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^{18}F-Labelled vorozole analogues as PET tracer for aromatase

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One- and two-step syntheses for the ^{18}F-labelling of 6-[(*S*)-(4-chlorophenyl)(1*H*-1,2,4-triazol-1-yl)methyl]-1-(2-[^{18}F]fluoroethyl)-1*H*-benzotriazole, [^{18}F]FVOZ, 1 and 6-[(*S*)-(4-chlorophenyl)(1*H*-1,2,4-triazol-1-yl)methyl]-1-[2-(2-[^{18}F]fluoroethoxy)ethyl]-1*H*-benzotriazole, [^{18}F]FVOO, 2 were developed. In the two-step synthesis, the nucleophilic fluorination step was performed by reacting (*S*)-6-[(4-chlorophenyl)-(1*H*-1,2,4-triazol-1-yl)methyl]-1*H*-benzotriazole (VOZ) with either the ^{18}F-labelled ethane-1,2-diyl bis(4-methylbenzenesulfonate) or the oxydiethane-2,1-diyl bis(4-methylbenzenesulfonate). The radiochemical yields were in the range of 9–13% after the 110–120 min total syntheses and the specific radioactivities were 175 $\pm$ 7 GBq/μmol and 56 GBq/μmol for compounds 1 and 2, respectively. In the one-step synthesis, the precursor 2-{6-[(4-chlorophenyl)(1*H*-1,2,4-triazol-1-yl)methyl]-1*H*-1,2,3-benzotriazol-1-yl}ethyl 4-methylbenzenesulfonate (7) or 1-[2-(2-bromoethoxy)ethyl]-6-[(4-chlorophenyl)(1*H*-1,2,4-triazol-1-yl)methyl]-1*H*-benzotriazole (8) was directly labelled via an ^{18}F nucleophilic substitution to give the corresponding tracer. The labelled compounds were obtained in 36–99% radiochemical yield after 75-min syntheses. The specific radioactivities are 100 GBq/μmol for compound 1 and 80 GBq/μmol for compound 2. *In vitro* autoradiography using frozen rat brains illustrated specific binding in the medial amygdala, the bed nucleus of stria terminalis and the preoptic area, all of which corresponded well to the result of ^{11}C-labelled vorozole.

Keywords: n. c. a nucleophilic ^{18}F-fluorination; ^{18}F-labelled VOZ analogues; aromatase

Introduction

Aromatase is an enzyme that converts androgens (C_{19} steroids) to estrogens (C_{18}) and may play a role in mood and mental status.[1] (*S*)-6-[(4-Chlorophenyl)(1*H*-1,2,4-triazol-1-yl)methyl]-1-methyl-1*H*-benzotriazole, VOZ, is a nonsteroidal aromatase inhibitor that reversibly binds to the heme domain of aromatase. [*N*-Methyl-^{11}C]vorozole, [^{11}C]VOZ, is an interesting high-affinity aromatase-binding radiotracer[2] used in positron emission tomography (PET). The radiotracer has previously shown high and specific binding to aromatase-rich tumor reference placenta[2] and ovarian tissues.[3] Recently, [^{11}C]VOZ has also demonstrated a high affinity for brain aromatase in the amygdala.[1] Finally, ^{11}C-labelled vorozole can be used to study the alternation of aromatase expression in the brain by anabolic–androgenic steroid treatment *in vivo*.[4] Although [^{11}C]VOZ has good biological properties, we were interested in developing ^{18}F-labelled analogues. Owing to longer half-life, these could thus be used as tools for visualizing the aromatase enzyme in a variety of applications, e.g. such as for depression or Alzheimer's disease, which might be influenced by steroid hormones.[5]

In this paper, we report the one- and two-step radiolabelling syntheses of ^{18}F-labelled vorozole analogues, i.e. 6-[(*S*)-(4-chlorophenyl)(1*H*-1,2,4-triazol-1-yl)methyl]-1-(2-[^{18}F]fluoroethyl)-1*H*-benzotriazole, [^{18}F]FVOZ, **1** and 6-[(*S*)-(4-chlorophenyl)(1*H*-1,2,4-triazol-1-yl)methyl]-1-[2-(2-[^{18}F]fluoroethoxy)ethyl]-1*H*-benzotriazole, [^{18}F]FVOO, **2**. The two tracers have been evaluated in some preclinical studies using *in vitro* autoradiography and metabolite studies.

Results and discussion

Two-step labelling

The ^{18}F-labelled analogues were synthesized in two steps. In the first step of the synthesis of compound **1**, [^{18}F]fluoride was reacted with ethane-1,2-diyl bis(4-methylbenzenesulfonate) to give **3**,[6] which in the second step was reacted with the pre-treated precursor **5** to obtain the ^{18}F-labelled product (Schemes 1 and 2). Efficient alkylation was achieved when the substrate was deprotonated using KOH. The reaction was heated to 70°C for 15 min during the first step and to 150°C for 15 min during the second step. The ^{18}F-labelled product **2** was synthesized from the intermediate 2-(2-[^{18}F]fluoroethoxy)ethyl 4-methylbenzenesulfonate[7] (**4a**) or 1-bromo-2-(2-[^{18}F]fluoroethoxy)ethane (**4b**), which were synthesized from oxydiethane-2,1-diyl bis(4-methylbenzenesulfonate) (**a**) or 2-bromoethyl ether (**b**), respectively (Schemes 1 and 2). The

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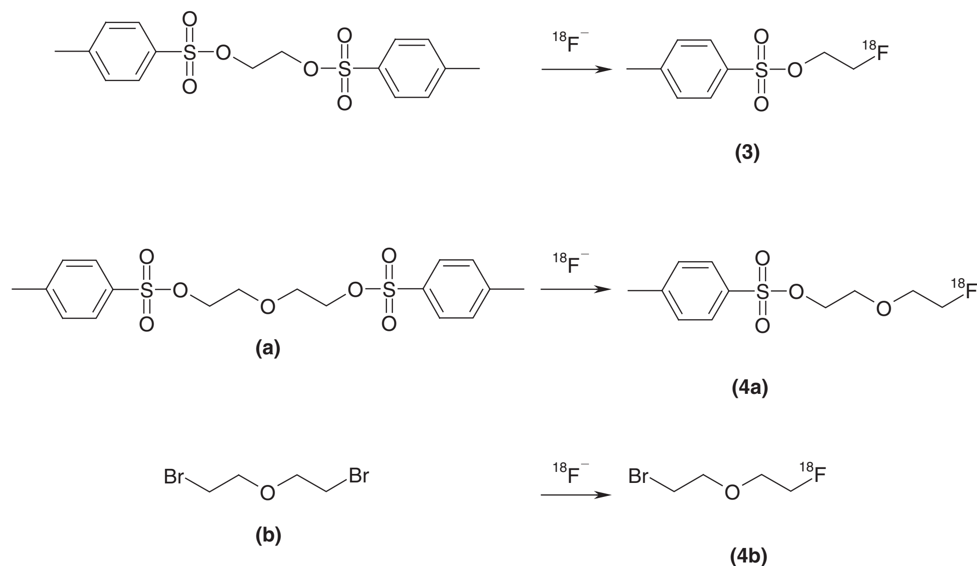
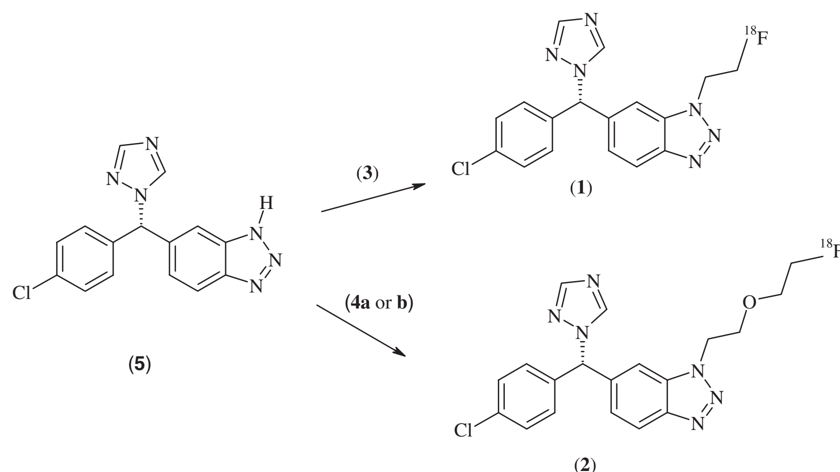


Scheme 1. ^{18}F-Labelled intermediates.



Scheme 2. Two-step synthesis of ^{18}F-labelled analogues.

Table 1. Radiochemical yields of compound **2**	
Precursor	Radiochemical yield (%)
4a	15 ± 3 (*n* = 2)
4b	5 ± 1 (*n* = 3)

n = Number of experiments.

analytical yield of the first step was between 76 and 84%. The highest decay-corrected (d.c.) radiochemical yield for compound **2** was obtained with **4a** (Table 1), due to tosylate's better leaving group character.[8] The radiochemical purity of compounds **1** and **2**, determined by analytical HPLC, was >96%. The radiochemical yields (d.c.) were in the range of 9–13% after 110–120 min synthesis from EOB (Table 2). The specific radioactivity, measured at the end of the labelling synthesis was 175 ± 7 GBq/μmol for compound **1** and 56 GBq/μmol for compound **2**, respectively.

One-step labelling

In order to perform the radiolabelling in one step, relevant precursors were synthesized (Scheme 3). Precursor **7** was synthesized in two steps. In the first step, 2-iodoethanol was reacted with **5**, which had been pre-treated with potassium hydroxide, to obtain the corresponding alcohol **6**. Then, 4-methylbenzenesulfonyl chloride was added to give **7**. Precursor **8** was synthesized by adding 2-bromoethyl ether to compound **5**, which had been pre-treated with potassium hydroxide. The precursors were ^{18}F-labelled with no-carrier-added [^{18}F]fluoride (Scheme 4). In the one-step synthesis the radiochemical yields (d.c.) for compounds **1** and **2** were 36–99%, after 75-min syntheses from EOB (Table 2). The specific radioactivities, measured at the end of the labelling syntheses, were 100 GBq/μmol for compound **1** and 80 GBq/μmol for compound **2**.

In the two-step ^{18}F-alkylation reaction, two significant products were formed, as alkylation occurred on the first and third nitrogen atoms of the triazole ring. The major

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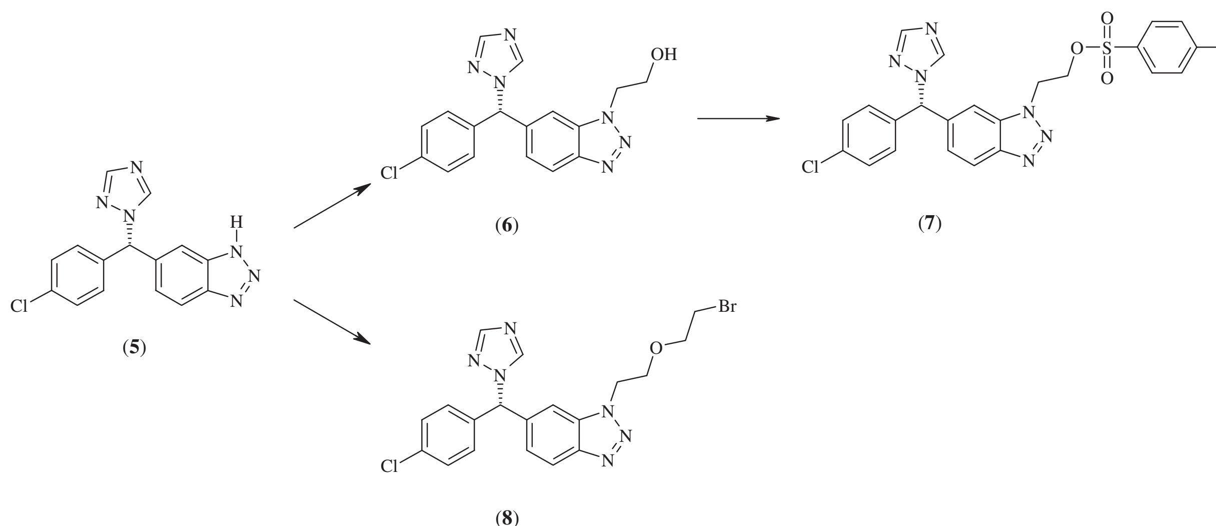
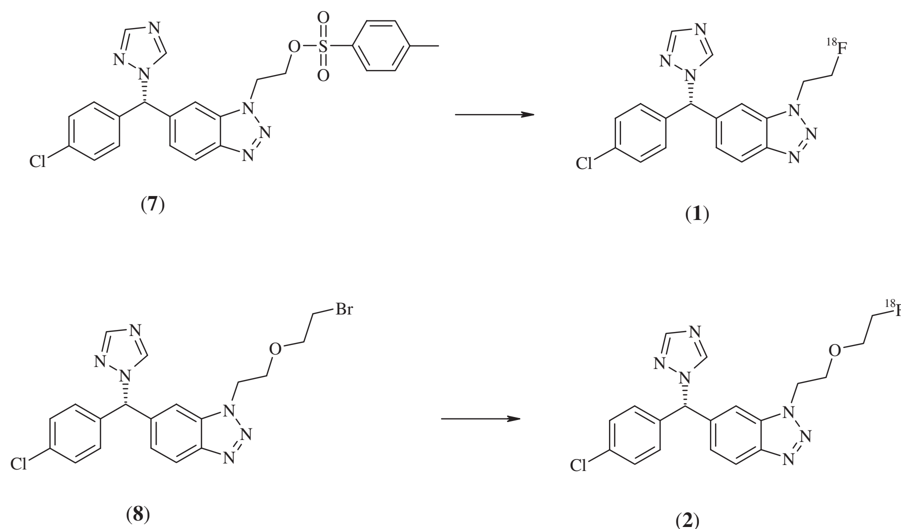
Table 2. Radiochemical yields for compounds **1** and **2**

Compound	Reaction steps	Radiochemical yield[a] (%)	Specific activity (GBq/μmol)[b]
1	One	>99 ($n=1$)	100 ($n=1$)
1	Two	11±2 ($n=7$)	175±7 ($n=2$)
2	One	36±13 ($n=4$)	80 ($n=1$)
2	Two	15±3 ($n=2$)	56 ($n=1$)

n = Number of experiments.
[a]Decay-corrected based on [^{18}F]fluoride at the start and radioactivity of HPLC-purified product.
[b]Ratio of radioactivity to amount of substance, decay-corrected to time at the start of synthesis.



Scheme 3. Precursor synthesis.



Scheme 4. One-step ^{18}F-labelling.

product was the desired product. This may be due to delocalization of negative charge in the base-generated anion in the triazole ring, with the major electron densities on the first and third nitrogen atoms. The identities of ^{18}F-labelled analogues **1** and **2** were assessed by HPLC comparison with the synthesized references. The structures of the precursors **7** and **8**, used in the one-step ^{18}F-labelling synthesis, were identified by NOE diff, HSQC and HMBC NMR analysis and shown to have the alkyl chains on the first nitrogen atom in both cases.

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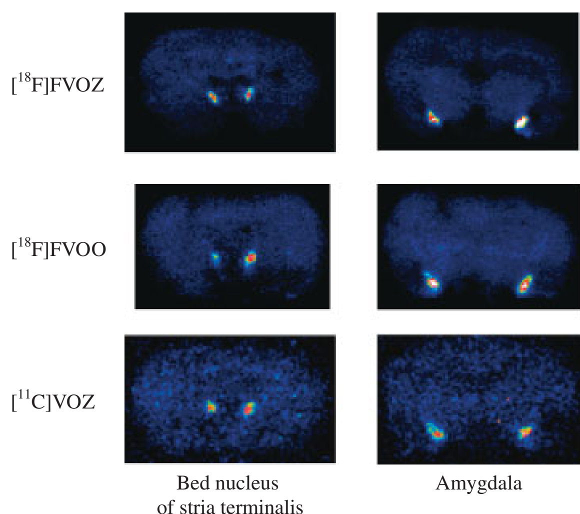

Figure 1. Autoradiographic images of [^{18}F]FVOZ, [^{18}F]FVOO and [^{11}C]VOZ in the male rat brain. This figure is available in colour online at www.interscience.wiley.com/journal/jlcr.

Analysis of radiolabelled metabolites in plasma

A metabolite study was performed on [^{18}F]FVOZ and [^{18}F]FVOO. For each radioligand one male rat was injected via the tail vein with 50 MBq. After 40 min, blood was collected and the protocol developed for metabolite analysis of [^{11}C]VOZ was followed.[1] Metabolite analysis of plasma revealed that 30% of [^{18}F]FVOZ and 9% of [^{18}F]FVOO were intact after 40 min of injection.

Autoradiography

Rat brain autoradiography was used to demonstrate the distribution of [^{18}F]FVOZ, [^{18}F]FVOO and [^{11}C]VOZ (Figure 1). The distribution patterns were similar for all tracers, with specific binding in the medial amygdala, bed nucleus of stria terminalis and preoptic area. By adding vorozole, binding of labelled vorozole in these regions was blocked. This result is consistent with an earlier report[9] that showed high amounts of aromatase activity in these regions of rat brain.

Experimental

General

Liquid chromatographic analysis was performed with a Hitachi LaChromElite, pump L-2130, injector L-220 and an L-2400 UV-detector in series with a β^+-flow detector. The following mobile phases were used: MeCN:H_2O (50:7) (A), 25 mM KH_2PO_4 (B), 0.05 M ammonium formate pH 3.5 (C) and MeCN (D). For analytical LC, a Discovery ODS, 5 μm × 250 mm × 4.6 mm column and an ACE 5 C18-HL 250 mm × 4.6 mm column were used at a flow rate of 1.5 ml/min. For semi-preparative LC, an ACE 5 C18-HL 250 mm × 10 mm column was used at a flow of 5 ml/min. Synthia®, an automated synthesis system, was used for LC injection and fraction collection. Data collection and LC control were performed with the use of a Beckman System Gold chromatography software package (USA). Radioactivity was measured in an ion chamber (Veenstra Instrumenten bv, VDC-202, Holland). For coarse estimations of radioactivity during synthesis, a portable dose-rate meter was used (Långenäs elektriska AB, Sweden). When analyzing the ^{18}F-labelled compounds, unlabelled reference substances were used for comparison in LC runs. Synthesis of the references was conducted under nitrogen atmosphere using dried glassware and magnetic stirring. All anhydrous solvents were bought from commercial suppliers. Mass spectra were recorded at a Quattro Premier from Waters, which has a triple quadrupole with electrospray ionization, operated in positive mode or on Finnigan AQA using mobile phases MeCN (0.1% formic acid) and H_2O (0.1% formic acid). A Gilson 322 pump and Phenomenex® Gemeni 5 μm C18 110A 150 mm × 3.00 mm column were also used. ^{1}H, ^{13}C, ^{19}F, NOE diff, HMBC and HSQC NMR spectra were recorded in $CDCl_3$ (7.26 ppm ^{1}H, 77.0 ppm ^{13}C) on a Varian Unity 400 spectrometer (400 MHz for ^{1}H, 100.6 MHz for ^{13}C and 376.3 MHz for ^{19}F nuclei) or on a Varian Inova spectrometer (500 MHz for ^{1}H and 125 MHz for ^{13}C nuclei). ^{19}F NMR spectra were recorded in $CDCl_3$, with $CFCl_3$ as the reference.

^{18}F-production

[^{18}F]Fluoride was produced at Uppsala Imanet using the Scanditronix MC17 Cyclotron and the ^{18}O(p, n) ^{18}F nuclear reaction through proton irradiation of ^{18}O-enriched water (95%, Rotem). The product solution of [^{18}F]fluoride in water was transferred from the cyclotron target by an HPLC pump and trapped on a QMA filter (ABX, advanced biochemical compounds, Pre-conditioned Sep-PAK®, Light QMA Cartridge with CO_3^{2-} as counter ions, Radeberg). The column was purged with helium for 1 min. The [^{18}F]fluoride adsorbed on the resin was eluted into a reaction vial with 2 ml of the following solution: 12 ml of a 96:4 (by volume) acetonitrile:water mixture containing 55.85 ± 0.37 mg (n = 4) of K2.2.2 and 12.73 ± 0.13 mg (n = 4) of K_2CO_3. The solution was then evaporated and co-evaporated with anhydrous acetonitrile to dryness in a nitrogen stream at 110°C.

General method for two-step/one-vessel ^{18}F-labelling

The dried complex $[K/K2.2.2]^{+18}F^-$ was dissolved in anhydrous DMF (0.2 ml). A solution of the first reagent ethane-1,2-diyl bis(4-methylbenzenesulfonate) was used in the synthesis of **1** and oxydiethane-2,1-diyl bis(4-methylbenzenesulfonate) was used in the synthesis of **2** in anhydrous MeCN (0.2 ml), and the reaction mixture was heated in a closed vessel at 70°C for 15 min. Following this reaction, a solution of the precursor **5** in anhydrous DMF (0.3 ml) and 1 M KOH (10 μl) was added. The reaction mixture was heated for another 15 min at 150°C. The crude product was dissolved in nanopure H_2O (2 ml) and injected onto the semi-preparative LC (**1** and **2**; t_R = 9.3 and 10.2 min, respectively), mobile phase C:D (55:45). The product was formulated with propylene glycol and phosphate buffer (pH 7.5, 1:16). Radiochemical purity (>98%) and analytical radiochemical yield (14–60%) were determined by analytical LC. Analytical LC (**1** and **2**; t_R = 4.3 and 4.9 min, respectively), mobile phase A:B (55:45).

General method for one-step ^{18}F-labelling

The dried complex $[K/K2.2.2]^{+18}F^-$ was dissolved in anhydrous DMF (0.2 ml). The precursor **7** or **8** dissolved in anhydrous DMF (0.3 ml) was added and the reaction mixture was heated in a closed vessel at 150°C for 15 min. The crude product was dissolved in nanopure H_2O (2 ml) and injected onto the semi-

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preparative LC (**1** and **2**; t_R = 9.3 and 10.2 min, respectively) mobile phase C:D (55:45). The product was formulated in propylene glycol and phosphate buffer (pH 7.5, 1:16). Radiochemical purity (>98%) and analytical radiochemical yield (21–59%) were determined by analytical LC. Analytical LC (**1** and **2**; t_R = 4.3 and 4.9 min, respectively), mobile phase A:B (55:45).

Precursor and reference compounds

*1-[2-(2-Bromoethoxy)ethyl]-6-[(4-chlorophenyl)(1H-1,2,4-triazol-1-yl)methyl]-1H-benzotriazole (**8**)*

To a solution of **5** (25 mg, 0.08 mmol) in DMF, KOH (1 M, 80 μl) was added. The solution was cooled to 0°C and 2-bromoethyl ether (100 μl, 0.8 μmol) was added. The mixture was brought to room temperature and stirred for 3.5 h. The crude product was extracted with CH_2Cl_2 and H_2O and further purified by preparative HPLC (CH_2Cl_2:MeOH, 9.5:0.5) to give the title compound **8** as an oil (11.8 mg, 31%). ^1H NMR ($CDCl_3$): δ 8.05–8.00 (m, 2H), 7.73–7.69 (m, 1H), 7.45–7.44 (m, 1H), 7.37–7.34 (m, 2H), 7.18–7.15 (m, 1H), 7.13–7.08 (m, 2H), 6.90 (s, 1H), 4.81 (dt, 2H), 3.96 (dt, 2H), 3.67 (dt, 2H), 3.27 (dt, 2H). ^{13}C NMR ($CDCl_3$): δ 152.8, 143.8, 137.4, 136.3, 129.9, 129.6, 127.7, 124.3, 120.7, 119.8, 111.9, 110.9, 71.3, 70.2, 67.2, 48.97, 30.4. LC-MS (ESI^+): *m/z* 462 $[M+H]^+$.

*2-{6-[(4-Chlorophenyl)(1H-1,2,4-triazol-1-yl)methyl]-1H-benzotriazol-1-yl}ethanol (**6**)*

To a solution of **5** (50 mg, 0.16 mmol) in DMF, KOH (1 M, 160 μl) was added. The solution was cooled to 0°C and 2-iodoethanol (13 μl, 0.16 μmol) was added. The mixture was heated to 80°C and stirred for 2 h. The crude product was extracted with CH_2Cl_2 and $NaHCO_3$ (sat.) and purified by preparative TLC (CH_2Cl_2/MeOH 9.5:0.5) to give the title compound **6** as an oil (17 mg, 30%). ^1H NMR ($CDCl_3$): δ 7.88–7.78 (m, 3H), 7.27–7.21 (m, 3H), 7.03–6.97 (m, 3H), 6.77 (s, 1H), 4.61 (dt, 2H), 4.07 (dt, 2H). ^{13}C NMR ($CDCl_3$): δ 152.4, 143.5, 137.5, 133.9, 129.6, 129.4, 127.6, 124.1, 120.5, 119.6, 110.8, 109.8, 66.9, 61.3, 50.8. LC-MS (ESI^+): *m/z* 355 $[M+H]^+$.

*2-{6-[(4-Chlorophenyl)(1H-1,2,4-triazol-1-yl)methyl]-1H-1,2,3-benzotriazol-1-yl}ethyl 4-methylbenzenesulfonate (**7**)*

To a solution of **6** (29 mg, 0.08 mmol) in pyridine at 0°C, 4-methylbenzenesulfonyl chloride (17 mg, 0.09 mmol) was added. The solution was stirred for 2.5 h. CH_2Cl_2 was added and the crude product was extracted with H_2O and further purified by preparative TLC (CH_2Cl_2/MeOH 9:1) to give the title compound **7** as a yellow solid (9.1 mg, 22%). ^1H NMR ($CDCl_3$): δ 8.08–8.01 (m, 2H), 7.53–7.47 (m, 2H), 7.41–7.33 (m, 4H), 7.26–7.12 (m, 5H), 6.90 (s, 1H), 4.87 (dt, 2H), 4.47 (dt, 2H), 2.39 (d, 3H). ^{13}C NMR ($CDCl_3$): δ 152.8, 146.0, 145.7, 145.5, 143.7, 135.8, 134.3, 133.9, 131.9, 130.0, 129.6, 127.8, 124.5, 120.9, 110.7, 68.3, 67.1, 47.5, 21.8. LC-MS (ESI^+): *m/z* 509 $[M+H]^+$.

*6-[(S)-(4-Chlorophenyl)(1H-1,2,4-triazol-1-yl)methyl]-1-(2-fluoroethyl)-1H-benzotriazole (**1**)*

To a solution of **5** (3.8 mg, 0.013 mmol) in anhydrous DMF (0.3 ml) and 1 M KOH (12.8 μl), 1-bromo-2-fluoroethane (1 μl, 0.013 mmol) was added. The reaction mixture was heated at 150°C for 30 min. The product was purified by preparative TLC (eluents C:D, 55:45) to give the title compound **1** (2.9 mg, 63%). Analytical LC (t_R = 4.3 min), eluents A:B (55:45). ^1H NMR ($CDCl_3$): δ 8.07 (s, 1H), 8.03 (s, 1H), 7.81–7.78 (m, 1H), 7.64–7.60 (m, 1H), 7.42–7.34 (m, 3H), 7.15–7.09 (m, 2H), 6.90 (s, 1H), 4.94–4.90 (m, 2H), 4.88–4.79 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 152.9, 143.7, 138.0, 136.3, 135.9, 135.2, 129.8, 129.6, 128.1, 124.4, 120.9, 110.8, 82.3 ($^3J_{C,F}$ = 174.8 Hz), 67.0, 49.0 ($^2J_{C,F}$ = 21.6 Hz). ^{19}F NMR ($CFCl_3$): δ −219.8 (m, F). LC-MS (ESI^+): *m/z* 357 $[M+H]^+$.

*6-[(S)-(4-Chlorophenyl)(1H-1,2,4-triazol-1-yl)methyl]-1-[2-(2-fluoroethoxy)ethyl]-1H-benzotriazole (**2**)*

To a solution of **8** (4.9 mg, 0.011 mmol) in THF, 1 M TBAF (31 μl in THF) was added, and the mixture was stirred for 4 h. The crude product was extracted with CH_2Cl_2 and H_2O. The product was purified by preparative HPLC to give the title compound **2** (2.6 mg, 61%). Analytical LC (t_R = 4.9 min), eluents A:B (55:45). ^1H NMR ($CDCl_3$): δ 8.54 (m, 1H), 8.06–7.99 (m, 2H), 7.71–7.68 (m, 2H), 7.38–7.32 (m, 2H), 7.13–7.09 (m, 2H), 6.89 (s, 1H), 4.85–4.78 (m, 2H), 4.25–4.18 (m, 2H), 4.03–3.94 (m, 2H), 3.68–3.54 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 152.0, 143.2, 142.1, 141.3, 134.7, 134.4, 133.7, 131.5, 125.1, 124.1, 114.0, 81.0, 68.2, 68.0, 64.5, 40.7. ^{19}F NMR ($CFCl_3$): δ −223.0 (m, F). LC-MS (ESI^+): *m/z* 401 $[M+H]^+$.

Biology

Frozen rat brains were sectioned (25 μm) with a cryomicrotome (Microm HM 560, Microm, Germany) and put on superfrost glass slides. The slides were kept in a freezer (−20°C) until they were used. At the start of the experiment, the slides were preincubated for 10 min in TRIS-HCl buffer (50 mM, pH 7.4). They were then transferred to containers containing [^{18}F]FVOZ, [^{18}F]FVOO or [^{11}C]VOZ in TRIS buffer. In a duplicate set of containers, 1 μM of unlabelled vorozole was added to block specific binding. After incubation for 50 min ([^{18}F]FVOZ and [^{18}F]FVOO) or 30 min ([^{11}C]VOZ), the slides were washed 3 × 2 min in buffer. The slides were dried in an oven (37°C) and then exposed to phosphor imaging plates (Molecular Dynamics, USA) for 4 h ([^{18}F]FVOZ and [^{18}F]FVOO) or 40 min ([^{11}C]VOZ) and scanned in a Phosphor Imager Model 400S (Molecular Dynamics).

Metabolite study

The metabolite analyses of [^{18}F]FVOZ and [^{18}F]FVOO in plasma were performed with one rat each 40 min after injection. The plasma was obtained using the reported method for [^{11}C]VOZ.[1] The sample was analyzed by HPLC to separate the radioligands from their radioactive metabolites. The sample (90 μl) was injected on an ACE 5 C18-HL 250 mm × 10 mm column, and the tracer and its metabolite were eluted with the solvents mixture C:D (**1** and **2**; 45:55 and 55:45 vol/vol, respectively) at a flow rate of 5 ml/min. The eluent from the column was collected in two fractions. The metabolite eluted in the first fraction (metabolites for compounds **1** and **2**; t_R = 1.9 and 1.9 min, respectively) and the tracer in the second fraction (**1** and **2**; t_R = 3.4 and 5.0 min, respectively). Observation of the UV peak from the unlabelled standard as well as the peak of labelled vorozole on a radio detector indicated that [^{18}F]FVOZ eluted in the second fraction. Even if no detectable radiopeak co-eluted with the unlabelled standard of FVOO, the fraction was collected and the radioactivity of the second fraction was measured in a γ-counter. After 40 min, 30% [^{18}F]FVOZ and 9% [^{18}F]FVOO were intact in the plasma.

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Conclusions

The ^{18}F-labelled vorozole analogues are tracers that can be used in PET for detection of the enzyme aromatase. [^{18}F]FVOO was metabolized more quickly than [^{18}F]FVOZ. The described one- and two-step syntheses give general methods to synthesize ^{18}F-labelled analogues. The developed one-step ^{18}F-fluorination method provides higher reproducibility and radiochemical yield and might easily be automated in the future.

Acknowledgement

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