Journal of Labelled Compounds and Radiopharmaceuticals
J Label Compd Radiopharm 2007; **50**: 1169–1175.
Published online 10 September 2007 in Wiley InterScience
(www.interscience.wiley.com). DOI: 10.1002/jlcr.1413

JLCR

Research Article

N-2-(4-*N*-(4-[^{18}F]Fluorobenzamido)phenyl)-propyl-2-propanesulphonamide: synthesis and radiofluorination of a putative AMPA receptor ligand

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Received 15 November 2006; Revised 31 January 2007; Accepted 1 June 2007

Abstract: Arylpropylsulphonamides are in the focus of research as α-amino-3-hydroxy-5-methyl-4-isoxazolpropionic acid (AMPA) receptor ligands. A new fluorine-18-labelled potentiator of AMPA receptors was synthesized as a potential radiotracer for cerebral imaging with positron emission tomography. Using *N*-2-(4-*N*-(4-nitrobenzamido)-phenyl)-propyl-2-propanesulphonamide (**7**) as labelling precursor for a Kryptofix 2.2.2®/K_2CO_3-activated nucleophilic radiofluorination, the putative AMPA receptor ligand *N*-2-(4-*N*-(4-[^{18}F]fluorobenzamido)phenyl)-propyl-2-propanesulphonamide [^{18}F]**8** was obtained in one step. Optimization of the reaction parameters time, temperature, solvent and concentration gave a radiochemical yield of 38 ± 8% at 180°C in dimethylsulphoxide within 30-min reaction time. After a solid-phase extraction followed by a high-performance liquid chromatography separation, the product could be obtained in radiochemical yields of 5 ± 1.5%. Radiochemical purity was higher than 95% and the specific activity amounted to 77 ± 40 GBq/μmol. First *in vitro* assays with rat brain slices revealed a high non-specific binding and a uniform distribution of [^{18}F]**8** not lending it for *in vivo* imaging purposes.

Keywords: AMPA receptor ligand; n.c.a. radiofluorination; potentiator; fluorine-18; positron emission tomography

Introduction

As the major excitatory neurotransmitter in the mammalian central nervous system, glutamate activates a diversity of ionotropic and metabotropic receptors. The ionotropic subspecies of these receptors are named after the first identified selective agonists, which were *N*-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazolpropionic acid (AMPA) and kainate.[1] The AMPA receptor subtype is known to play an important role in memory and learning,[1] but also seems to play a significant role in the aetiology of disorders of the human brain, such as ischaemic stroke or epilepsy.[2]

Whereas agonists for this subclass of receptors mainly base on the structure of AMPA itself and derived compounds, antagonists with a significant affinity for the AMPA receptor consist mainly of two classes of compounds, namely quinoxalinediones and related structures (e.g. NBQX **1**) or 2,3-benzodiazepines (e.g. GYKI 53655 **2**) (for structures see Figure 1).[3]

Further on there exist allosteric modulators, which do not inhibit or excite the receptor directly. However, they are of great interest, as they amplify the effects of agonists or antagonists on the receptor. The so-called AMPAkines, a series of benzamides (for example, Aniracetam **3** and CX 516 **4**, see Figure 1), showed promising effects as positive modulators (also called potentiators) and have lately been of great interest for potential use as drugs for memory enhancement.

The labelling of such an AMPAkine with fluorine-18 could lead to a new class of radioligands that would enable a first look at the AMPA receptor system *in vivo*. With tritiated LY395153 (**5**, see Figure 1), Zarrinmayeh *et al.* described a molecule with a benzamide structure and sulphonamide functionality, which showed promising results during *in vitro* tests using rat cortical membranes or recombinant human GluR4 receptors.[4,5] The *in vitro* binding in rat cortex, but also at

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recombinant human GluR4 receptors, revealed a reasonable specific binding. This molecule was the origin for the synthesis of a labelled potentiator that could be a potential radiotracer for cerebral imaging. Since the benzamide and sulphonamide moieties are the major binding parts of the molecule to the receptor, it could be hoped that the potency of the potentiator is not affected by substitution of a hydrogen atom with a fluorine atom on the aromatic ring. Since the aminocarbonyl moiety as electron-withdrawing group enables nucleophilic labelling in para-position of the arene,[6] with fluorine-18 under activation with Kryptofix 2.2.2®, this was attempted according to Scheme 1.[7]

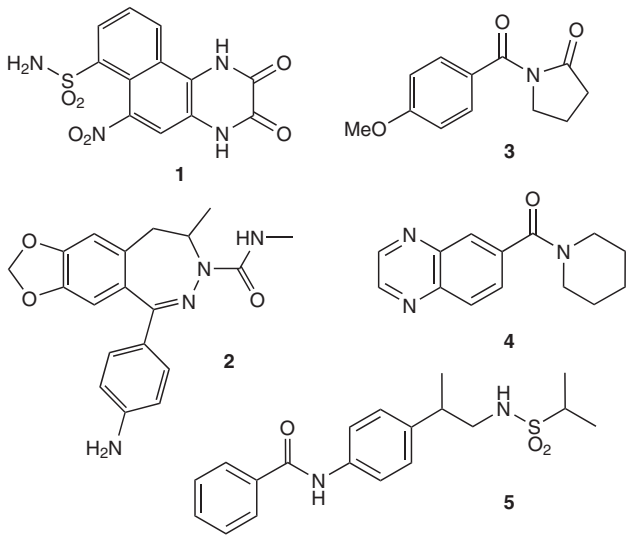


Figure 1 Examples of AMPA antagonists and allosteric modulators.

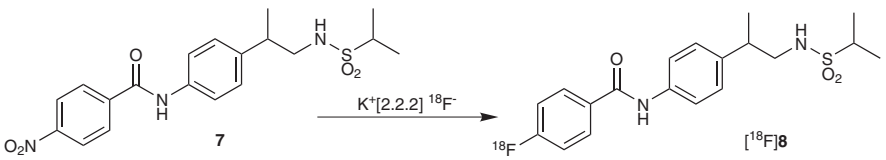
Results and discussion

Preparation of precursor and standard

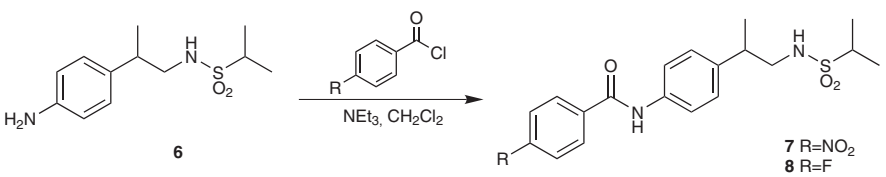
The authentic compound *N*-2-(4-*N*-(4–fluorobenzamido)phenyl)propyl-2-propanesulphonamide (**8**) and the corresponding nitro derivative **7** to be used as labelling precursor were synthesized following the procedure by Zarrinmayeh *et al.*[4] with comparable results. One exception was the formation of the intermediate *N*-2-(4-(*N*′,*N*′-dibenzylamino)phenyl)propyl-2-propanesulphonamide, which was obtained in significantly lower yields of 21% instead of 63% as reported.[4] This is probably due to utilization of triethylamine as given in the instructions for synthesis in the supporting information provided in Zarrinmayeh *et al.*,[4] instead of diaza(1,3)bicyclo[5.4.0]undecane (DBU) as originally suggested.[4]

The intermediate *N*-2-(4-aminophenyl)propyl-2-propansulphonamide (**6**) was synthesized in five steps from 4-aminobenzyl cyanide. Products **7** and **8** were obtained through reaction of compound **6** with 4-nitrobenzoyl chloride and 4-fluorobenzoyl chloride, respectively (see Scheme 2). Yields were 70 and 90% for compounds **7** and **8**, respectively.

Purification of compounds **7** and **8** was not possible with (*flash*-)column chromatography or preparative thin-layer chromatography (TLC). Several eluent mixtures were applied using TLC and two of them, which showed promising results, were utilized for (*flash*-) column chromatography and preparative TLC. But neither ethyl acetate/*n*-hexane (50/50; v/v) nor acetone/*n*-hexane (50/50; v/v) gave a significant raise in purity. Best results were acquired through recrystallization from acetone/*n*-hexane, which raised the purity up to ~98% (determined by high-performance liquid



Scheme 1 Radiosynthesis of *N*-2-(4-*N*-(4-[^{18}F]fluorobenzamido)phenyl)-propyl-2-propanesulphonamide [^{18}F]**8**.



Scheme 2 Synthesis of *N*-2-(4-*N*-(4-nitrobenzamido)phenyl)propyl-2-propanesulphonamide (**7**) and *N*-2-(4-*N*-(4-fluorobenzamido)phenyl)propyl-2-propanesulphonamide (**8**).

DOI: 10.1002.jlcr

chromatography, HPLC). To achieve higher grades of purity, a preparative HPLC was deployed. Thereby ⩾99% of pure compounds **7** and **8** could be isolated.

Since precursor **7** was not easily available in high-grade purity, labelling reactions were performed using the ~98% pure product. Unless other numbers are given, all labelling experiments were repeated three times and average values are given.

Optimization of labelling conditions

After the production of [^{18}F]fluoride through the ^{18}O(p,n)^{18}F nuclear reaction on enriched [^{18}O]H_2O, the fluoride was azeotropically dried in the presence of Kryptofix 2.2.2® and K_2CO_3 and then utilized in a nucleophilic reaction[8] with the nitroprecursor **7** to give n.c.a. *N*-2-(4-*N*-(4-[^{18}F]fluorobenzamido)phenyl)-propyl-2-propanesulphonamide ([^{18}F]**8**).

No noteworthy formation of radioactive by-products occurred until 30 min of reaction time. However, yields of by-products varied between 2 and 10% after 60 min depending on the reaction conditions.

In order to optimize the conditions of the radiofluorination reaction, different solvents, temperatures and concentrations were used. Optimization started with the variation of solvents at selected reaction temperatures and times. Since the precursor is not sufficiently soluble in acetonitrile, *N,N*–dimethylformamide (DMF), dimethylacetamide (DMA) and dimethylsulphoxide (DMSO) were tested. Results with DMF and DMA were rather unsatisfactory. Even though the temperature was risen from 130 to 150°C, radiochemical yields did not exceed 5% after 60 min and several by-products occurred in radiochemical yields as high as those of the desired product [^{18}F]**8**. DMSO proved to be the most suitable solvent for the aromatic radiofluorination of **7**. As shown in Figure 2, very high temperatures and extended reaction times were necessary in order to achieve satisfactory radiochemical yields. Radio–TLC control showed that precursor **7** and the labelled product [^{18}F]**8** were stable under these conditions, and that within 30 min by-products occurred only with small radiochemical yields. Therefore, work was continued using these conditions.

The concentration of precursor **7** was varied between 0.015 and 0.049 mol/l. Figure 3 illustrates that radiochemical yields rose with higher concentrations as expected; however, significantly lower yields were observed at a high concentration of 0.049 mol/l. Because preliminary experiments showed higher yields when using equimolar amounts of Kryptofix and precursor, all experiments were performed under these conditions. The lower yields at high concentrations may be caused by the resulting high overall concentrations in the reaction solution. A concentration of 0.035 mol/l showed highest yields (see Figure 3). Thus, in summary, the optimized reaction conditions correspond to a concentration of 0.035 mol/l of precursor in DMSO at a temperature of 180°C with an equimolar amount of Kryptofix®. Radiochemical yields are 38 ± 8% after 30-min reaction time ($n = 10$) and raise up to 63 ± 5% after 60-min reaction time ($n = 5$) (see Figure 4).

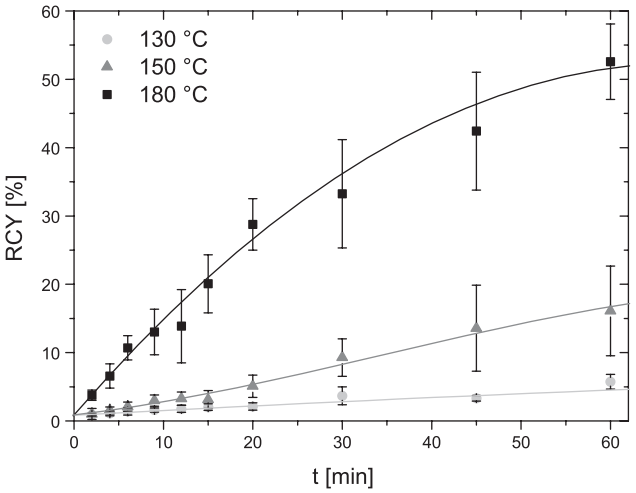


Figure 2 Radiochemical yields for the [^{18}F]fluoride-for-nitro exchange on *N*-2-(4-*N*-(4-nitrobenzamido)phenyl)propyl-2-propanesulphonamide at three different temperatures in DMSO at a concentration of 0.025 mol/l.

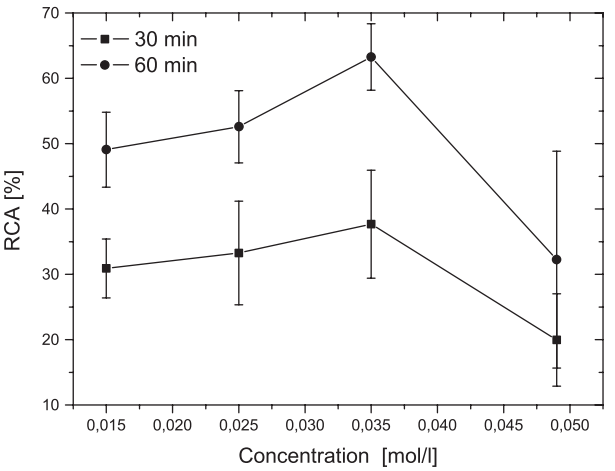


Figure 3 Radiochemical yields for the [^{18}F]fluoride-for-nitro exchange on *N*-2-(4-*N*-(4-nitrobenzamido)phenyl)propyl-2-propanesulphonamide at different concentrations of precursor in DMSO at 180°C.

DOI: 10.1002.jlcr

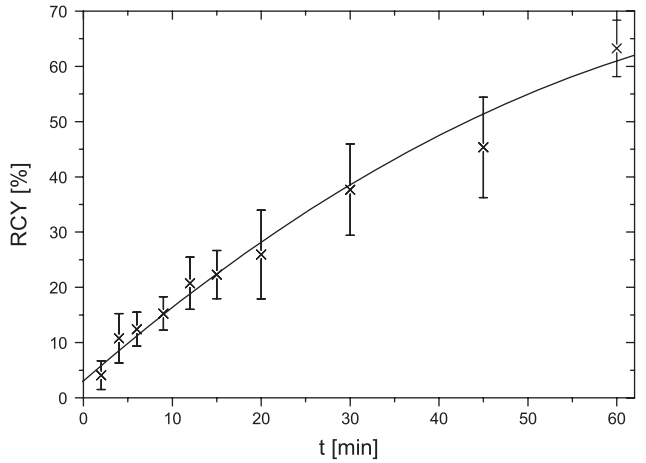


Figure 4 Time dependence of the [^{18}F]fluoride-for-nitro exchange on *N*-2-(4-*N*-(4-nitrobenzamido)phenyl)propyl-2-propanesulphonamide at a concentration of 0.035 mol/l of precursor in DMSO at 180°C.

Preparative experiments

In order to save time during the preparation of the desired product, the reaction was stopped with water after 30 min. For isolation, a solid-phase extraction was utilized, followed by semi-preparative reversed-phase HPLC purification. The obtained product fraction of eluent was passed though a Waters Sep-Pak® Plus C18 cartridge and the retained product was eluted thereof with ethanol.

Radioactive labelling with the objective of isolating the desired product was performed with 5 mg (12.5 μmol) of labelling precursor.

The specific activity of product [^{18}F]**8** was measured by comparing the area of the detected UV-peak to a standard curve relating mass to UV-absorbance. If no UV-peak could be detected, the detection limit was used to determine the lower threshold of the specific activity. The detection limit of the HPLC system used for this purpose for compound **8** is at an amount of 1.75 pmol. Under these conditions, the specific activity was $\geqslant 77 \pm 40$ GBq/μmol ($n = 3$).

In vitro binding assays

Autoradiography of rat brain slices in the presence of **8** and [^{3}H]AMPA revealed the typical AMPA receptor-binding distribution[9] with high binding in the hippocampus, followed by cortex striatum and cerebellum, while low binding was detected in the thalamus. Whereas the receptor antagonist 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX) blocked the [^{3}H]AMPA up to a rate of 90%, it was not expected that the potentiator **8** would block the [^{3}H]AMPA binding; however, it did not potentiate the [^{3}H]AMPA binding on frozen brain slices while similar compounds like LY395153 (**5**, see Figure 1) potentiated AMPA receptor-mediated inward currents in cerebellar Purkinje neurons with an EC_{50} of 300 nmol at room temperature.[4]

Image scanning after the [^{18}F]**8** assay displayed a uniform binding distribution, no influence of unlabelled CNQX and only 30–40% blocking power by macroscopic amounts of **8** on the binding. This leads to the assumption that the radioligand binding represents a remarkable part of non-specific binding, which was higher than that found with [^{3}H]**5** in rat cortex (10–15%) or in recombinant human GluR4 receptors (20–25%).[4,5]

Experimental

General

All chemicals were purchased from Aldrich (Taufkirchen, Germany), Merck (Darmstadt, Germany), Fluka (Buchs, Suisse), KMF (St. Augustin, Germany) or Acros Organics (Geel, Belgium) and were used without further purification.

For TLC, pre-coated plates of silica gel 60 (Polygram SIL G/UV254 40×80 mm) were purchased from Macherey-Nagel (Germany). They were analysed at a wavelength of 254 nm. The eluent used was acetone/*n*-hexane (40/60; v/v). Radioactivity on TLC plates was measured with an Instant Imager™ (Packard).

Mass spectra were measured on a Thermoquest Automass Multi III Mass Spectrometer. ^{1}H-, ^{13}C- and ^{19}F-NMR spectra were recorded on a Bruker DPX Avance 200 using the signal of the appropriate standard as reference. DMSO-d_6 was used as solvent. All chemical shifts are given in ppm. Elemental analysis was done at the Central Institute of Analysis of the Forschungszentrum Jülich GmbH with a Leco CHNOS-932 Microelement analyser. Melting points were determined with a Büchi B-540 melting point apparatus and are uncorrected.

Analytical HPLC was performed on a system consisting of a Knauer WellChrom Mini-Star K500 pump, a Rheodyne 7125 injector block, a Merck/Hitachi L4000 UV/Vis photometer with the wavelength set to 254 nm and a NaI(Tl) well-type scintillation detector (EG&G Ortec, Modell 925 Scint Amplifier and Bias Supply).

Semi-preparative HPLC was performed on a different system than the one mentioned above; it consisted of a Merck/Hitachi L6000 pump, a Rheodyne 7125 injector block, a Merck/Hitachi L4000 UV/Vis Photometer with the wavelength set to 254 nm and a NaI(Tl) well-type

DOI: 10.1002.jlcr

scintillation detector (EG&G Ortec, Modell 925 Scint Amplifier and Bias Supply).

Organic syntheses of precursor and standard

N-2-(4-Aminophenyl)propyl-2-propansulphonamide (**6**) was synthesized with slight modifications according to the procedure of preparation described by Zarrinmayeh *et al.*[4] in five steps starting from 4-aminobenzyl cyanide. In order to protect the amino group, the 4-aminobenzyl cyanide was derivatized with benzyl bromide which gave 68% of the protected product. The reagent was then methylated in the α-position with methyl iodide resulting in 96% of 2-(4-(*N*,*N*-dibenzylamino)phenyl)propionitrile. This was quantitatively converted into 2-(4-(*N*,*N*-dibenzylamino)phenyl)propylamine utilizing a borane dimethyl sulphide complex. Reaction with isopropanesulphonyl chloride gave 21% of the corresponding *N*-2-(4-(*N*,*N*-dibenzylamino)phenyl)propyl-2-propanesulphonamide, which was deprotected under standard conditions with hydrogen and palladium on activated carbon to give 96% of compound **6**.

N-2-(4-*N*-(4-Nitrobenzamido)phenyl)propyl-2-propanesulphonamide (7) and *N*-2-(4-*N*-(4-fluorobenzamido)phenyl)propyl-2-propanesulphonamide (8)

A solution of **6** (0.79 or 0.68 mmol, respectively) in 5 ml dichloromethane was treated with triethylamine (1.5 eq) and 4-nitrobenzoyl chloride (1.5 eq) or 4-fluorobenzoyl chloride (1.5 eq), respectively. The mixture was stirred under argon at ambient temperature until no residual educt could be detected via TLC.

Ten millilitre of water was added to stop the reaction and the product was extracted with ether (3 × 10 ml). The combined organic phases were washed with brine (50 ml) and dried over Na_2SO_4. The solvent was removed *in vacuo* and the remaining solid was recrystallized from acetone/*n*-hexane to give 288 mg (0.71 mmol; 90%; purity: 98% by HPLC) of light yellow crystals of **7** and 180 mg (0.48 mmol, 70%; purity: 98% by HPLC) of light pink crystals of **8**, respectively.

Compounds **7** and **8** were purified using the semi-preparative HPLC system utilizing a Nucleosil 100-7 C18 (250 × 20 mm) column under isocratic conditions with an eluent mixture of acetonitrile/water (50/50; v/v) at a flow rate of 8 ml/min.

Compound **7**: R_f : 0.46; m.p.: 182–183°C; ^{1}H NMR (200.13 MHz, d_6-DMSO), δ (ppm): 10.56 (s, N–H); 8.26 (t, 2H); 8.21 (m, 2H); 7.74 (d, 2H); 7.26 (d, 2H); 7.06 (t, N–H); 3.11 (m, 3H); 2.87 (d, 1H); 1.22 (m, 9H); ^{13}C NMR (50.32 MHz, d_6-DMSO), δ (ppm): 164.54 (C═O); 149.98 (C–NO_2); 141.50 (C); 141.18 (C); 137.84 (C); 131.39 (Aryl C–H); 130.06 (Aryl C–H); 128.29 (2 × Aryl C–H); 124.36 (2 × Aryl C–H); 121.43 (2 × Aryl C–H); 52.19 (C–H); 50.36 (CH_2); 40.44 (C–H); 20.04 (CH_3); 17.17 (2 × CH_3); mass spectrum (*m*/*e*): 405.9 (M^+, 100%), 811 (2 × M^+, 35%); analysis calculated for $C_{19}H_{23}N_3O_5S$: C, 56.28%; H, 5.72%; N, 10.36%; O, 19.73%; S, 7.91%; found: C, 55.10%; H, 5.74%; N, 10.30%; O, 22.40%; S, 7.79%.

Compound **8**: R_f: 0.49; m.p.: 195–198°C; ^{1}H NMR (200.13 MHz, d_6-DMSO), δ (ppm): 10.23 (s, 1H, N–H); 8.05 (t, 2H); 7.70 (d, 2H); 7.38 (t, 2H); 7.24 (d, 2H); 7.06 (t, 1H, N–H); 3.09 (m, 1H); 2.85 (m, 2H), 1.17 (m, 9H); ^{13}C NMR (50.32 MHz, d_6-DMSO), δ (ppm): 165.11 (C–O, C–F); 140.69 (C); 138.19 (C); 132.27 (C); 131.22 (2 × Aryl C–H); 128.21 (2 × Aryl C–H); 121.31 (2 × Aryl C–H); 116.18 (2 × Aryl C–H); 52.15 (C–H); 50.38 (CH_2); 40.42 (C–H); 20.07 (CH_3); 17.17 (2 × CH_3); ^{19}F NMR (188.28 MHz, d_6-DMSO), δ (ppm): −109.38; mass spectrum (*m*/*e*): 379.2 (M^+, 100%), 757.4 (2 × M^+, 20%); analysis calculated for $C_{19}H_{23}FN_2O_3S$: C, 60.30%; H, 6.13%; N, 7.40%; O, 12.68%; S, 8.47%; found: C, 59.30%; H, 6.41%; N, 7.45%; O, 14.30%; S, 8.28%.

Production of [^{18}F]fluoride

[^{18}F]Fluoride was produced routinely at the BC 1710 (JSW) cyclotron at the Institute of Nuclear Chemistry of the Forschungszentrum Jülich GmbH using the ^{18}O(p,n)^{18}F reaction on nuclear-enriched [^{18}O]H_2O. The produced [^{18}F]fluoride was purified through electrostatic adsorption on a Sigradur®-Anode and following desorption into pentadistilled water.[10]

Labelling synthesis

General

The labelling synthesis was carried out in a 2.5 ml Wheaton reaction vial that was closed with a silicone septum and screw cap. The vial was equipped with two steel needles, one of which lead to an oil-sealed vacuum pump, while the other led to the argon supply. The vial was heated to about 80°C under argon stream using an oil bath, while the pressure was reduced to about 800 mbar. Depending on the amount of precursor to be used, between 5 and 10 mg (13.28–26.56 μmol) of Kryptofix 2.2.2® and 6.5–13 μl (6.5–13 μmol) of a 1 M solution of potassium carbonate in water were mixed with aqueous [^{18}F]fluoride (between 80 and 120 MBq). The solution was then mixed with 1 ml of acetonitrile and transferred into the Wheaton vial. Under the aforementioned pressure and temperature conditions, the solvent was evaporated until dryness and the residue was dissolved with 1 ml of acetonitrile. This

DOI: 10.1002.jlcr

step was repeated twice in order to azeotropically remove residual water. Then total vacuum was applied for 5 min and the pressure afterwards set to ambient with argon.

Optimization conditions

The vial was transferred to a second oil bath with a temperature of 130–180°C. Between 3 and 10 mg (24.66 μmol) of precursor **7** was dissolved in 0.5–1.6 ml of solvent (DMF, DMA or DMSO) and transferred via a syringe into the reaction vessel.

The progress of the radioactive synthesis was controlled with radio-TLC and HPLC. For this purpose, after defined time intervals, aliquots of 10 μl were taken with a Hamilton syringe, put into an Eppendorf vial and then diluted with 30 μl of dichloromethane. As an eluent for radio-TLC, acetone/*n*-hexane (40/60; v/v) was used. On each silica TLC plate besides the labelled product, a run was performed using the non-labelled compound **8** to compare the R_f-values of the other spots. Under these conditions the labelled product [^{18}F]**8** had a R_f-value of 0.49, while fluoride remained at the starting point.

In order to analyse the course of the reaction, a dedicated analytical HPLC system was established. A mixture of 45/55 acetonitrile/water (v/v) as eluent and a flow rate of 2 ml/min in combination with a Kromasil 100-5 C18 (250 × 4.6 mm) column offered best separation conditions.

Preparative runs

After azeotropically drying the aqueous [^{18}F]fluoride (between 80 and 160 MBq) in the presence of 5 mg of Kryptofix and 6.5 μl of a 1 M solution of potassium carbonate in water, the vial was transferred to a second oil bath with a temperature of 180°C. For the preparative synthesis of [^{18}F]**8** only 5 mg (12.33 μmol) of precursor was used. Five milligram of precursor was dissolved in 0.35 ml of DMSO and transferred to the reaction vial via a syringe.

After 30 min of reaction time, the reaction was stopped by adding 4.5 ml of water. The obtained aqueous solution was then slowly passed through a Phenomenex Strata® C18-E cartridge (conditioned with 3 ml ethanol and washed with 5 ml water) to remove residual fluorine-18 and Kryptofix 2.2.2®. The cartridge was then washed with 5 ml water and dried in a moderate argon stream for 2 min. After elution of the product with 500 μl of acetonitrile, less than 5% of the radioactivity was left on the cartridge. The solution was injected into the semi-preparative HPLC system in two fractions of 250 μl, in order to avoid overcharging the semi-preparative HPLC column. Using a reversed-phase column (Kromasil 100-10 C18 250 × 10 mm) with an eluent system consisting of tetrahydrofuran/water (40/60; v/v) at a flow rate of 5 ml/min gave the 98% pure product at a k'-value of 8.1 (purity was determined by analytical HPLC).

The two obtained product fractions were unified, diluted with 5 ml water and passed through a Waters Sep-Pak® Plus C18 cartridge (first washed with 3 ml ethanol and afterwards rinsed with 5 ml water) to perform a solvent exchange. After washing the cartridge with 5 ml water and drying it under a moderate argon stream for 2 min, the desired product was eluted with 500 μl of ethanol. Radiochemical yield amounted to 5 ± 1.5% after a total reaction time of 120 min. The product was 95% radiochemically pure.

For determination of the specific activity with analytical HPLC, the detection limit of the analytical HPLC system for the authentic compound **8** was used, since no UV-peak was measurable. Based on the standard curve this limit was reached at a threshold of 1.75 pmol.

An aliquot of 50 μl was taken from the ethanol solution. The aliquot was transferred to a 1.5 ml Eppendorf vial and its radioactivity was measured. Relating to the above given threshold, the specific activity was $\geqslant 77 \pm 40$ GBq/μmol ($n = 3$).

Preliminary *in vitro* assays

For autoradiography, frozen brains of Wistar rats were cut horizontal into 20 μm thick sections at −18°C (Leica AG Microsystems, Germany), mounted onto gelatine-coated object glasses (LO-Laboroptik GmbH) and stored at −80°C until use.

For ligand-binding assays, the brain sections were thawed and dried at room temperature. After pre-incubation for 15 min, at 4°C in 50 mM Tris–HCl containing 0.5 mM $CaCl_2$, the cryosections were additionally incubated with 50 mM KSCN and about 2.3 nM [^{3}H]AMPA (Perkin Elmer) or about 6 nM [^{18}F]**8** in the buffer for 45 min at 4°C. To determine the non-specific binding, adjacent sections were incubated in the presence of up to 15 μM **8** or CNQX (AMPA antagonist). After this treatment, the sections were washed twice for 15 s ([^{3}H]AMPA) or for 1 min ([^{18}F]**8**) in buffer without KSCN at 4°C, dipped in deionized water, dried and exposed for four days ([^{3}H]AMPA) or 60 min ([^{18}F]**8**) to a phosphor image plate (Fuji). A laser phosphor imager (BAS 5000, Fuji) controlled with software by the vendor (Version 3.14, Raytest, Germany) scanned the images.

DOI: 10.1002.jlcr

Conclusion

A Kryptofix 2.2.2®/K_2CO_3-activated nucleophilic radiofluorination reaction for the AMPA potentiator *N*-2-(4-*N*-(4-[^{18}F]fluorobenzamido)-phenyl)-propyl-2-propanesulphonamide ([^{18}F]**8**) was developed and its radiochemical yield was optimized. It was produced reliably in radiochemical yields of $5 \pm 1.5\%$ within 120 min and a specific activity of $\geqslant 77 \pm 40$ GBq/μmol. From the first *in vitro* assays it can be concluded that [^{18}F]**8**, due to its high non-specific binding and the uniform binding distribution, appears to be a rather unsuitable ligand to image AMPA potentiator-binding sites.

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