/heptane: 50/50, R_f: [^{18}F] –**7c**: 0.7 and R_f: [^{18}F]-**1**: 0.0; (B) eluent: CH_2Cl_2/MeOH: 95/05, the latter containing 0.5% of aqueous 28% ammonia, R_f: [^{18}F] –**7c**: 0.95 and R_f: [^{18}F]-**1**: 0.3). The residue was re-dissolved in 2 ml of CH_2Cl_2 and concentrated again to dryness to minimize TFA presence (at 65–75°C under a gentle nitrogen stream for 2–3 min). Finally, the above residue was re-dissolved in 1.0 ml of the HPLC solvent used for purification and the crude was injected onto HPLC (HPLC A). Isocratic elution gave pure [^{18}F]-**1** ([^{18}F]F_2PhEP) (R_t: 14.0 min), separated from the unlabelled *N*-Boc-deprotected precursor for labelling (ClFPhEP: R_t: 16.5 min).

(B) Procedure (optimized conditions) using 7-tert-butoxycarbonyl-2-exo-(2′-bromo-3′-(4-fluorophenyl)-pyridin-5′-yl)-7-azabicyclo[2.2.1] heptane (7b) as precursor for labelling: DMSO (600 µl) containing 1.0 mg of the bromo derivative **7b** (2.23 µmol) as precursor for labelling were directly added into the Vacutainer® tube containing the dried K[^{18}F]F-K_{222} complex. The tube (not sealed) was thoroughly vortexed (15 s) and then placed in a dedicated microwave oven (at 250 W, for 1.5 min) without stirring the contents. The remainder of the synthesis used the same procedure as described above. HPLC purification (HPLC A) gave pure [^{18}F]-**1** ([^{18}F]F_2PhEP) (R_t: 14.0 min), well separated from the unlabelled *N*-Boc-deprotected precursor for labelling (BrFPhEP: R_t: 17.8 min).

(C) Formulation of [^{18}F]F_2PhEP ([^{18}F]-1): Formulation of the labelled product for *i.v.* injection was effected as follows: The HPLC-collected fraction containing the radiotracer was diluted with water (50 ml). The resulting solution was passed through a Sep-pak®Plus C18 cartridge (Waters, washed with 2 ml of EtOH and then rinsed with 10 ml of water prior to use). The cartridge was washed with 10 ml of water and partially dried by applying a nitrogen stream for 10 s. The radiotracer was eluted with 2 ml of EtOH (less than 10% of the total radioactivity was left on the cartridge) followed by 8 ml

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of physiological saline and filtered on a 0.22 μm GS-Millipore filter (vented). Finally, physiological saline was added to lower the EtOH concentration below 10%. This whole process was performed using a remote-controlled dedicated home-made device based on a literature procedure.[46]

(D) Quality control of [^{18}F]F_2PhEP ([^{18}F]-1): The radiotracer preparation was visually inspected for clarity, absence of colour and particulates. An aliquot of the preparation was removed for determination of pH using standard pH-paper. Chemical and radiochemical purities were also assessed on this aliquot by HPLC (HPLC B), with a sample of authentic **1** (F_2PhEP) (R_t: 1.55 min). Particular attention was paid to the absence of non-radioactive (*N*-Boc-deprotected)-precursors (ClFPhEP: R_t: 1.72 min or BrFPhEP: R_t: 1.89 min). Chemical and radiochemical stability of the entire preparation was tested by HPLC (HPLC B) at regular 15-min intervals during 120 min. Specific radioactivity of the radiotracer was calculated from three consecutive HPLC analyses (average) and determined as follows: The area of the UV absorbance peak corresponding to the radiolabelled product was measured (integrated) on the HPLC chromatogram and compared to a standard curve relating mass to UV absorbance. Administration to animals was performed within 30 min following the end of the synthesis.

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