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Research Article

Alternative methods for labeling the 5-HT_{1A} receptor agonist, 1-[2-(4-fluorobenzoylamino)ethyl]-4-(7-methoxynaphthyl)piperazine (S14506), with carbon-11 or fluorine-18

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Summary

1-[2-(4-Fluorobenzoylamino)ethyl]-4-(7-methoxynaphthyl)piperazine (S14506) is one of the most potent and selective agonists at 5-HT_{1A} receptors. For the purpose of prospective 5-HT_{1A} receptor imaging with positron emission tomography and the investigation of radioligand metabolic pathways, S14506 was labeled with a positron emitter, either carbon-11 ($t_{1/2} = 20.4$ min) or fluorine-18 ($t_{1/2} = 109.7$ min), at different positions. Thus, [*O-methyl*-^{11}C]S14506 was obtained in a radiosynthesis time of 35 min by treating *O-desmethyl*-S14506 with [^{11}C]iodomethane and tetrabutylammonium hydroxide in N,N–dimethylformamide. The overall decay-corrected radiochemical yield (RCY) of [*O-methyl*-^{11}C]S14506 ranged between 6 and 24% and the specific activity (SA) between 1343 and 3101 Ci/mmol (mean 2390; $n = 30$). [*carbonyl*-^{11}C]S14506 was synthesized through a microwave-enhanced direct coupling of *in situ* generated [^{11}C]organocarboxymagnesium bromide with amine precursor. RCYs ranged from 10 to 18%. [^{18}F]S14506 was prepared via nucleophilic aromatic fluoridation of the 4-nitro analog in 14–35% RCY and with SA ranging from 1063 to 2302 Ci/mmol (mean 1617; $n = 14$) in a radiosynthesis time of 115 min. Heating the radiofluoridation mixture for 5 min at 180°C in a single mode microwave cavity gave similar RCY and SA to

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heating for 30 min in an oil bath at the same temperature.

Key Words: agonist; carbon-11; fluorine-18; 5-HT_{1A}; radioligand; microwave

Introduction

An effective agonist radioligand for brain serotonin type-1A (5-HT_{1A}) receptors might be a useful tool for selective investigation of these functional G-protein coupled receptors. Many potent and selective 5-HT_{1A} receptor agonists have been labeled with tritium and radioiodine and used successfully for studying brain 5-HT_{1A} receptors *in vitro*.[1–4] Development of radioligands for *in vivo* brain imaging with PET (positron emission tomography) based on agonists is under active pursuit[5–15] but has not achieved the same level of success, mainly due to two major obstacles. Firstly, agonists bind only to receptors that are coupled to a G-protein, which represent only a variable fraction of the receptors available for binding to antagonist. Secondly, the binding of the agonist is generally transient, since agonist binding converts the receptor into a G-protein dissociated conformational state that usually has low affinity for the agonist.[16]

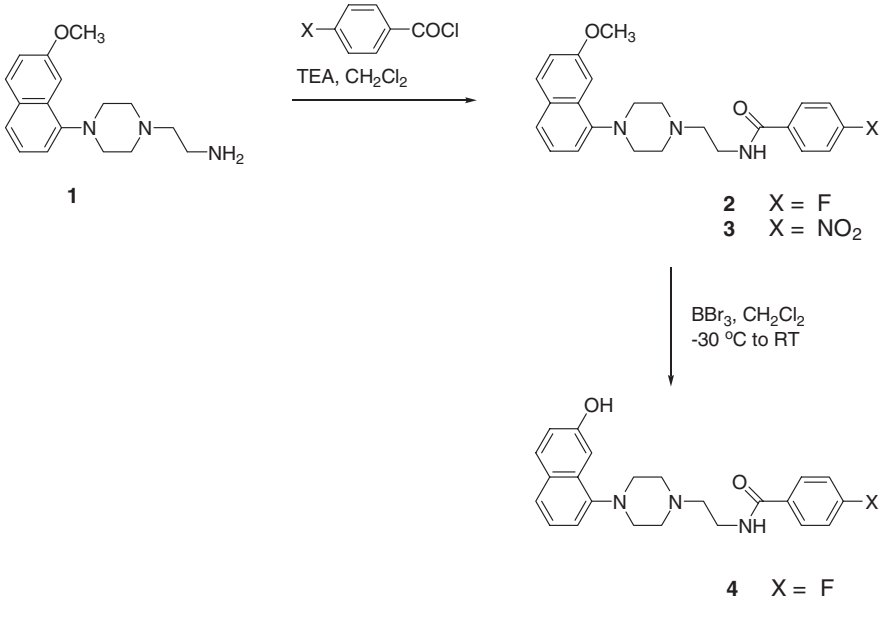
S14506 [1-[2-(4-fluorobenzoylamino)ethyl]-4-(7-methoxynaphthyl)piperazine; **2**] is one of the most potent and selective agonists at 5-HT_{1A} receptors ($K_i = 0.98$ nM).[17–20] Its affinities for adrenergic, dopaminergic, histaminergic, opioidergic, GABAergic, cholinergic and other serotonergic binding sites are at least 100-fold less than for 5-HT_{1A} receptors.[17] Measurement of the *in vivo* accumulation of tritium at one hour after intravenous injection of [^{3}H]S14506 into mice revealed that radioactivity in the 5-HT_{1A} receptor-rich hippocampus is 2.5 times more than in receptor-poor cerebellum.[18] Under *in vitro* conditions, the specific binding of [^{3}H]S14506 was similar to that of the antagonist 5-HT_{1A} receptor radioligand, [^{3}H]WAY 100635, in that [^{3}H]S14506 binds to both the G-protein coupled and uncoupled forms of the 5-HT_{1A} receptor with a nanomolar affinity. Thus, [^{3}H]S14506 contrasts with the prototypical 5-HT_{1A} agonist ligand, 8-OH-DPAT [(±)-8-hydroxy-2-(di-*n*-propylamino)tetralin], which has a nanomolar affinity for the G-protein coupled form of the receptor only.[20] Because S14506 interacts with 5-HT_{1A} receptors in a unique manner differing from that of other 5-HT_{1A} receptor agonists, potentially it might be developed as a PET radioligand for imaging a sub-set of 5-HT_{1A} receptors *in vivo*.

Here we report the development of synthetic procedures for labeling S14506 with positron emitters at three alternative positions so that [*O-methyl*-^{11}C]S14506 (**5**), [*carbonyl*-^{11}C]S14506 (**6**) and [^{18}F]S14506 (**7**) are now readily available to be used for prospective PET imaging and also the investigation of radioligand metabolic pathways.

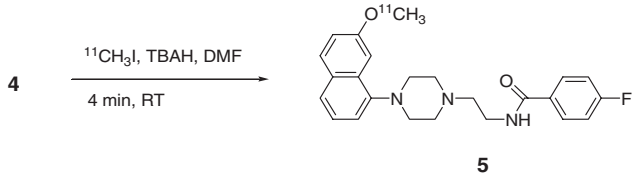
Results and discussion

S14506 (**2**) and precursors for labeling (**1**, **3**, **4**) were synthesised from commercially available materials. The key starting material, 1-[2-aminoethyl]-4-(7-methoxynaphthyl)piperazine (**1**), was prepared following the literature procedure.[21] 1–[2–(4–Fluorobenzoylamino)ethyl]-4-(7-methoxynaphthyl)piperazine (S14506; **2**)[21] and its 4-nitro analog (**3**) were obtained in high yields by acylation of **1** with the appropriate acid chloride (Scheme 1). Treatment of **2** with boron tribromide in dichloromethane gave *desmethyl*-S14506 (**4**)[21] in 72% yield. This compound was converted into the dihydrochloride salt in diethyl ether for long-term storage.

[*O-methyl*-^{11}C]S14506 (**5**) was rapidly prepared by treating the free base of the phenol (**4**) with [^{11}C]iodomethane in the presence of TBAH (tetrabutylammonium hydroxide; 0.167 M solution in methanol) in DMF (*N,N*-dimethylformamide) (Scheme 2) for 4 min at RT (room temperature) in an Autoloop device[22] (Bioscan) coupled to a MeI Microlab (GE). The free base **4**



Scheme 1. Syntheses of S14506 (2) and precursors 3 and 4 for radiosyntheses



Scheme 2. Synthesis of [*O-methyl*-^{11}C]S14506 (5)

was liberated from the dihydrochloride salt for prompt use in this radiosynthesis by treatment with saturated aqueous sodium bicarbonate in ethyl acetate. No methylation of the free base occurred in the absence of TBAH. In the presence of TBAH, methylation was highly selective for oxygen versus nitrogen. Radioligand **5** was purified by gradient reverse phase HPLC with acetonitrile and 0.01 M aqueous ammonium formate as mobile phase components. The product eluted at about 10.2 min. Decay-corrected radiochemical yields (RCYs) ranged from 6 to 24% with an average specific activity (SA) of about 2390 Ci/mmol at the end of radiosynthesis (Table 1). Radiochemical purity was greater than 98% and chemical purity greater than 97%.

Initially, a classical method for the preparation of [*carbonyl*-^{11}C]S14506 (**6**) was explored, based on ^{11}C-carboxylation of a Grignard reagent followed by conversion into the [^{11}C]acid chloride for reaction with amine precursor in THF (tetrahydrofuran).[23] However, results from the semi-automation of this process within a Synthia Grignard reaction module[24] were inconsistent. An alternative method of microwave-enhanced direct coupling of *in situ* generated [^{11}C]organocarboxymagnesium bromide with amine precursor[25] was also explored and gave more consistent results.

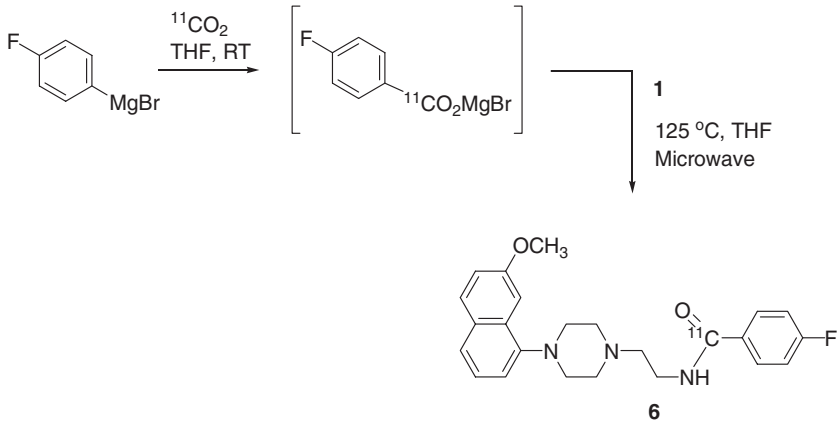
In this method (Scheme 3) the precursor, 1-[2-aminoethyl]-4-(7-methoxynaphthyl)piperazine dihydrochloride, had to be converted into the free base (**1**) with saturated aqueous sodium bicarbonate solution. [^{11}C]Carbon dioxide was trapped in a vial containing *p*-fluorophenylmagnesium bromide in THF at RT with about 80% efficiency. A solution of **1** in THF was injected into this vial and the mixture irradiated in a single mode microwave oven at 125°C for 2–5 min. Either dilute hydrochloric acid or dilute sulfuric acid in THF was used to quench the reaction. The mixture, after 10-fold dilution with HPLC mobile phase, was injected directly onto a semi-preparative size HPLC reverse phase column for separation. The RCY of **6** by this method ranged from 10 to 18%. SA was not determined.

Radioligand **7** was prepared by aromatic nucleophilic fluoridation of the 4-nitro precursor (**3**) in the presence of potassium carbonate and Kryptofix 2.2.2 (4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo-[8,8,8]hexacosane; K2.2.2) in DMSO (dimethyl sulfoxide) (Scheme 4). Initial experiments performed at

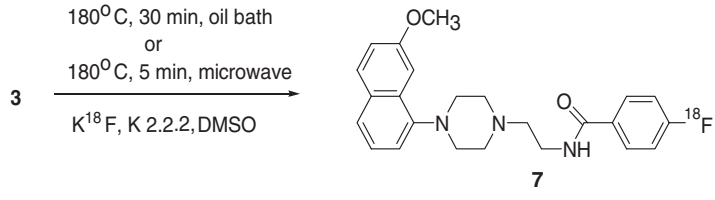
Table 1. Synthesis parameters for the radiolabeled versions of S14506

Radioligand	Synthesis time (min)	RCY (%, decay-corrected)	SA[a] (Ci/mmol)
5	35	6–24	2390 ($n = 30$)
6	30	10–18	N/D[b]
7	115	14–35	1617 ($n = 14$)

[a] At end of radiosynthesis.
[b] N/D = not determined.



Scheme 3. Synthesis of [*carbonyl*-^{11}C]S14506 (6)



Scheme 4. Synthesis of [^{18}F]S14506 (7)

Table 2. Effect of temperature on RCY of [^{18}F]S14506 (7)

Entry	Microwave conditions	RCY[a] (%)	Oil bath conditions	RCY[a] (%)
1	—		120°C, 30 min	<1[b]
2	150°C, 10 min	12	150°C, 50 min	18
3	180°C, 10 min	42	180°C, 30 min	37
4	180°C, 5 min	39	—	
5	200°C, 10 min	51, 58	200°C, 10 min	31
6	200°C, 5 min	34	200°C, 30 min	38
7	200°C, 2 min	18	200°C, 50 min	36

[a] RCYs are based on the activity collected from the HPLC fraction of the product eluting between 55 and 58 min as a percentage of the radioactivity introduced into the radiosynthesis.
[b] Estimation based on radiochromatogram peak areas.

120°C (oil bath) generated almost no amount of **7**. Investigation revealed that, although aromatic fluoridation of the nitro precursor at low temperature (e.g. 120°C) was inefficient, increasingly higher reaction temperatures gave increasingly useful RCYs (Table 2). Although heating of the reaction mixture in DMSO to 200°C gave the highest RCY, these conditions caused significant compound decomposition and were more demanding on the instrumentation.

Production of **7** was therefore performed at 180°C, either under microwave conditions (300 W, 5 min) in a single mode microwave cavity or under thermal conditions (30 min; oil bath). Each method gave **7** in similar RCY and SA (Table 1). This product was purified by HPLC with a retention time of 56 min, using acetonitrile–0.1 M aqueous ammonium formate (38:62 v/v) as mobile phase. RCY ranges from 14 to 35% and SA from 1063 to 2302 Ci/mmol (mean 1617; $n = 14$) in a radiosynthesis time of 115 min. Radiochemical purity was greater than 99% and chemical purity greater than 95%.

Experimental

Materials

TBAH (1 M solution in methanol) was diluted to 0.167 M with methanol (high-purity solvent; Burdick & Jackson). The following materials were obtained from Aldrich and used as received: 4-fluorophenylmagnesium bromide (2.0 M solution in diethyl ether packaged under nitrogen in Sure/Seal^{TM} bottle), 4-nitro-benzoyl chloride (98%), 4-fluoro-benzoyl chloride (98%), boron tribromide (1 M in dichloromethane), Kryptofix 2.2.2 (98%), ammonium formate (99.995%), potassium carbonate (99%), sodium hydroxide (97%), sodium bicarbonate (99.7%), sodium sulfate (98%), acetonitrile (anhydrous, 99.8%), dichloromethane (99.9%), DMF (anhydrous, 99.8%), DMSO (anhydrous, 99.9%), methanol (99.93%), THF (99.9 + %, anhydrous), sulfuric acid (95–98%) and TEA (triethylamine; 99.5%). Hydrochloric acid (AR; Mallinkrodt), phosphoric acid (85% in water, ACS grade; EM Science) and acetonitrile (high-purity solvent, Burdick & Jackson) for HPLC mobile phase were also used without further treatment.

General instrumentation and methods

Microwave irradiation was performed with a Discover microwave reactor (CEM). HPLC analyses were performed on a system comprising a Gold HPLC module [System Gold 126 solvent module coupled with a 166 UV absorbance detector ($\lambda = 254$ nm); Beckman Coulter] plus a flow-count radioactivity detector (diode or PMT; Bioscan). Labeled compounds were separated by HPLC on a reverse phase column (Luna C18, 10 μm, 100 Å, 250 × 10 mm id; Phenomenex) and identified by co-elution from the column with non-labeled standards. QC (quality control) was carried out with analytical HPLC on a C-18 Luna column (250 mm × 4.6 mm; 10 μm; Phenomenex) eluted at 2 ml/min with acetonitrile–10 mM ammonium formate (65:35 v/v) (R_t of **5–7** = 5.1 min). Radioactivity was measured using a calibrated dose calibrator (Atomlab 300; Biodex Medical Systems).

No-carrier-added (NCA) [^{11}C]carbon dioxide was prepared by the $^{14}N(p,\alpha)^{11}C$ nuclear reaction induced in a nitrogen gas target (pressure 150

p.s.i.) containing oxygen (1%), with a cyclotron (PETtrace; GE) proton beam (16 MeV). Irradiations were performed for 5 min with a 5 μA beam for research runs and for 20 min with a 45 μA beam for radioligand production runs. NCA [^{18}F]fluoride ion was prepared through the ^{18}O(p,n)^{18}F nuclear reaction by irradiating [^{18}O]water (95 atom %) for 120 min with a proton beam (17 MeV; 20 μA) from the same cyclotron.

1-[2-(4-Nitro-benzoylamino)ethyl]-4-(7-methoxynaphthyl)piperazine (**3**)

1-[2-Aminoethyl]-4-(7-methoxynaphthyl)piperazine (**1**, 1.01 g; 3.55 mmol) was dissolved in dichloromethane (50 ml). TEA (0.90 g; 8.91 mmol) and 4-nitrobenzoyl chloride (0.66 g; 3.55 mmol) dissolved in dichloromethane (5 ml) were added and the mixture stirred at RT for 2 h. The reaction was then quenched with water (50 ml). The organic layer was separated off and the aqueous layer extracted with dichloromethane (2 × 15 ml). The combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo* yielding a slightly yellow oil (1.58 g). Flash chromatography (silica gel, CH_2Cl_2–MeOH, 98:2, 0.1% TEA) gave **3** as a yellow oil (0.98 g; 2.26 mmol; 64%) that crystallized upon standing (mp 134–136°C). ^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) 2.72 (dt, $J_a = 7.3$ Hz, $J_b = 5.8$ Hz, 6H), 3.09 (br, 4H), 3.58–3.61 (m, 2H), 3.89 (s, 3H), 6.98–7.12 (m, 2H), 7.14–7.24 (m, 1H), 7.37–7.48 (m, 2H), 7.62–7.70 (m, 1H), 7.89 (dt, $J_a = 8.8$ Hz, $J_b = 4.8$ Hz, 2H), 8.16–8.24 (m, 2H). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) 34.0, 50.1, 51.0, 52.7, 53.8, 99.6, 112.9, 115.6, 115.7, 121.0, 121.1, 121.2, 121.3, 125.7, 127.4, 127.5, 127.5, 127.6, 137.6, 145.6, 147.0, 155.0, 155.1, 162.8. IR (neat, cm^{-1}): 3328, 2940, 2815, 1722, 1650, 1519, 1346, 1261, 1137, 1018, 829, 721. MS (CI, *m/z*): 435.1 $[M + 1]^+$.

1-[2-(4-Fluorobenzoylamino)ethyl]-4-(7-hydroxynaphthyl)piperazine (**4**)

1-[2-(4-Fluorobenzoylamino)ethyl]-4-(7-methoxynaphthyl)piperazine (**2**; 1.75 g; 4.30 mmol) was dissolved in dichloromethane under nitrogen and cooled to −30°C. Boron tribromide (1 M in dichloromethane; 20.5 ml; 20.5 mmol) was added dropwise while a temperature below −25°C was maintained. The reaction mixture was allowed to warm slowly to RT and stirred for another 1 h. The sand-colored suspension was carefully treated with ammonia (25% in water; 4 ml) to destroy excess reagent. The precipitate was filtered off and the mother liquor was dried (Na_2SO_4), filtered and concentrated *in vacuo* to yield the crude product as a slightly yellow oil (1.56 g). Flash chromatography (silica gel, CH_2Cl_2–MeOH, 97:3 v/v, 0.1% TEA) gave pure **4** as a white foam (1.21 g; 3.08 mmol; 72%). The free base was converted into the hydrochloride salt [m.p. > 225°C (decomp.); Lit.[21] 216°C] by treatment of the amine with hydrogen chloride (1 M in diethyl ether; 3.1 ml). ^{1}H-NMR (DMSO-d_6,

300 MHz): δ (ppm) 3.26–3.34 (m, 2H), 3.43 (d, $J = 12.8$ Hz, 6H), 3.79 (d, $J = 9.9$ Hz, 4H), 7.06–7.15 (m, 2H), 7.22 (dt, $J_a = 5.1$ Hz, $J_b = 2.6$ Hz, 1H), 7.32 (dt, $J_a = 6.2$ Hz, $J_b = 2.6$ Hz, 2H), 7.42 (s, 1H), 7.53 (d, $J = 8.1$ Hz, 1H), 7.76 (dd, $J_a = 6.2$ Hz, $J_b = 2.6$ Hz, 1H), 8.07–8.11 (m, 2H), 9.13 (br, 1H), 11.24 (br, 1H). ^{13}C-NMR (DMSO-d_6, 75 MHz): δ (ppm) 31.5, 38.9, 46.2, 49.2, 95.5, 102.3, 112.5, 112.8, 115.9, 119.8, 121.3, 126.2, 126.9, 127.4, 127.5, 127.56, 127.7, 143.4, 152.9, 162.9, 169.7. IR (KBr, cm^{-1}): 3382, 3187, 2939, 2823, 1637, 1602, 1525, 1496, 1457, 1241, 1216, 1141, 1020, 883, 846, 829, 746. MS (CI, m/z): 394.0 $[M + 1]^+$.

[O-methyl-^{11}C]S14506 (**5**)

O-Desmethyl precursor (**4**, free amine; 1.0 mg; 0.002 mmol) and TBAH (0.167 M in methanol; 14 μl) were dissolved in DMF (80 μl). The mixture was loaded into the sample loop of an Autoloop (Bioscan). [^{11}C]Iodomethane, generated according to the 'gas phase method' in a PETtracer MeI MicroLab system (GE), was swept through the loop in helium gas for 4–6 min at a flow rate of 12 ml/min. When the radioactivity reached a maximum, the reactants were kept within the loop at RT for 4 min. The reaction mixture was then injected onto the semi-preparative size column and eluted at 6 ml/min with acetonitrile–10 mM ammonium formate (55:45 v/v), with the proportion of acetonitrile increased linearly to 65% over 15 min. The product **5** ($R_t = 10.2$ min) was collected in a clean pear-shaped flask. The solvent was removed under reduced pressure and the residue dissolved in saline (3–10 ml) containing ethanol (5% v/v). For use in PET imaging in rhesus monkey, the final dose was filtered through a Millex-GV (0.22 μm, 33 mm diameter) sterilization filter. The radiosynthesis time was about 35 min. An aliquot (100 μl) was removed from the dose vial and used for QC with analytical HPLC.

[carbonyl-^{11}C]S14506 (**6**)

Within an argon-protected glovebox, Grignard reagent (*p*-F-C_6H_4MgBr, 2 M solution in ether; 100 μl) and THF (400 μl) were added to a standard Pyrex glass microwave reaction vessel (10 ml; CEM). The vessel was crimp-sealed with a PTFE-coated septum. [^{11}C]Carbon dioxide, first collected in a 5-loop stainless-steel tube (o.d. 1/16 in) cryogenic trap, equipped with a cartridge containing a mixture of chromium(III) oxide and copper(II) sulfate on silica gel to remove nitrogen oxides and another cartridge of phosphorus(V) oxide to remove moisture,[26] was bubbled into the vial at 5 ml/min at RT for about 6 min via PEEK tubing (1/16 in o.d.) pierced through the septum. Amine **1** (1.5 mg; 0.005 mmol) in THF (100 μl) was added to the reaction mixture using an epidermal needle also at RT. The mixture was then irradiated in the

microwave reactor at 125°C and 300 W for 2–5 min. At the end of irradiation, stock sulfuric acid (1 M in THF; 200 µl) and water (200 µl) were added successively through epidermal needles. The aqueous layer (~250 µl) containing inorganic salts was removed. The organic layer (~700 µl) containing the ^{11}C-labeled products was analyzed by HPLC on a reverse phase semi-preparative size column eluted at 6 ml/min with a gradient of methanol–10 mM ammonium formate, starting at 40% methanol increasing linearly to 90% over 6 min and then maintained at 90% for 8 min (R_t of **6** = 10.0 min).

[^{18}F]S14506 (**7**)

Cyclotron-produced [^{18}F]fluoride ion in [^{18}O]water was mixed in a borosilicate glass vessel (1 ml; Chemglass, customer designed) with potassium carbonate (0.5 mg; 0.004 mmol) and Kryptofix 2.2.2 (5.0 mg; 0.013 mmol) in water–acetonitrile (1:9 v/v; 100 µl) and then dried by three cycles of addition and evaporation of acetonitrile (0.5 ml per addition). The residue was dissolved in DMSO (200 µl) and transferred to a standard glass microwave reaction vial (10 ml) containing the nitro precursor **3** (1.0 mg; 0.002 mmol). The mixture was heated in an oil bath or irradiated in a single mode microwave cavity (Discover; CEM). The reaction mixture was cooled to near RT and quenched with acetonitrile–0.1 M ammonium formate (60:40 v/v; 1.8 ml). This solution was injected onto the semi-preparative size HPLC column and eluted at 6 ml/min with acetonitrile–0.1 M aqueous ammonium formate (38:62 v/v) (R_t of **7** = 56 min). **7** was collected in a 50 ml polypropylene conical tube and further diluted with water (50 ml) in a 100 ml glass flask. This solution was passed through a C-18 Sep-Pak, followed by water (10 ml). Radioactivity was eluted from the Sep-Pak with ethanol (1.0 ml). The eluate was collected in a sterile vial (10 ml) and diluted with physiological saline (9.0 ml). For experiments using **7** in monkey, this solution was filtered through a syringe-driven sterile filter (Millex-MP, 0.22 µm, 25 mm diameter). An aliquot (100 µl) was removed from the dose vial and used for QC with analytical HPLC. The total radiosynthesis time was 115 min.

Conclusions

S14506 can be labeled with no-carrier-added carbon-11 or fluorine-18 at any one of three different positions in acceptable RCY. Application of microwave heating enhanced the [^{11}C]amide synthesis and [^{18}F]fluoridation. These radioligands (**5–7**) are now available for evaluation with PET *in vivo*.

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