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Carbon-14 radiosynthesis of the benzofuran derivative and β-amyloid plaque neuroimaging positron emission tomography radioligand AZD4694

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In support of a metabolite study, the β-amyloid plaque neuroimaging positron-emission tomography radioligand AZD4694 was labeled with carbon-14 in 10 radiosynthetic steps starting from radiolabeled carbon dioxide. [^{14}C]AZD4694 was labeled in the benzofuran heterocycle with a specific activity of 2.1 GBq/mmol and with a radiochemical purity of >99%. The described synthesis constitutes a general method to carbon-14-labeled substituted benzofurans.

Keywords: AZD4694; benzofuran; BOC t-butyloxycarbonyl; PET radioligand; amyloid

Introduction

Alzheimer's disease (AD) was identified more than a century ago on the basis of histopathologic observations. The diagnosis of AD, however, is a clinical challenge, and a definite diagnosis can still only be made post-mortem. Positron emission tomography (PET) neuroimaging of Aβ plaques with radioligands such as the thioflavin derivatives [^{11}C]Pittsburgh compound B and [^{18}F]flutemetamol and the stilbene derivatives [^{18}F]florbetaben (18F-BAY94-9172) and [^{18}F]florbetapir (18F-AV-45) is a promising tool that might support and increase specificity when diagnosing preclinical AD.[1–4] PET neuroimaging of cerebral Aβ plaques might also be useful for the evaluation of new therapies aiming to modify plaque load and for patient stratification in clinical trials.[7,8]

[^{18}F]AZD4694 (2-(2-^{18}F-fluoro-6-(methylamino)-3-pyridyl)benzofuran-5-ol), a pyridinyl benzofuran, is a recently developed second-generation β-amyloid PET ligand.[7] Because of the longer-lived fluorine-18 radioisotope used for labeling, the radioligand has potential for wider clinical application than C-11-labeled agents. Clinical studies suggest that it reaches equilibrium quickly, permitting scans following a relatively short radiotracer uptake period, and is associated with relatively high specific to nonspecific white matter binding, permitting amyloid imaging with high sensitivity.[8] It has been shown *ex vivo* that after intravenous administration in aged Tg2576 transgenic mice, the trititiated isotopologue [^{3}H]AZD4694 binds to β-amyloid deposits in a reversible manner.[7] In brain tissue taken from humans diagnosed with AD, [^{3}H]AZD4694 selectively labeled β-amyloid deposits in the gray matter and showed a low level of nondisplaceable binding in plaque-devoid white matter. Because of its demonstrated excellent *in vitro* imaging properties, [^{3}H]AZD4694 is a valuable *in vitro* β-amyloid imaging tool, which creates the possibility of using [^{3}H]AZD4694 in preclinical translational bridging studies to validate clinical [^{18}F]AZD4694 PET imaging protocols. The synthesis of [^{3}H]AZD4694 and [^{18}F]AZD4694 has been described previously.[9]

A prerequisite for a PET radioligand suitable for sensitive imaging of Aβ plaques in a patient with AD is no or at least very low amount of radioactive metabolites passing the blood–brain barrier. Radioactive metabolites that enter the brain may obscure brain PET measurements by adding to both specific and nonspecific binding. Identification of radiolabeled metabolites is an essential part of the validation of a PET radioligand intended for use as an imaging biomarker or diagnostic. For this purpose, AZD4694 was required in its carbon-14-labeled form.

Results and discussion

In this paper, the radiosynthesis of [^{14}C]AZD4694 is reported. [^{14}C]AZD4694 was labeled in the benzofuran heterocycle of the molecule because this label placement should, when incubated with liver hepatocytes and microsomes, generate a similar profile of radiolabeled metabolites as to what can be expected from [^{18}F]AZD4694 *in vivo*. A putative metabolic pathway among fluorine-18-labeled PET radioligands is *in vivo* defluorination resulting in free fluorine-18 in the blood. Identification of radiolabeled defluorinated metabolites of [^{14}C]AZD4694 would suggest this as a potential metabolic pathway. *In vivo* high uptake of radioactivity in the skull is indicative of this metabolic pathway. In the clinical PET studies reported with [^{18}F]AZD4694, the uptake of radioactivity in the skull has been insignificant, indicating that defluorination is a nonsignificant metabolic pathway.[8]

A two-step synthesis to substituted carbon-14-labeled [C3-^{14}C]benzofuranone from the corresponding [*carbonyl*-^{14}C]2-methoxybenzoic

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acid has been previously described by Wadsworth *et al.*[10] However, this synthesis utilizes diazomethane in the ring closure step, and it was desirable to find a route past this hazardous and potentially explosive reagent. Instead, a labeling route to [^{14}C]AZD4694 based on a benzofuranone synthesis described by Carvalho *et al*. was developed, which, as well as the method by Wadsworth *et al*., opens up the possibility to use carbon dioxide as labeled precursor.[11]

The synthesis of [^{14}C]AZD4694 was accomplished as shown in Scheme 1. The described synthesis constitutes a diazomethane-free alternative to the method developed by Wadsworth *et al*. and is a general method for the synthesis of carbon-14-labeled benzofurans.

The methoxymethyl-protected phenol starting material **2** was synthesized from the corresponding substituted bromo phenol **1** by alkylation with bromomethyl methyl ether. Lithiation of **2** with *n*-BuLi at −78 °C and condensation with $^{14}CO_2$ afforded the specifically carbon-14-labeled acid **3**. Esterification and deprotection of **3** with ethanol in the presence of sulfuric acid gave the ethyl salicylate **4**.[12] Treatment of **4** with ethyl bromoacetate generated **5**[13], which was hydrolyzed in basic media to produce the diacid **6**.[12] Ring closure of **6** in refluxing AcOH/Ac_2O in the presence of sodium acetate afforded compound **7**, which was directly hydrolyzed in acidic media to the required 3(2*H*)-benzofuranone **8**.[11] Reduction of 3(2*H*)-benzofuranone **8** with sodium borohydride and subsequent dehydration with HCl afforded **9** as a solid.[14] The 5-methoxybenzofuran **9** was lithiated with *n*-BuLi at −78 °C, before treatment with triisopropylborate to yield the boronic acid **10**. BOC-protected 2-methylamino-5-bromopyridine **16** was synthesized in three steps in high yield from the commercially available 2-amino-5-fluoropyridine **13**. Compound **10** was reacted with **16** under Suzuki reaction conditions to afford the 2-pyridylbenzofuran **11**. This step also removed the BOC-group of the substituted pyridine. Subsequent demethylation of **11** with boron tribromide yielded [^{14}C]AZD4694. The demethylation needed strict temperature control to avoid substitution of the fluorine by bromine. The final product was purified on reversed-phase HPLC to give >99% radiochemical-purity and UV-purity with a specific activity of 2.1 GBq/mmol.

The total radiochemical yield calculated from $^{14}CO_2$ was 5% over 10 radiochemical steps. [^{14}C]AZD4694 was stored at −18 °C as a solid. No signs of decomposition were observed after 10 months under these storage conditions.

Conclusion

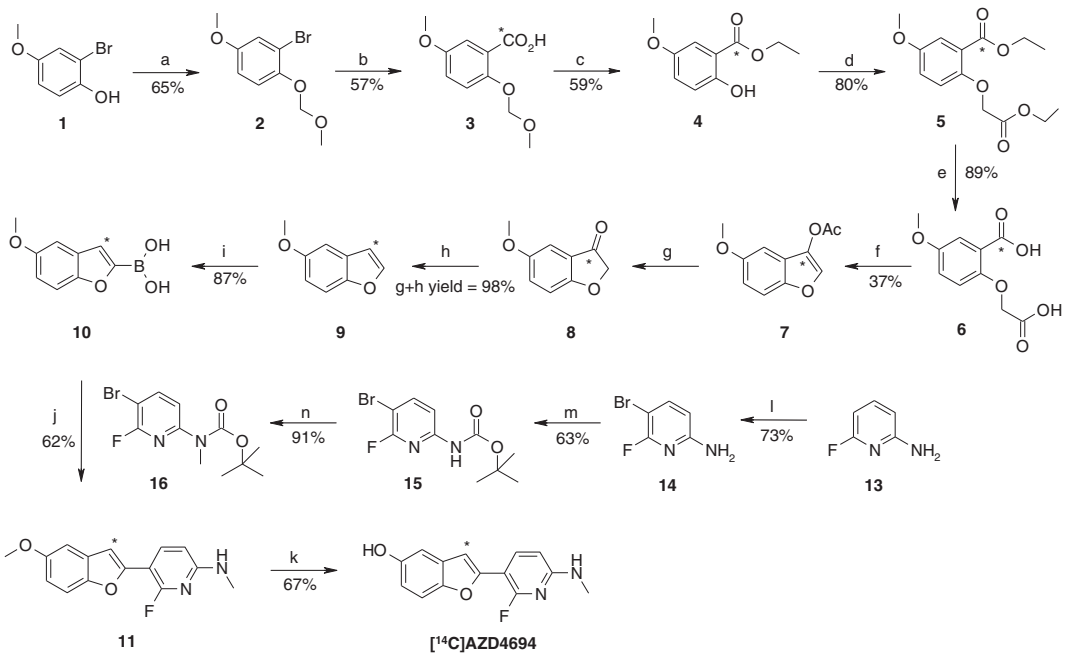
Carbon-14-labeled AZD4694 was synthesized with a total yield of 5% over 10 steps starting from [^{14}C]CO_2 to afford the product with a specific activity of 2.1 GBq/mmol and with a radiochemical purity of >99%. The described synthesis constitutes a general method to carbon-14-labeled benzofurans.

Experimental

General

All solvents used were of analytical grade and commercially available. Anhydrous solvents were routinely used for reactions. Reactions were typically run under an inert atmosphere of nitrogen or argon. The microwave reaction was performed in a Biotage Initiator Eight (Biotage AB, Uppsala, Sweden). $^{14}CO_2$ was handled in a $^{14}CO_2$ manifold system from RC TRITEC AG, Teufen, Switzerland. Flash column chromatography was performed using RediSep(R) (Teledyne Isco, Lincoln, Nebraska, USA) silica gel columns. The identities of appropriate-labeled intermediates as well as the final product were established by co-elution via HPLC or TLC with authentic nonlabeled material.

High-performance liquid chromatography radiochemical purity analyses were performed on an Agilent 1100, HPLC-system with a binary pump, an auto-injector, a diodide array detector (Agilent Technologies, Kista, Sweden), and a column oven, coupled in series with a Packard



Scheme 1. Synthesis of [^{14}C]AZD4694. Reagents: (a) bromomethyl methyl ether, NaH, DMF, room temperature, 1 h; (b) $^{14}CO_2$, BuLi, THF, −78 °C to room temperature, 1 h; (c) EtOH, H_2SO_4, reflux, 2 days; (d) NaI, K_2CO_3, ethyl bromoacetate, DMF, room temperature, 2 days; (e) NaOH, MeOH, THF, reflux, 2 days; (f) NaOAc, HOAc, Ac_2O, reflux, 4 h; (g) HCl, MeOH, H_2O, 75 °C, 1.5 h; (h) *i*. $NaBH_4$, EtOH, room temperature, 2 h; *ii*. HCl, room temperature, 1 h; (i) BuLi, THF, triisopropylborate, −78 °C, 1 h; (j) $Pd(PPh_3)_2Cl_2$, aqueous Na_2CO_3, EtOH, microwave 110 °C, 1 h (k) BBr_3, CH_2Cl_2, 0 °C, 18 h; (l) N-bromo succinimide, MeCN, room temperature, 1 h; (m) sodium bis(trimethylsilyl)amide, di-*tert*-butyl dicarbonate, THF, room temperature, overnight; (n) MeI, NaH, DMF, room temperature, 45 min. * denotes position of carbon-14 label.

Radiomatic Flow Scintillator 525TR (Chemical Instruments AB, Lidingö, Sweden), equipped with a solid scintillator (SolarScint) cell with a volume of 32 μL. The column used was a Zorbax SB-C18 (2.1 × 100 mm, 3.5 μm) (Agilent Technologies Sweden, Kista, Sweden). The column temperature was set to 40 °C and the flow rate to 0.5 mL/min. A linear gradient was applied, starting at 100% A (A: 10 mM NH_4OAc in 5% MeCN) and ending at 95% B (B: MeCN), in 13.5 min.

Mass spectra were recorded on a Waters LC/MS (Waters Sverige AB, Sollentuna, Sweden) consisting of an Alliance 2795 (LC), a Waters PDA 2996, and a ZMD single quadrupole mass spectrometer. The mass spectrometer was equipped with an electrospray ion source operated in a positive or negative ion mode. The capillary voltage was 3 kV, and the cone voltage was 30 V. The mass spectrometer was scanned between *m/z* 100–600 with a scan time of 0.7 s. The column temperature was set to 40 °C. The diode array detector was scanned from 200 to 400 nm.

^{1}H NMR spectra were recorded on a Bruker DRX-600, a Bruker DPX-400, or a Bruker AVANCE III 500 spectrometer and were referenced to residual solvent peak (Bruker BioSpin Scandinavia AB, Solna, Sweden).

Preparative HPLC of [^{14}C]AZD4694 was performed on an LC system consisting of a Gilson 131 XL sample injector, Gilson prepFC fraction collector, a Gilson 322 dual head pump, a Gilson UV/VIS 151 diode array detector set at 254 nm, a Kromasil C8 column 250 × 20 mm, 5 μm (Dr. Maisch HPLC GmbH, Germany), and an isocratic elution at 70%MeOH in 50 mM NH_4OAc at a flow rate of 10 mL/min.

2-Bromo-4-methoxy-1-(methoxymethoxy)benzene (2)

A solution of 2-bromo-4-methoxyphenol (**1**) (2.2 g, 10.8 mmol) in dimethylformamide (DMF, 11 mL) was stirred and cooled at 0 °C as NaH (0.52 g, 13 mmol) was added in one portion. After stirring at room temperature for 20 min, bromomethyl methyl ether (2.0 mL, 22 mmol) was added in one portion. The reaction was stirred at room temperature for 1 h. Water (40 mL) was added, and the mixture was extracted with EtOAc (3 × 40 mL). Flash chromatography (25 g silica, heptane:CH_2Cl_2 gradient) afforded the product as an oil (2.68 g, 65% yield).

^{1}H NMR (500 MHz, DMSO-d_6) δ: 7.13–7.18 (m, 2H) 6.91 (dd, *J* = 9.14, 3.15 Hz, 1H) 5.17 (s, 2H) 3.72 (s, 3H) 3.40 (s, 3H).

5-Bromo-6-fluoro-pyridin-2-amine (14)

To a stirred solution of 2-amino-5-fluoropyridine (5.37 g, 47.9 mmol) in MeCN (250 mL) at 0 °C under nitrogen was added with N-bromosuccinimide (9.3 g, 52.4 mmol), and the reaction was stirred at room temperature for 1 h. The solvent was evaporated, and the residue was redissolved in EtOAc and water. The separated organic phase was washed with water and brine. After drying with Na_2SO_4, filtration and evaporation of the residue was recrystallized from heptane/EtOAc (6.7 g, 73% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.60 (t, *J* = 8.51 Hz, 1H) 6.26 (dd, *J* = 8.35, 1.42 Hz, 1H) 3.81–4.94 (m, 2H).

t-Butyl 5-bromo-6-fluoropyridin-2-ylcarbamate (15)

To a solution of 5-bromo-6-fluoropyridin-2-amine (**14**) (4.1 g, 21.5 mmol) in THF (60 mL) was slowly added a solution of 1 M sodium bis(trimethylsilyl)amide in THF (34.3 mL, 34.3 mmol) at 0 °C. A solution of di-*tert*-butyl dicarbonate (4.9 mL, 21.5 mmol) in THF (40 mL) was added slowly to the reaction at 0 °C. The reaction was then warmed to room temperature and stirred over night. Saturated aqueous NH_4Cl (20 mL) was added, and the mixture was extracted with ethyl acetate (2 × 40 mL). The combined organic layers were dried with Na_2SO_4, filtered, and evaporated. The residue was purified by flash chromatography (silica, 7.5% ethyl acetate in heptane) to afford the product as a solid (3.9 g, 63% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.75 (dd, *J* = 8.59, 1.26 Hz, 1H) 7.87 (t, *J* = 8.59 Hz, 1H) 7.37 (br. s., 1H) 1.52 (s, 9H).

t-Butyl *N*-(5-bromo-6-fluoro-2-pyridyl)-*N*-methyl-carbamate (16)

To a solution of *t*-butyl 5-bromo-6-fluoropyridin-2-ylcarbamate (**15**) (2.0 g, 6.9 mmol) in DMF (30 mL) was added NaH (0.38 g, 9.6 mmol) at 0 °C. The solution was stirred for 10 min at 0 °C after which MeI (0.55 mL, 8.9 mmol) was added. After stirring for 45 min at room temperature, aqueous saturated NH_4Cl (30 mL) was added, and the resulting mixture was extracted with EtOAc (3 × 40 mL). The combined organic layers were washed with brine, dried with Na_2SO_4, filtered, and evaporated. The residue was purified by flash chromatography (silica, with 5% EtOAc in heptane as eluent) to afford the product as a solid (1.90 g, 91% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.83 (t, *J* = 8.84 Hz, 1H) 7.69 (dd, *J* = 8.46, 1.39 Hz, 1H) 3.37 (s, 3H) 1.54 (s, 9H).

[COOH-^{14}C]5-Methoxy-2-(methoxymethoxy)benzoic acid (3)

A solution of 2-bromo-4-methoxy-1-(methoxymethoxy)benzene (**2**) (690 mg, 2.8 mmol) in THF (6 mL) was cooled and stirred under nitrogen at −78 °C. BuLi (1.6 M in hexanes, 1.9 mL, 3.1 mmol) was added dropwise, and the mixture was stirred for an additional 1 h at −78 °C. The reaction mixture was transferred to a $^{14}CO_2$ manifold and evacuated at −78 °C. $^{14}CO_2$ (0.145 g, 3.16 mmol, 7 GBq) was charged to the reaction at −78 °C, and after warming to room temperature, the reaction mixture was stirred for 1 h. The mixture was then washed with EtOAc (5 mL), and concentrated HCl was added until precipitation (pH approximately = 3) of a solid. The slurry was extracted with ethyl acetate (3 × 10mL), and the combined organic layers were dried with Na_2SO_4, filtered, and evaporated. The residue (oil) was used in the next step without further purification (344 mg, 58% yield).

[Carboxy-^{14}C]ethyl 2-hydroxy-5-methoxy-benzoate (4)

A solution of [^{14}C]5-methoxy-2-(methoxymethoxy)benzoic acid **3** (402 mg, 1,88 mmol) and H_2SO_4 (95%, 100 μL, 1.9 mmol) in EtOH (8 mL) was heated at reflux for 2 days. The solution was neutralized with saturated $NaHCO_3$. Water was added, and the reaction was extracted with EtOAc (5 × 10 mL). After drying the combined organic layers with Na_2SO_4, the solution was filtrated and evaporated to afford a residue that was subjected to flash chromatography (12 g silica, heptane:CH_2Cl_2, 3:7) to afford **4** as an oil (221 mg, 59% yield).

[Carboxy-^{14}C]ethyl 2-(2-ethoxy-2-oxo-ethoxy)-5-methoxy-benzoate (5)

To a stirred solution of NaI (32 mg, 0.21 mmol) and K_2CO_3 (161 mg, 0.17 mmol) in DMF (1.5 mL) was added [^{14}C]ethyl 2-hydroxy-5-methoxy-benzoate **4** (210 mg, 1.06 mmol) dissolved in DMF (1.5 mL). The mixture was stirred for 10 min after which ethyl bromoacetate (0.130 mL, 1.17 mmol) was added in one portion. The solution was stirred at room temperature for 24 h. A second portion of ethyl bromoacetate (0.03 mL, 0.3 mmol) was added, and the reaction was stirred for another 24 h. Water (2 mL) was added, and the mixture was extracted with Et_2O (3 × 10 mL). After drying with Na_2SO_4, filtration, and evaporation, the residue was subjected to flash chromatography (4 g silica; CH_2Cl_2:MeOH 100:2) to give the product as an oil (241 mg, 80% yield).

[Carboxy-^{14}C]2-(carboxymethyloxy)-5-methoxy-benzoic acid (6)

A solution of [^{14}C]ethyl-2-(2-ethoxy-2-oxoethoxy)-5-methoxybenzoate **5** (308 mg, 1.08 mmol) in THF (1 mL) and MeOH (1 mL) was stirred as NaOH (2.2 mL, 5 M) was added; a white solid started to precipitate. The reaction mixture was heated at reflux for 4 h during which it turned pink. Water (5 mL) was added, and the mixture was washed with EtOAc (5 × 5 mL), which decolorized the mixture. The reaction was acidified with concentrated HCl and extracted with EtOAc (5 × 10mL). The combined organic extracts were dried with Na_2SO_4, filtered, and evaporated to give the product (221 mg, 89% yield), which was used in the next step without further purification.

[3-^{14}C]5-Methoxy-1-benzofuran-3-yl acetate (7)

A solution of 2-(carboxymethoxy)-5-methoxybenzoic acid **6** (110 mg, 0.48 mmol), NaOAc (165 mg, 2.0 mmol), HOAc (495 µl, 8.65 mmol), and acetic anhydride (825 µl, 8.74 mmol) was stirred under reflux for 11 h. Water was added, and the mixture was extracted with EtOAc (3 × 10 mL). The combined organic layers were dried with Na_2SO_4, filtered, and evaporated. The residue was subjected to flash chromatography (4 g silica, heptane: CH_2Cl_2 7:3 and then CH_2Cl_2), which afforded the product as solid (37 mg, 37% yield).

[3-^{14}C]5-Methoxybenzofuran-3-one (8)

A solution of 5-methoxybenzofuran-3-yl acetate **7** (73 mg, 0.35 mmol) in MeOH (0.8 mL) and water (0.2 mL) was stirred as a drop of concentrated HCl was added, and the reaction was stirred at 75 °C for 1.5 h. The solvent was evaporated, and the residue was used in the next step without further purification.

[3-^{14}C]5-Methoxybenzofuran (9)

A solution of [^{14}C]5-methoxybenzofuran-3-one (**8**) (70 mg, 0.4 mmol) in EtOH (1 mL) was added to a solution of $NaBH_4$ (31.9 mg, 0.84 mmol) in ethanol (1 mL), and the reaction was stirred at room temperature for 2 h. HCl (200 µL, 2 M) was added, and the reaction was stirred for 1 h at room temperature. Water (5 mL) was added, and the solution was extracted with Et_2O (5 × 5 mL). After drying with Na_2SO_4, filtering, and evaporation, the residue was subjected to flash chromatography (4 g silica, heptane:CH_2Cl_2 7:3), which afforded the product as solid (62 mg, 98% yield from **7**).

[3-^{14}C](5-Methoxybenzofuran-2-yl)boronic acid (10)

A solution of [^{14}C]methoxybenzofuran **9** (64 mg, 0.43 mmol) in THF (1.5 mL) cooled at −78 °C was stirred as BuLi (1.6 M in hexanes, 0.28 mL) was added slowly, and the reaction was stirred for 1 h at −78 °C. Triisopropyl borate (0.2 mL, 0.8 mmol) was added, and the reaction was stirred for 1 h at −78 °C. HCl (2 mL, 2 M) was added to the reaction mixture, and the resulting solution was extracted with EtOAc (4 × 5 mL). The combined organic layers were dried with Na_2SO_4, filtered, and concentrated to approximately 100 µL. Heptane (approximately 1.5 mL) was added upon which a solid precipitated. The solid was isolated by centrifugation, followed by filtration, and was dried under vacuum (72 mg, 87% yield).

[3-^{14}C]6-Fluoro-5-(5-methoxybenzofuran-2-yl)-*N*-methyl-pyridin-2-amine (11)

A solution of [^{14}C](5-methoxybenzofuran-2-yl)boronic acid **10** (72 mg, 0.37 mmol), *tert*-butyl 5-bromo-6-fluoropyridin-2-yl(methyl)carbamate **16** (113 mg, 0.37 mmol), 2 M Na_2CO_3 (0.557 mL, 1.11 mmol) and 1,1′-bis(diphenylphosphino)ferrocene dichloropalladium(II) dichloromethane complex (13.6 mg, 0.02 mmol) in THF (2.5 mL) was deoxygenated by bubbling nitrogen through the mixture for 10 min before capping. The reaction was heated for 1 h at 110 °C by microwaves. Water was added, and the mixture was extracted with EtOAc (3 × 10 mL). The combined organic layers were dried with Na_2SO_4, filtered, and evaporated. The residue was dissolved in CH_2Cl_2 (2 mL) and cooled at 0 °C, and TFA (500 µl, 6.49 mmol) was added. The mixture was stirred at room temperature for 30 min; after which, it was neutralized with saturated $NaHCO_3$ and extracted with CH_2Cl_2 (4 × 5 mL). The combined organic layers were dried with Na_2SO_4, filtered, and evaporated. The residue was dissolved in CH_2Cl_2 (approximately 2 mL). Heptane (approximately 3 mL) was added until the product precipitated. The solid was collected by centrifugation and further triturated with heptane before being dried under vacuum (56 mg, 55% yield).

[3-^{14}C]2-[2-Fluoro-6-(methylamino)-3-pyridyl]benzofuran-5-ol [^{14}C]AZD4694

A solution of [^{14}C]6-fluoro-5-(5-methoxybenzofuran-2-yl)-*N*-methyl-pyridin-2-amine (**11**) (56 mg, 0.20 mmol) in CH_2Cl_2 (3 mL) was cooled at −78 °C while BBr_3 (400 µL, 4.23 mmol) was added. The reaction was stirred at 0 °C for 18 h; after which, it was cooled at −78 °C, and a small amount of water was added. Saturated aqueous $NaHCO_3$ was added, and the mixture was extracted with EtOAc (5 × 5 mL). After drying with Na_2SO_4, filtration, and evaporation, the residue was subjected to flash chromatography (4 g silica, heptane:EtOAc 6:4). Final purification was conducted on reversed-phase HPLC. Most of the MeOH was evaporated, saturated aqueous $NaHCO_3$ was added, and the solution was extracted with ethyl acetate (4 × 5 mL). The combined organic layers were dried with Na_2SO_4, filtered, and evaporated to afford the title product as a solid (35.6 mg, 67% yield). The radiochemical purity was >99%, and the specific activity was 2.1 GBq/mmol.

LC/MS (M + H): 259 (10.2%) 260 (1.6%) 261 (100%) 262 (15.2%) 263 (1.8%). ^{1}H NMR (600 MHz, MeOD-d_4) δ: 8.02 (dd, J = 9.89, 8.61 Hz, 1H) 7.27 (d, J = 8.68 Hz, 1H) 6.91 (d, J = 2.42 Hz, 1H) 6.78 (d, J = 2.99 Hz, 1H) 6.71 (dd, J = 8.68, 2.42 Hz, 1H) 6.44 (dd, J = 8.40, 1.85 Hz, 1H) 2.89 (*s*, 3H).

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References

[1] W. E. Klunk, H. Engler, A. Nordberg, Y. Wang, G. Blomqvist, D. P. Holt, M. Bergström, I. Savitcheva, G.-F. Huang, S. Estrada, B. Ausén, M. L. Debnath, J. Barletta, B, J. C. Price, J. Sandell, B. J. Lopresti, A. Wall, P. Koivisto, G. Antoni, C. A. Mathis, B. Långström, *Ann. Neurol.* **2004**, *55*, 306–319.
[2] N. Nelissen, K. van Laere, L. Thurfjell, R. Owenius, M. Vandenbulcke, M. Koole, G. Bormans, D. J. Brooks, R. Vandenberghe, *J. Nucl. Med.* **2009**, *8*, 1251–1259.
[3] C. Rowe, C. Ackerman, U. Browne, W. R. Mulligan, K. L. Pike Kerry, G. O'Keefe, H. Tochon-Danguy, G. Chan, S. U. Berlangieri, G. Jones, K. L. Dickinson-Rowe, H. P. Kung, W. Zhang, M. P. Kung Mei, D. Skovronsky, T. Dyrks, G. Holl, S. Krause, M. Friebe, L. Lehman, S. Lindemann, L. M. Dinkelborg, C. L. Masters, V. L. Villemagne, *Lancet Neurol.*, **2008**, *7*, 129–135.
[4] D. F. Wong, P. B. Rosenberg, Y. Zhou, A. Kumar, V. Raymont, H. T. Ravert, R. F. Dannals, A. Nandi, J. R. Brasic, W. Ye, J. Hilton, C. Lyketsos, H. F. Kung, A. D. Joshi, D. M. Skovronsky, M. J. Pontecorvo, *J. Nucl. Med.* **2010**, *6*, 913–920.
[5] C. A. Mathis, B. J. Lopresti, W. E. Klunk, *Nucl. Med. Biol.* **2007**, *34*, 809–822.
[6] J. O. Rinne, D. Brooks, M. Rossor, N. Mortin, N. C. Fox, R. Bullock, W. E. Klunk, C. A. Mathis, K. Blennow, J. Barakos, A. A. Okello, S. Rodriguez, M. de Llano, E. Liu, M. Koller, K. M. Gregg, D. Schenk, R. Black, M. Grundman, *Lancet Neurol.* **2010**, *9*, 363–372.
[7] A. Jureus, B.-M. Swahn, J. Sandell, F. Jeppsson, A. E. Johnson, P. Johnström, J. A. M. Neelissen, D. Sunnemark, L. Farde, S. P. S. Svensson, *J. Neurochem.* **2010**, *114*, 784–794.
[8] Z. Cselényi, M. Eriksdotter Jönhagen, A. Forsberg, C. Halldin, P. Julin, M. Schou, P. Johnström, K. Varnäs, S. Svensson, L. Farde, *J. Nucl. Med.* **2012**, *53*, 415–424.
[9] B.-M. Swahn, J. Sandell, D. Pyring, M. Bergh, F. Jeppsson, A. Juréus, J. Neelissen, P. Johnström, M. Schou, S. Svensson, *Bioorg. Med. Chem. Lett.* **2012**, *22*, 4332–4337.
[10] A. H. Wadsworth, H. A. Mitchell, I. Fellows, D. R. Sutherland, *J. Labelled Compd. Radiopharm.* **1996**, *38*, 863–871.
[11] C. F. Carvalho, M. V. Sargent *J. Chem. Soc., Perkin Trans. 1* **1984**, 1605–1612.
[12] N. Hadj-esfandiari, L. Navidpour, H.Shadnia, M. Amini, N. Samadi, M. A. Faramarzi, A. Shafiee, *Bioorg. Med. Chem. Lett.* **2007**, *17*, 6354–6363.
[13] C. R. Edwards, M. J. Readhead, N. J. Tweddle, *Het. Chem.* **1987**, *24*, 495–496.
[14] Y. Kawase, S. Nakamoto *Bull. Chem. Soc. Jpn.* **1962**, *35*, 1624–1625.