Rapid Synthesis of *N,N'*-Disubstituted Piperazines. Application to the Preparation of No Carrier Added 1-(4-[^{18}F]Fluorophenyl)piperazine and of an [^{18}F]-Selective Ligand of Serotoninergic Receptors (5HT$_2$ antagonist)

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An efficient and rapid method of piperazine formation (>50%, 30 min) involving the reaction of *N,O,O'*-tris(toluene-*p*-sulfonyl)bis(2-hydroxyethyl)amine **3** and 4-fluoroaniline in an alcohol or in hexamethylphosphoramide has been developed. It has been applied to the preparation of 1-(4-[^{18}F]fluorophenyl)piperazine **6b**, a new precursor in [^{18}F]-labelling for positron emission tomography studies. Compound **6b** was obtained in 7–15% decay corrected radiochemical yield in a synthesis time of 145–165 min counted from the labelled precursor [^{18}F]fluoride and a radiochemical purity greater than 98% after HPLC purification. The utility of **6b** was demonstrated by the synthesis of the [^{18}F]naphthosultam **8b**, a selective antagonist of 5-HT$_2$ receptors. Compound **8b** was obtained radiochemically pure in 50 min from **6b** (including HPLC) and in an overall yield of 2.5–12% (decay corrected) from [^{18}F]fluoride.

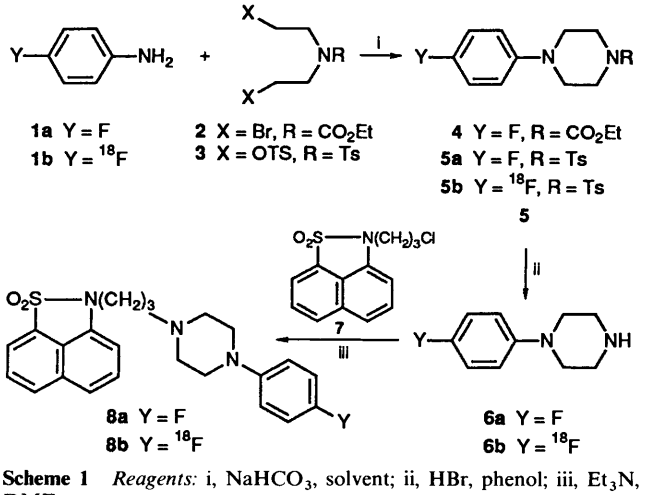
Positron emission tomography (PET) is a non-invasive technique in which positron-emitter labelled compounds are used as probes in the *in vivo* study of biochemical processes.[1] Among the positron emitting isotopes of major interest (^{11}C, ^{13}N, ^{15}O, ^{18}F) fluorine-18 (β^+: 96.9%) has the attraction of a relatively long half-life of 110 min, allowing multistep syntheses and the study of moderately slow physiological processes.[2] Moreover it can be readily produced and in large quantities in the nuclear reaction ^{18}O(p,n)^{18}F using a 16 MeV medical cyclotron. Fluorine itself forms a highly stable bond with carbon, is often considered to be isosteric with hydrogen, and its electronegativity and hydrogen bonding capability allow it to be a replacement of hydroxy. In addition, it appears in a large number of biologically active compounds.[3]

Production of radiopharmaceuticals labelled with short lived radionuclides for PET requires optimization of procedures or novel reactions so that all syntheses occur as efficiently and quickly as possible and that all handling and transfer is kept to a minimum. In addition, the preparation of radiopharmaceuticals, with a distribution based upon uptake by high affinity, limited capacity binding systems (receptor binding), requires labelling methods that will operate without added carrier fluorine in order to produce agents of high specific radioactivity. The limited availability of different ^{18}F-precursors[4] is one restriction in obtaining new molecules for PET. It is envisaged that access to a number of fluorine-18 labelled compounds of pharmaceutical interest (see refs. 5 and 6) might be possible *via* 1-(4-[^{18}F]fluorophenyl)piperazine **6b**.[7] One such compound would be the fluorine-18 naphthosultam derivative (2-{3-[4-(4-[^{18}F]fluorophenyl)piperazin-1-yl]propyl}-2*H*-naphth[1,8*cd*]-isothiazole 1,1-dioxide) **8b**, a potent and selective antagonist of the serotoninergic receptor 5-HT$_2$.[8]

Formation of **6b** by electrophilic substitution with [^{18}F]F$_2$ was not considered, as this method results in products of low specific radioactivity.[2,9] Direct introduction of [^{18}F]fluoride in a nucleophilic substitution was not a practical alternative due to the absence of an electron-withdrawing group *para* or *ortho* to the aromatic position of interest.[10,11] It was necessary, therefore, to introduce the fluoride at a stage prior to piperazine ring formation. We describe here a rapid ring closure between 4-fluoroaniline and derivatives of bis(2-hydroxyethyl)amine, providing a route to 1-(4-fluorophenyl)piperazine under conditions suitable for, and subsequently successfully transferred to, fluorine-18-chemistry.

Results and Discussion

N-Phenylpiperazines substituted at the *para* position with electron donating substituents have been obtained by ring closure of an appropriately substituted aniline and bis(2-chloroethyl)amine hydrochloride in the presence of sodium carbonate.[6] A 30% yield in a reaction time of 50 h was obtained. Similar yields resulted of the use of bis(2-hydroxyethyl)amine and hydrobromic acid at 180–190 °C.[12] The reaction of α,α,α-[^{18}F]trifluorotoluidine with *N,N*-bis-(2-bromoethyl)-*N*-(methoxycarbonyl)amine yielded the expected piperazine in 50% yield in 2 h.[13] This is the only example reported involving a short-lived isotope, but has the drawback of being performed at a carrier level. The characteristics of these reactions being not compatible with fluorine-18 chemistry (no solvent, long reaction time, excess of amine), we have studied the rapid synthesis of (4-fluorophenyl)piperazines from 4-fluoroaniline and suitable substrates under stable isotope conditions (Scheme 1).



Scheme 1 *Reagents:* i, $NaHCO_3$, solvent; ii, HBr, phenol; iii, Et_3N, DMF

Table 1 Reaction of 4-fluoroaniline with bis(2-hydroxyethyl)amine derivatives (equimolar ratio) at 130 °C

Reagent	Solvent	*t*/min	Yield (%)
2	None	120	12
3	None	120	18
2 + $NaHCO_3$	DMSO	20	5
2 + $NaHCO_3$	HMPA	15	15–20
2 + $NaHCO_3$	HMPA	60	18
3 + $NaHCO_3$	HMPA	30	50–60
3 + $NaHCO_3$	HMPA	60	58
3 + Cs_2CO_3	DMF	120	37
3 + $NaHCO_3$	Butanol	30–120	44–54

Table 2 Reaction of 4-[^{18}F]fluoroaniline **1b** with bis(2-hydroxyethyl)amine derivatives in the presence of $NaHCO_3$

Reagent	Solvent	*T*/°C	*t*/min	Yield of **5b**[a] (%)
2	HMPA or butanol	130	30	unidentified product(s)
3	HMPA or toluene DMSO or DMF	130	30	no reaction
3	butanol	130	30	27–35
3	butanol	150–170	30–40	42–62
3	butanol	180[b]	7	35
3	octanol	180	40	57

[a] Determined by radio TLC. [b] Under these conditions, the solvent was evaporated during the reaction.

The results presented in Table 1 showed that ethyl 4-(4-fluorophenyl)piperazine-1-carboxylate **4** and 4-(4-fluorophenyl)-1-toluene-*p*-sulfonylpiperazine **5a** were obtained respectively in 15–20 and 50–60% yields in 15–30 min when using hexamethylphosphoramide (HMPA) as a solvent in the presence of sodium hydrogen carbonate, conditions recently used in the alkylation of aromatic amines.[14] Similar results were obtained in butanol but no improvement was observed with longer reaction times or using caesium carbonate as a base.[15]

The rapid deprotection of **5a** in 1-(4-fluorophenyl)piperazine **6a** (66% yield in 30 min) was achieved with hydrobromic acid and phenol according to a previously described method.[16]

These results were transferred to fluorine-18 chemistry. 4-[^{18}F]Fluoroaniline **1b** was prepared in two steps (40% decay corrected) from [^{18}F]potassium, caesium[10] or tetramethylammonium fluoride.[17] Its reaction as a free base with **2** in HMPA resulted in formation of a [^{18}F]-labelled polar product that we have not attempted to identify. With amine **3**, under the same conditions, no reaction was observed and 4-[^{18}F]fluoroaniline was recovered. Attempts were made in a variety of solvents and under different conditions (temperature and time). The crude reaction mixture was analysed by radio TLC and the ratio (expressed in terms of percentage of the total radioactivity) of 4-(4-[^{18}F]fluorophenyl)-1-toluene-*p*-sulfonylpiperazine **5b** is shown in Table 2. The best conditions for the formation of **5b** were obtained in octanol or butanol, in the reaction between **1b** and **3**. Radio TLC showed only the presence of the cycloadduct **5b** (57–62%) with unchanged [^{18}F]fluoroaniline **1b**.

Although surprising, it is not unusual for a different result to be obtained when a reaction is attempted at the tracer level since all chemical reagents are in large excess when compared to the radioactive precursor.[18] Moreover, competitive side reactions of non-radioactive chemical impurities could not be ruled out in the reactions using **1b** which was quickly purified by Sep-Paks. The unstability of the ethoxycarbonyl amine **2**[19] compared to the sulfonamide **3** and a possible reaction of HMPA at temperatures higher than 120 °C[20] could explain the by-product(s) observed in the reaction of **1b** with the bis(bromoethyl) derivative **2**.

The treatment of **5b** with hydrobromic acid and phenol at 110–120 °C for 20–30 min followed by a silica Sep-Pak purification yielded the unprotected fluorophenylpiperazine **6b** in 42–76% radiochemical yield from **5b** (7–15% from [^{18}F]-fluoride, decay corrected) and a radiochemical purity greater than 80%. Purification by HPLC on normal phase gave **6b** analytically pure. The synthesis time of the piperazine **6b** was 80–100 min counted from **1b** or 145–165 min from the labelled fluoride. Typically, 16.3 MBq (0.47 mCi) of **6b** were prepared from 148.1 MBq (4.27 mCi) of 4-[^{18}F]fluoroaniline in 80 min, and overall from 603.1 MBq (16.8 mCi) of [^{18}F]fluoride in 150 min. A preliminary measurement of the specific radioactivity of **6b** was found to be 87 MBq μmol^{-1} (2.36 mCi μmol^{-1}) starting from 333 MBq (9 mCi) of [^{18}F]fluoride. This value, which was lower than expected (see ref. 21), might arise from fluoride contaminations of both the target water and the inorganic reagents used.[1]

The utility of **6b** as a precursor in radiolabelling was demonstrated by the synthesis of the *N*,*N*′-disubstituted piperazine **8b**. Literature preparation of this naphthosultam involves *N*-alkylation of commercial 1-(4-fluorophenyl)piperazine with the naphthosultam derivative **7** (toluene, Et_3N, reflux, several hours, 83%).[8] Using DMF (*N*,*N*-dimethylformamide) as a solvent at 110 °C for 20 min we have been able to obtain **8a** in 77% yield in 20 min. Under these conditions, the [^{18}F]piperazine **6b** was alkylated by the chlorocompound **7** and the [^{18}F]-labelled derivative **8b** was obtained after Sep-Pak purification in 35–84% yield from **6b** (radiochemically purity > 85%). HPLC on normal phase gave **8b** analytically pure (overall synthesis time from **6b** including HPLC: 50 min).

All the new labelled compounds were identified by comparison of their retention times in HPLC (**6b** and **8b**), R_f in TLC (**5b**, **6b** and **8b**) and co-elutions with authentic samples. None of the reaction (or purification) times have been optimized. Work is in progress to shorten the overall synthesis time using microwave activation.[22] This would allow the preparation of sufficient quantities of **8b** for the study of the serotoninergic system in living brain by PET.

In conclusion the present work provides an efficient and rapid route (yield > 50% in 30 min) to *N*-(fluorophenyl)piperazines from fluoroaniline and tris(toluene-*p*-sulfonyl)bis(2-hydroxyethyl)amine. The method has been successfully applied to the preparation of 1-(4-[^{18}F]fluorophenyl)piperazine. A rapid alkylation of this new labelled precursor has allowed the synthesis of the [^{18}F]naphthosultam derivative **8b** (2.5–12% radiochemical yield from [^{18}F]fluoride, decay corrected, in 185–200 min overall preparation time) and could be extended to the synthesis of other [^{18}F]radiopharmaceuticals.

Experimental

General.—IR spectra were recorded on a Perkin-Elmer 684 spectrometer and ^{1}H NMR spectra on either a Varian EM360A or a JEOL FX200 at 60 or 200 MHz respectively, using deuteriochloroform as solvent and tetramethylsilane as internal reference. The ^{13}C and ^{19}F NMR spectra were obtained on a Bruker WP 80 SY at 20.15 and 79.39 MHz respectively. All chemical shifts (δ) are quoted in parts per million and the coupling constants (J) are given in Hz. The m.p.s were determined on a Reichert hot stage microscope and are uncorrected.

No carrier added aqueous [^{18}F]fluoride was produced by the ^{18}O(p,n) reaction using enriched water (90–98%, ^{18}O, 1 cm^3) using a baby cyclotron (CGR Mev 325) and a stainless steel or titanium target. Bombardment was carried out for 60 min with a 15 μA beam of 16 MeV. Only a small part [around 37 MBq

(10 mCi)] of the total radioactivity was used for the experiments. The [^{18}O]H_2O was separated from [^{18}F]fluoride using a Bio-Rad [0.2 g, AG 1-X8 Resin (100–200 mesh, chloride form] anion exchange resin, the fluoride eluted from the column with water (1 cm^3) then aqueous potassium carbonate (0.5 cm^3, 6 mg cm^{-3}).[2,9]

Radioactivity determinations were carried out by a Capintec Radioisotope Calibrator (CRC-12i). Identification and radiochemical purities were determined by TLC on Merck $60F_{254}$ (5735) silica gel plates using a Berthold automatic TLC-linear analyser, and authentic stable isotope samples as reference.

Preparative HPLC was carried out on a Waters Associates HPLC system consisting of two pumps (501) with automated gradient controller (680), U6K injector and UV detector (M 490) in series with a scintillation (Nardeux) detector. Separations were performed on a normal phase column (Waters μ Porasil, 300 × 7.8 mm, 10 μm). The integrations of UV absorbance and radioactivity were carried out with a Waters M745 integrator.

Tetrahydrofuran (from sodium–benzophenone), diethyl ether (from CaH_2), 40–65 °C light petroleum (from P_2O_5), hexamethylphosphoramide (HMPA) and triethylamine were distilled before use. Other solvents were purchased to the standard required (anhydrous, HPLC or analytical grade). *N,N*-Bis-(2-bromoethyl)-*N*-ethoxycarbonylamine **2**,[23] *N,O,O'*-tris-(toluene-*p*-sulfonyl)bis(2-hydroxyethyl)amine **3**[24,25] were prepared as described in the literature.

Ethyl 4-(4-*Fluorophenyl*)*piperazine*-1-*carboxylate* **4**.—*Method A*. A mixture of **2** (0.1 g, 0.33 mmol) and 4-fluoroaniline (0.036 g, 0.03 cm^3, 0.33 mmol) was heated at 130 °C for 2 h. The mixture was purified by column chromatography on silica gel using ether–light petroleum (1:1) as eluent, giving the compound **4** (0.01 g, 12%) as a white powdery solid.

Method B. A solution of **2** (0.1 g, 0.33 mmol), 4-fluoroaniline (0.036 g, 0.03 cm^3, 0.33 mmol) and $NaHCO_3$ (0.05 g, 0.66 mmol) in HMPA (0.5 cm^3) was heated at 130 °C for 15 min. After cooling, the mixture was partitioned between water and dichloromethane, the organic phase separated and dried (Na_2SO_4), and the solvent evaporated under reduced pressure. Purification by column chromatography on silica gel, using ether–light petroleum (1:1) as eluent, gave **4** (0.015 g, 18%), m.p. 59–61 °C (Found: C, 61.9; H, 6.8; F, 7.7; N, 10.9. $C_{13}H_{17}FN_2O_2$ requires C, 61.9; H, 6.75; F, 7.5 N, 11.1%); ν_{max}(KBr)/cm^{-1} 1700 (C=O); δ_H(200 MHz) 1.29 (3 H, t, *J* 7, CH_3), 3.06 (4 H, t, *J* 5, CH_2NCO_2), 3.63 (4 H, t, *J* 5, CH_2NAr), 4.17 (2 H, q, *J* 7, CO_2CH_2) and 6.89–6.98 (4 H, m, aryl); δ_C(20.15 MHz) 14.7 (CH_3), 43.8 and 50.5 (NCH_2CH_2N), 61.4 (CO_2CH_2), 115.5 (d, J_F 22.2, aryl), 118.5 (d, J_F 7.2, aryl), 148.1 (aryl), 155.5 (CO_2) and 151.7–163.6 (d, J_F 240, aryl); δ_F −123.96; *m/z* 252 (M^+, 17%), 223 (1.5), 207 (2.6), 179 (1.4), 150 (26), 123 (13), 122 (12.5), 95 (6.1) and 56 (100).

4-(4-*Fluorophenyl*)-1-*toluene*-p-*sulfonylpiperazine* **5a**.—*Method A*. A mixture of **3** (0.15 g, 0.26 mmol) and 4-fluoroaniline (0.025 cm^3, 0.26 mmol) was heated at 130 °C for 2 h. The mixture was purified by column chromatography on silica gel, using ether–light petroleum (1:1) as eluent to give the title compound (0.016 g, 18%), as a white powdery solid.

Method B. A solution of **3** (0.15 g, 0.26 mmol), 4-fluoroaniline (0.025 cm^3, 0.26 mmol) and $NaHCO_3$ (0.044 g, 0.52 mmol) in HMPA (0.5 cm^3) was heated at 130 °C for 1 h. After cooling, the mixture was partitioned between water and dichloromethane, the organic phase separated and dried (Na_2SO_4), and the solvent evaporated under reduced pressure. Purification by column chromatography on silica gel using ether–light petroleum (1:1) as eluent gave **5a** (0.051 g, 58%) as a white powdery solid. R_f (CH_2Cl_2–MeOH 95:5) 0.85; R_f (ether–light petroleum 1:1) 0.49; m.p. 189–191 °C (Found: C, 59.8; H, 5.5; N, 8.0; S, 9.5. Calc. for $C_{17}H_{19}FN_2O_2S$: C, 61.1; H, 5.7; N, 8.4; S, 9.6%); ν_{max}(KBr)/cm^{-1} 2840, 1510, 1440, 1350, 1340 and 1160; δ_H(200 MHz) 2.43 (3 H, s, $ArCH_3$), 3.15 (8 H, s, NCH_2CH_2N), 6.77–6.98 (4 H, m, aryl), 7.34 (2 H, d, *J* 8, aryl) and 7.67 (2 H, d, *J* 8, aryl); δ_C(20.15 MHz) 21.5 ($ArCH_3$), 46.2 and 50.3 (NCH_2CH_2N), 115.7 (d, J_F 22.2, aryl), 118.9 (d, J_F 7.6, aryl), 128.0 (aryl), 129.8 (aryl), 133.1 (aryl), 143.9 (aryl), 147.5 (aryl) and 152.1–163.9 (d, J_F 240, aryl); δ_F(75.39 MHz) −123.04; *m/z* 334 (M^+, 15%), 179 (100), 155 (18.5), 91 (56) and 56 (65).

1-(4-*Fluorophenyl*)*piperazine* **6a**.—A solution of **5a** (0.04 g, 0.12 mmol) and phenol (0.02 g, 0.24 mmol) in aqueous HBr (1 cm^3, 48% solution in water) was heated under reflux for 30 min. After cooling, the mixture was made basic with NaOH (2 mol dm^{-3}) and then extracted with dichloromethane. The organic phase was separated, dried (Na_2SO_4), and the solvent evaporated under reduced pressure. Purification by column chromatography on silica gel, using CH_2Cl_2–MeOH–Et_3N (5:1:0.06), gave the title compound (0.014 g, 66%) as a brown oil.[6,12] R_f (CH_2Cl_2–MeOH–NEt_3 5:1:0.06) 0.42; ν_{max}(film)/cm^{-1} 2940, 2810, 1505, 1450, 1230 and 1160; δ_H(60 MHz) 3.1 (8 H, s, NCH_2CH_2N) and 6.8–7.1 (4 H, m, aryl); *m/z* 180 (M^+, 76%), 138 (100), 122 (16), 95 (22), 84 (13), 75 (15) and 56 (30).

2-{3-[4-(4-*Fluorophenyl*)*piperazin*-1-*yl*]*propyl*}-2H-*naphth*-[1,8-cd]-*isothiazole* 1,1-*Dioxide*, RP 62203 **8a**.—2-(3-Chloropropyl)-2*H*-naphth[1,8-*cd*]isothiazole 1,1-dioxide **7** (0.05 g, 0.18 mmol) was added to a solution of 1-(4-fluorophenyl)-piperazine (0.064 g, 0.36 mmol) and triethylamine (0.054 g, 0.075 cm^3, 0.54 mmol) in DMF (0.75 cm^3) and the mixture heated at 110 °C for 20 min. It was then partitioned between ethyl acetate and water, the organic phase separated and dried (Na_2SO_4), and the solvent evaporated under reduced pressure. Purification by column chromatography on silica gel, using ethyl acetate as solvent gave the title compound (0.058 g, 77%) as a white powdery solid. R_f (light petroleum–AcOEt, 1:1) 0.35; m.p. 95–96 °C (lit.,[8] 95–97 °C); ν_{max}(KBr)/cm^{-1} 2940, 2820, 1585, 1505, 1490, 1450, 1320, 1170 and 1130; ^{1}H NMR and mass spectrometry data were in agreement with those reported previously.[8]

4-[^{18}F]*Fluoronitrobenzene*.[10]—Aqueous [^{18}F] fluoride was added to a mixture of K_2CO_3 (5 mg, 36 μmol) and Kryptofix222 (25 mg, 66.4 μmol) and the water evaporated azeotropically (acetonitrile) at 110 °C under a stream of N_2. 1,4-Dinitrobenzene (5 mg, 29.7 μmol) in DMSO (0.3 cm^3, dry) was then added and the mixture heated at 140 °C for 20 min. After cooling, water (1 cm^3) was added and the mixture loaded onto a C_{18} Sep-Pak (pre-wet with methanol and water). The Sep Pak was rinsed with water (5 cm^3) and dried under pressure before elution of 4-[^{18}F]fluoronitrobenzene with THF (3 cm^3), and used in crude form. Average radiochemical yields: 35–75% decay corrected; radio chemical purity >85%; overall synthesis time: 45 min.

4-[^{18}F]*Fluoroaniline* **1b**.[11]—The 4-[^{18}F]fluoronitrobenzene in THF (2 cm^3) was added to a mixture of 10% palladium on carbon (15 mg) and hypophosphoric acid (0.1 cm^3) and heated at 70 °C for 10 min. After cooling the mixture was loaded onto a C_{18} Sep-Pak (pre-wet with THF) and eluted onto a K_2CO_3 column. Elution of the column with ether followed by evaporation of the solvent under reduced pressure, gave the compound **1b**, R_f 0.67 (CH_2Cl_2–MeOH, 95:5). Average radiochemical yield: 25–40% from [^{18}F]fluoride, radiochemical purity 74–100%; 65–70 min from [^{18}F]fluoride.

4-(4-[^{18}F]*Fluorophenyl*-1-*toluene*-p-*sulfonyl*)*piperazine* **5b**.—The 4-[^{18}F]fluoroaniline in dichloromethane (0.2 cm^3) was added to the tristosylate **16** (15 mg, 26.4 μmol) and $NaHCO_3$ (10 mg, 119 μmol) and the solvent evaporated at 30 °C under a stream of nitrogen. After addition of butanol (0.2 cm^3) the mixture was heated at *ca.* 120–180 °C for 7–30 min. On cooling, dichloromethane (1 cm^3) was added and the mixture loaded onto a silica-gel Sep-Pak (pre-wet with dichloromethane). Elution with dichloromethane (3 cm^3) and evaporation of the solvent under reduced pressure gave the N-*toluenesulfonyl-piperazine* **5b**. R_f (CH_2Cl–MeOH, 95:5) **5b** 0.85; **1b** 0.60.

1-(4-[^{18}F]*Fluorophenyl*)*piperazine* **6b**.—A solution of **5b** in dichloromethane (0.2 cm^3) was added to phenol (15 mg) and the solvent evaporated under a stream of nitrogen. Aqueous hydrogen bromide (0.1 cm^3, 48% in H_2O) was then added and the mixture heated at 140 °C for 30 min. On cooling, the mixture was partitioned between water and dichloromethane and the solution made basic with aqueous NaOH (5 mol dm^{-3}). The organic phase was separated and the aqueous layer extracted with dichloromethane. The combined organic phase was dried (Na_2SO_4 column) and the solvent removed under reduced pressure to give **6b** with unchanged **5b** and **1b** [R_f (CH_2Cl_2–MeOH–NEt_3, 5:1:0.06) **6b** 0.42; **5b** 0.97; **1b** 0.76]. The purification was carried out by loading onto a silica-gel Sep-Pak (pre-wet with AcOEt). The compounds **5b** and **1b** were eluted with ethyl acetate (4 cm^3) and the piperazine **6b** (radiochemical purity >98%) with a mixture of CH_2Cl_2–MeOH–NEt_3 (5:5:1; 5 cm^3). **6b** can also be purified by HPLC [CH_2Cl_2–MeOH–NEt_3, 83:16:1, isocratic, flow 1 cm^3 min^{-1}, λ: 354 nm, t_R 14 min].

2-{3-[4-(4-[^{18}F]*Fluorophenyl*)*piperazin*-1-*yl*]*propyl*}-2H-*naphth*[1,8-cd]*isothiazole* 1,1-*Dioxide*, [^{18}F]RP 62203 **8b**.—A mixture of 1-(4-[^{18}F]fluorophenyl)piperazine **6b**, naphthosultam derivative **7** (5 mg, 0.024 mmol) and triethylamine (0.01 cm^3) in DMF (0.2 cm^3) was heated at 120 °C for 20 min. After cooling, the mixture was loaded onto a silica gel Sep-Pak (pre-wet with ethyl acetate) and eluted with ethyl acetate (5 cm^3). Evaporation of the solvent under reduced pressure gave *compound* **8b** (radiochemical purity >85%) [R_f (EtOAc) 0.69] which can be purified by HPLC [heptane–AcOEt, 40:60, isocratic, flow 1.5 cm^3 min^{-1}, λ: 354 nm, t_R 16.5 min].

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