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# Synthesis of 6-[$^{18}$F]fluoro-PBR28, a novel radiotracer for imaging the TSPO 18 kDa with PET

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ABSTRACT

6-Fluoro-PBR28 (*N*-(6-fluoro-4-phenoxypyridin-3-yl)-*N*-(2-methoxybenzyl)acetamide), a fluorinated analogue of the recently developed TSPO 18 kDa ligand PBR28, was synthesized and labelled with fluorine-18. 6-Fluoro-PBR28 and its 6-chloro/6-bromo counterparts were synthesized in six chemical steps and obtained in 16%, 10% and 19% overall yields, respectively. Labelling with fluorine-18 was performed in one single step (chlorine/bromine-for-fluorine heteroaromatic substitution) using a Zymate-XP robotic system affording HPLC-purified, ready-to-inject, 6-[$^{18}$F]fluoro-PBR28 (>95% radiochemically pure). Non-decay-corrected overall yields were 9–10% and specific radioactivities ranged from 74 to 148 GBq/μmol. In vitro binding experiments, dynamic μPET studies performed in a rat model of acute neuroinflammation (unilaterally, AMPA-induced, striatum-lesioned rats) and ex vivo autoradiography on the same model demonstrated the potential of 6-[$^{18}$F]fluoro-PBR28 to image the TSPO 18 kDa using PET.



Microglia activation is considered as the predominant cellular response to inflammation within the central nervous system (CNS). This process is characterized by a drastic change in the morphology of these cells and by the notable overexpression of the translocator protein (TSPO 18 kDa). The TSPO has been the focus of numerous studies over several decades and is clearly recognised as an early marker of neuroinflammation.[1] This has resulted in extensive efforts into the design of radiolabelled ligands for imaging of the TSPO using PET.[2–5]

The 3-isoquinolinecarboxamide PK11195 was the first TSPO ligand labelled with the short-lived positron-emitter carbon-11 ($T_{1/2}$: 20.38 min).[6] Today, [$^{11}$C]PK11195 remains the most cited radiotracer in this field and is still widely used in spite of severe limitations. Several new structures belonging to other chemical classes are now being developed as promising alternatives.[7] Amongst these, *N*-benzyl-*N*-(2-phenoxyaryl)acetamides have proved to be particularly interesting candidates. Indeed, in the late 1990s, two promising ligands DAA1097 (**A**) and DAA1106 (**B**) were identified for their pharmacological properties relative to TSPO (Fig. 1).[8–10] DAA1106 was therefore labelled with carbon-11[11,12] ([$^{11}$C]DAA1106, [$^{11}$C]**B**) and was shown to be more sensitive than the reference compound [$^{11}$C]PK11195. The discovery of [$^{11}$C]DAA1106 was rapidly followed by the development of [$^{18}$F]FMDAA1106 ([$^{18}$F]**C**) and [$^{18}$F]FE-DAA1106 ([$^{18}$F]**D**),[13] two radiofluorinated counterparts, that were evaluated[14] for their potential in imaging the TSPO. Successively, in 2005 and 2007, a novel $^{18}$F-labelled analogue of DAA1106 and the fluorine-18 version of DAA1106, obtained both in a single radiosynthetic step, were reported in the literature as potential TSPO radioligands: [$^{18}$F]PBR06 ([$^{18}$F]**E**)[15] and [$^{18}$F]DAA1106 ([$^{18}$F]**B**),[16] respectively. [$^{18}$F]PBR06 was labelled with introduction of the fluorine-18 at the *N*-acyl function by reacting [$^{18}$F]F$^-$ with the corresponding bromo precursor, while the synthesis of [$^{18}$F]DAA1106 was achieved by the nucleophilic reaction of [$^{18}$F]F$^-$ with a diaryliodonium salt precursor. [$^{18}$F]PBR06 was very recently evaluated in monkey and rat.[17,18] In 2006, [$^{11}$C]DAA1097 ([$^{11}$C]**A**) and its [$^{11}$C]methyl and [$^{11}$C]ethyl homologues, [$^{11}$C]**F** and [$^{11}$C]**G**, respectively (Fig. 1), were synthesized and evaluated as PET ligands for

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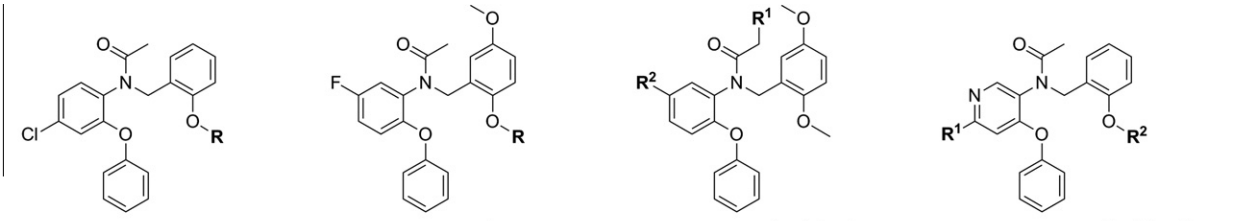



**Figure 1.** Structures of TSPO receptor radioligands featuring an aryloxyanilide backbone and structure of 6-[$^{18}$F]fluoro-PBR28 ([$^{18}$F]**15**).

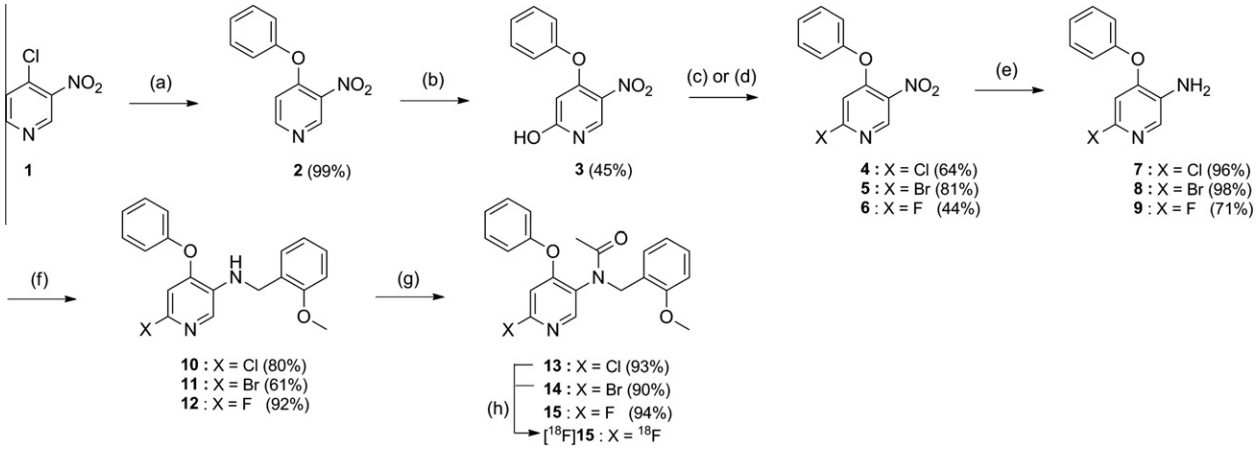
imaging brain TSPO in mice, rats and monkeys.[19] The radiolabelled compound [$^{11}$C]PBR28 ([$^{11}$C]**H**, Fig. 1), a closely related analogue of [$^{11}$C]DAA1106, has also been identified as a ligand displaying exceptional properties for the in vivo imaging of the TSPO using PET.[20–26]

The preparation of an $^{18}$F-analogue has also been achieved based on an *O*-[$^{18}$F]fluoroalkylation strategy of *O*-desmethyl PBR28, leading to compound [$^{18}$F]FEPPA ([$^{18}$F]**I**, Fig. 1) whose biodistribution properties and metabolism have been studied and compared with the parent molecule in rats.[27] The bioisosteric replacement of the C–F moiety present in the anilide ring of DAA1106 with a ring nitrogen in PBR28 leaves the latter structure with an interesting pyridine motif leaving open the option of fluorine introduction at an α-position. Moreover, the use of a suitable leaving group at the pyridine α-position would offer an opportunity for fluorine-18-labelling using the well-established nucleophilic *ortho*-heteroaromatic radiofluorination methodology.[28] This would permit the preparation of a novel radiofluorinated analogue, 6-[$^{18}$F]fluoro-PBR28 ([$^{18}$F]**15**), closely related to PBR28 (**H**) but also to compound **F**, circumventing the more common above mentioned (e.g., [$^{18}$F]FEDAA1106 and [$^{18}$F]FEPPA) 'fluoroalkyl derivatization strategy'. This Letter presents the synthesis of 6-fluoro-PBR28 (**15**), its radiolabelling with fluorine-18 and its preliminary in vitro and in vivo evaluation as a radiotracer to image the TSPO 18 kDa with PET.

The synthesis of non-radioactive 6-fluoro-PBR28 (**15**), needed as reference compound in radiochemistry and the two radiolabelling precursors (**13**, **14**) as well as radiosynthesis of fluorine-18-labelled compound 6-[$^{18}$F]fluoro-PBR28 ([$^{18}$F]**15**) are depicted in Scheme 1.

The preparation of 2-halo-5-nitro-4-phenoxypyridines **4**, **5** and **6**, as key intermediates, was required. These tri-substituted pyridines were produced by carrying out the displacement of the 4-chlorine of commercially available 4-chloro-3-nitropyridine (**1**) with the phenolate anion, prior to an α-hydroxy-functionalization at the 6-position of the pyridine ring. Thus, treatment of 4-chloro-3-nitropyridine (**1**) with phenol and NaH in THF at room temperature gave 3-nitro-4-phenoxypyridine **2**, which was selectively hydroxylated at the C-6 position with *tert*-butyl hydroperoxide (*t*-BuOOH) via vicarious nucleophilic substitution of hydrogen[29,30] in presence of potassium *tert*-butoxide (*t*-BuOK) as a base in DMF. Despite the low nucleophilicity of *t*-BuOK and the low reaction temperature (−50 to −30 °C), compound **3** was obtained in only moderate yield (38–45%) due to the formation of undesired 5-nitro-4-*tert*-butoxypyridin-2-ol (10–15%). The latter side-product formation resulted from the displacement of the very labile C-4 phenoxy group due to activation by both the ring nitrogen atom and the *ortho* nitro group. Hydroxypyridine **3**, isolated probably in its pyridone form, was converted to the corresponding 2-chloro-5-nitro-4-phenoxypyridine **4** with phosphorus oxychloride ($POCl_3$) in refluxing toluene. The bromo-derivative **5** was prepared following the same strategy using $POBr_3$ as brominating agent. The preparation of the 2-fluoro counterpart (**6**) was achieved from hydroxypyridine **3** too. The 2-hydroxy group of **3**, activated by the conjugated effects of the 5-nitro substituent and the ring nitrogen, was successfully replaced with fluorine when reacted with DAST in acetonitrile at 75 °C. Such a direct hydroxyl for fluorine exchange on an activated heteroaromatic ring using DAST, or a similar deoxo-fluorinating agent is, to our knowledge, reported for the first time.

Finally, 6-chloro-, 6-bromo- and 6-fluoro-PBR28 (**13**, **14** and **15**, respectively) were prepared according to the straightforward




**Scheme 1.** Chemical synthesis of radiolabelling precursors (**13**, **14**), reference compound 6-fluoro-PBR28 (**15**) and radiosynthesis of 6-[$^{18}$F]fluoro-PBR28 ([$^{18}$F]**15**). Reagents and conditions: (a) NaH, PhOH, THF, rt; (b) *t*-BuOOH, *t*-BuOK, DMF, −50 °C; (c) $POX_3$, toluene, 110 °C; (d) DAST, $CH_3CN$, 75 °C; (e) Fe, AcOH, rt; (f) 2-methoxybenzaldehyde, AcOH, $NaBH_3CN$, MeOH, rt; (g) $Ac_2O$, AcOH, 70 °C; (h) K[$^{18}$F]F-$K_{222}$, $K_2CO_3$, DMSO, 165 °C, 5 min.

three-step protocol,[31] depicted in Scheme 1, from the corresponding 5-nitro-4-phenoxypyridine substituted in the 2-position with either a chlorine, bromine or fluorine atom.

Reduction of nitropyridines **4**, **5** and **6** was achieved with iron dust in acetic acid yielding compounds **7**, **8** and **9**, respectively, in good to excellent yields (71–98%). Reductive alkylation of substituted 5-aminopyridines **7**, **8** and **9** with 2-methoxybenzaldehyde utilising sodium cyanoborohydride and a catalytic amount of acetic acid in methanol, followed by acylation of the resulting compounds **10**, **11** and **12** using acetic acid anhydride in hot acetic acid (70 °C), gave the expected halo-analogues of PBR28, **13**, **14** and **15**, respectively in good overall yields over three steps, ranging from 54% to 72%. Compounds **13**–**15** have been characterized using spectroscopic techniques.[32]

Radioligand [$^{18}$F]**15** was readily prepared, as shown in Scheme 1, in a single-step procedure by nucleophilic aromatic substitution on 2-halo pyridine derivatives (**13** or **14**) with [$^{18}$F]F$^-$ using standard conditions.[33,34] The reaction was performed on a Zymate-XP® robotic system using activated K[$^{18}$F]F–Kryptofix $K_{222}$ complex as the fluorinating reactant, in DMSO by heating at 165 °C for 5 min. After pre-purification on a C-8 PrepSep™ cartridge, [$^{18}$F]**15** was purified by semi-preparative HPLC on a Waters Symmetry® C-18 column and obtained in 16–18% ($n$ >10) radiochemical decay-corrected yield, based on [$^{18}$F]F$^-$, starting from the bromo derivative (**14**). The preparation of ready-to-inject 6-[$^{18}$F]fluoro-PBR28 ([$^{18}$F]**15**) was achieved within 90 min from the end of cyclotron fluorine-18 production, including HPLC-purification ($R_t$: 23–24 min)[35] and SepPak® Plus-based formulation. The identity of the product was confirmed by co-injection with an original sample of **15** on an analytical HPLC ($R_t$: 1.81 min).[36] As also demonstrated by HPLC analysis, the preparation was >95% chemically and >99% radiochemically pure. It was shown to be free of the non-radioactive precursor for labelling (**13**, $R_t$: 2.25 min or **14**, $R_t$: 2.50 min) and was chemically and radiochemically stable for at least 120 min. Typically, starting from a 37 GBq [$^{18}$F]F$^-$ batch, 3.3–3.7 GBq of 6-[$^{18}$F]fluoro-PBR28 ([$^{18}$F]**15**) could be obtained starting from **14**. Specific radioactivities ranged from 74 to 148 GBq/μmol. Comparable radiochemical yields were obtained using the chloro precursor for labelling with however a lower observed chemical purity (<70%). This is mainly due to the more difficult HPLC separation of [$^{18}$F]**15** from its labelling precursor when using the chloro derivative **13** compared to the bromo derivative **14** ($R_t$: [$^{18}$F]**15**: 23.5 min, **13**: 26 min, **14**: 33 min) in the conditions used.[35]

The measured log $D_{7.4}$ ($n$-octanol/buffer pH 7.4 partition coefficient) and log $P$ ($n$-octanol/water partition coefficient) values of [$^{18}$F]**15**, determined using the shake-flask method,[37] were 2.82 ± 0.14 and 2.77 ± 0.10, respectively. These values are in the range for adequate passive brain entry in vivo.[38,39]

The in vitro binding affinity ($K_i$) of **15** for TSPO was determined by competition with [$^3$H]PK11195 using membrane homogenates from rat heart as well as mitochondrial-enriched preparations derived from rat kidney and human embryonic kidney (HEK293) cells.[40] Compound **15** showed high affinity for TSPO as shown in Table 1.

No significant binding of **15** to the central benzodiazepine receptor (CBR) could be determined in competition experiments against [$^3$H]flunitrazepam (a reference CBR ligand) in a rat cerebral cortex homogenate screen (concentration–response curve showed less than 10% effect at 0.1 μM).

Compound **15** was assessed for its ability to increase pregnenolone synthesis by use of a well-developed steroidogenic assay.[41] Practically, pregnenolone release from rat C6 cells, exposed to 6-fluoro-PBR28 (**15**, 40 μM) or PK11195 (40 μM), was measured by competitive enzyme-linked immunoassay (ELISA). Compound **15** stimulated pregnenolone synthesis at levels 17% above the baseline, displaying lower potency than PK11195 (Table 2).

**Table 1**
$K_i$ values of **15** and PK11195 against [$^3$H]PK11195 for binding affinities to TSPO 18 kDa

| Compound | $K_i$ (nM, rat [a]) | $K_i$ (nM, rat [b]) | $K_i$ (nM, human [c]) |
|---|---|---|---|
| **15** | 0.44 ± 0.01 | 3.90 ± 0.30 | 1.19 ± 0.03 |
| PK11195 | 1.80 ± 0.04 | 9.30 ± 0.50 | 7.11 ± 0.35 |

[a] Membrane homogenates from rat heart.
[b] Mitochondrial fractions of rat kidney.
[c] Mitochondrial fractions of HEK293 cells. Values represent the mean ± SEM of at least three independent experiments carried out in duplicate.

**Table 2**
Effect of TSPO ligands on pregnenolone accumulation in rat C6 glioma cells

| Compound | Pregnenolone release (% above control)[a] |
|---|---|
| **15** | 16.45 ± 1.77 |
| PK11195 | 37 ± 1 |

[a] Experimental data represents the mean ± SEM of at least three independent experiments.

MicroPET studies of 6-[$^{18}$F]fluoro-PBR28 ([$^{18}$F]**15**) using AMPA lesioned rats[42–44] resulted in images with a high contrast between the lesioned area, indicated by the red arrows (Fig. 2), and the corresponding area in the intact contralateral hemisphere (ratio ipsi/contra: 2.2) at 60 min post-injection.

The brain kinetics of [$^{18}$F]**15** and [$^{11}$C]PK11195 in lesioned and non-lesioned striatum are shown in Figure 3. The two radioligands entered the brain rapidly and the maximum radioactivity uptake was reached within 1–2 min post-injection in both regions. The uptake of [$^{18}$F]**15** in the lesioned striatum remained at a plateau to the end of the imaging experiment while the control radioli-

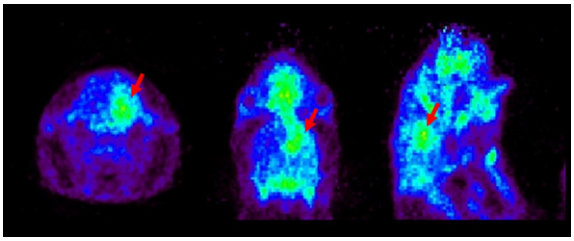


**Figure 2.** MicroPET axial, coronal and sagittal images (from left to right) with 6-[$^{18}$F]fluoro-PBR28 ([$^{18}$F]**15**) in AMPA lesioned rats 60 min post-injection. Red arrows indicate the visible right-side lesion.

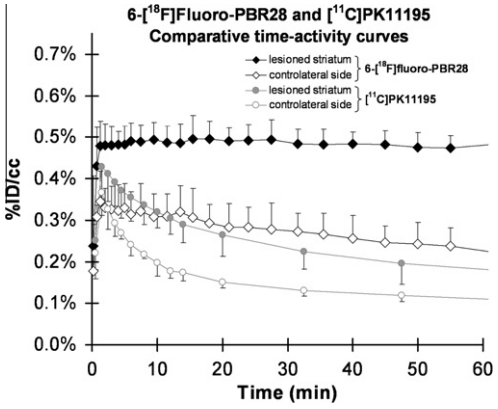



**Figure 3.** MicroPET time-activity curves for 6-[$^{18}$F]fluoro-PBR28 ([$^{18}$F]**15**) and [$^{11}$C]PK11195 in lesioned and non-lesioned striatum of rats.

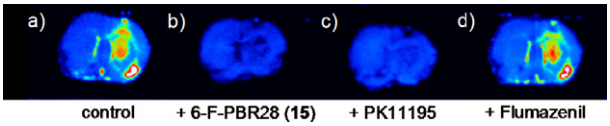



**Figure 4.** Ex vivo autoradiograms in AMPA lesioned rat brains of: (a) [$^{18}$F]**15** (6-[$^{18}$F]fluoro-PBR28, control), (b) [$^{18}$F]**15** + **15**, (c) [$^{18}$F]**15** + PK11195 and (d) [$^{18}$F]**15** + flumazenil.

gand, [$^{11}$C]PK11195, displayed a rapid clearance in the same region.

Ex vivo binding experiments were also performed with [$^{18}$F]**15** as depicted in Figure 4: autoradiography on brain sections resulted in a high ipsi- to controlateral ratio, which was abolished by an excess (20 nM) of non-radioactive **15** or PK11195 but not flumazenil.

In conclusion, 6-fluoro-PBR28 (**15**), a fluorinated analogue of the TSPO ligand PBR28, was synthesized and labelled with fluorine-18. The discussed biological evaluation studies demonstrate the potential of this radiofluorinated tracer to image in vivo the TSPO using PET.

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32. Characterisation data. Compound **13**: a colourless syrup, $R_f$ = 0.14 (heptane/EtOAc 7:3). $^1$H NMR ($CD_2Cl_2$): $\delta$ 7.96 (s, 1H), 7.48 (t, 2H, $J$ = 8.0 Hz), 7.34 (m, 2H), 7.27 (d, 1H, $J$ = 8.0 Hz), 6.96 (d, 2H, $J$ = 7.6 Hz), 6.91 (t, 1H, $J$ = 7.2 Hz), 6.82 (d, 1H, $J$ = 8.0 Hz), 6.56 (s, 1H), 5.10 (d, 1H, $J$ = 14.4 Hz), 4.82 (d, 1H, $J$ = 14.4 Hz), 3.63 (s, 3H), 1.97 (s, 3H). $^{13}$C NMR ($CD_2Cl_2$): $\delta$ 170.1 [C], 162.3 [C], 157.6 [C], 152.8 [C], 151.2 [C], 150.7 [CH], 131.1 [CH], 130.4 [2CH], 129.0 [CH], 128.2 [C], 126.3 [CH], 124.6 [C], 120.7 [2CH], 120.4 [CH], 110.3 [CH], 110.2 [CH], 54.9 [$CH_3$], 45.8 [$CH_2$], 21.9 [$CH_3$]. ESI(+)-FS-MS ($m/z$): 383/385 [M+H]$^+$. Compound **14**: a white solid, $R_f$ = 0.15 (heptane/EtOAc 7:3). $^1$H NMR ($CDCl_3$): $\delta$ 7.93 (s, 1H), 7.45 (t, 2H, $J$ = 8.0 Hz), 7.33 (m, 2H), 7.24 (m, 1H), 6.89 (m, 3H), 6.76 (d, 1H, $J$ = 8.0 Hz), 6.67 (s, 1H), 5.12 (d, 1H, $J$ = 14.0 Hz), 4.84 (d, 1H, $J$ = 14.0 Hz), 3.60 (s, 3H), 1.98 (s, 3H). $^{13}$C NMR ($CD_2Cl_2$): $\delta$ 169.9 [C], 161.9 [C], 157.6 [C], 152.7 [C], 151.1 [CH], 141.3 [C], 131.1 [CH], 130.4 [2CH], 129.0 [CH], 128.6 [C], 126.3 [CH], 124.6 [C], 120.7 [2CH], 120.4 [CH], 114.0 [CH], 110.2 [CH], 54.9 [$CH_3$], 45.8 [$CH_2$], 22.0 [$CH_3$]. ESI(+)-FS-MS ($m/z$): 427/429 [M + H]$^+$. Compound **15**: a colourless syrup, $R_f$ = 0.14 (heptane/EtOAc 7:3). $^1$H NMR ($CD_2Cl_2$): $\delta$ 7.80 (s, 1H), 7.48 (t, 2H, $J$ = 8.0 Hz), 7.34 (d, 2H, $J$ = 8.0 Hz), 7.26 (dt, 1H, $J$ = 7.6, 1.6 Hz), 6.97 (d, 2H, $J$ = 8.0 Hz), 6.91 (t, 1H, $J$ = 7.2 Hz), 6.81 (d, 1H, $J$ = 8.0 Hz), 6.13 (d, 1H, $J$ = 1.2 Hz), 5.11 (d, 1H, $J$ = 14.0 Hz), 4.82 (d, 1H, $J$ = 14.0 Hz), 3.63 (s, 3H), 1.97 (s, 3H). $^{13}$C NMR ($CD_2Cl_2$): $\delta$ 170.4 [C], 164.5 [C, d, $J^3_{C-F}$ = 11 Hz], 163.4 [C, d, $J^1_{C-F}$ = 236 Hz], 157.6 [C], 152.8 [C], 148.5 [CH, d, $J^3_{C-F}$ = 19 Hz], 131.1 [CH], 130.4 [2CH], 129.0 [CH], 127.1 [C], 126.4 [CH], 124.7 [C], 120.7 [2CH], 120.3 [CH], 110.2 [CH], 95.4 [CH, d, $J^2_{C-F}$ = 45 Hz], 55.0 [$CH_3$], 45.8 [$CH_2$], 21.9 [$CH_3$]. ESI(+)-FS-MS ($m/z$): 367 [M + H]$^+$. Anal. Calcd for: C, 68.84; H, 5.23; N, 7.65. Found: C, 68.61; H, 5.25; N, 7.59.
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35. HPLC purification of [$^{18}$F]**15**: semipreparative Waters SymmetryPrep® C-18 (300 × 7.8 mm; 7 μm)—eluent: $CH_3CN/H_2O$/low-UV PIC® B7 reagent (Waters): 35:65:2 (v/v/v)—flow rate: 5 mL/min—detection at $\lambda$: 254 nm.
36. Analytical HPLC control of [$^{18}$F]**15**: analytical Waters Symmetry-M® C-18 (50 × 4.6 mm; 3.5 μm)—eluent: $H_2O$ (containing low-UV PIC® B7 reagent (Waters), 20 mL for 1000 mL)/$H_2O/CH_3CN$ (30:70, v/v, containing low-UV PIC® B7 reagent (Waters), 20 mL for 1000 mL): 40:60 (v/v)—flow rate: 2.0 mL/min; temperature: 30 °C; detection at $\lambda$: 254 nm.
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