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Assessment of labelled products with different radioanalytical methods: study on ^{18}F -fluorination reaction of 4- ^{18}F fluoro-N-[2-[1-(2-methoxyphenyl)-1-piperazinyl]ethyl-N-2-pyridinyl-benzamide (p - ^{18}F]MPPF)

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Abstract The serotonin receptor 5-HT_{1A} ligand 4- ^{18}F fluoro-N-[2-[1-(2-methoxyphenyl)-1-piperazinyl]ethyl-N-2-pyridinyl-benzamide (p - ^{18}F]MPPF) was produced by a simplified method of Le Bars et al. Traditional oil bath heating was compared to microwave heating. Various radioanalytical methods, radio-Thin Layer Chromatography (TLC), High Pressure Liquid Chromatography (HPLC) and Mass Spectrometry (MS), were compared in the evaluation of the labelled product(s). The crude reaction mixture consisted of p - ^{18}F]MPPF and 2–4 radioactive by-products eluting after the product fraction, and the reverse-phase HPLC method failed occasionally to separate p - ^{18}F]MPPF from the radioactive by-product with close retention time. The heating method had no significant effect on the composition of labelled by-products. In

LC-(ESI)-MS analysis of p - ^{18}F]MPPF the labelled product was identified with m/z ratio of 435 ($[\text{M} + \text{H}^+]$). The other HPLC fractions were measured to have following m/z ratios: (1) 327; 349; (675) (2) 402; 407/408; (791) and (3) 436, suggesting different kind of decomposition of the labelled product and/or the inactive precursor. The ion trap mass spectrometer was sufficient for the qualitative analysis of p - ^{18}F]MPPF. However, differentiation of by-products arising from the decomposition of p - ^{18}F]MPPF or from its precursor p -MPPNO₂ proved to be challenging.

Keywords Radiolabelling · Fluorine-18 · MPPF · Radioanalytical methods · LC–MS

Introduction

Assessment of radiochemical incorporation yield and possible radiolabelled by-products is important in developing a synthesis method for any radiolabelled product. Thin Layer Chromatography (TLC) and High Pressure Liquid Chromatography (HPLC) combined with radioactivity detection are common tools for radiochemical analyses. However, both these methods have often limitations concerning e.g. sensitivity, resolution and/or practicality [1] and more than one radioanalytical method is needed to evaluate reliably the radiochemical incorporation of the desired radiolabelled product [2]. Identification of all radiolabelled products with the above-mentioned methods requires deep understanding of reaction mechanisms as well as availability of number of non-radioactive references. All references are rarely available and may be problematic to synthesise. However, Mass Spectrometry (MS) may solve this problem, being a more sensitive tool for qualitative analyses of radiopharmaceuticals [3–5].

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Development of radiosynthesis for various 5-HT_{1A} receptor ligands such as 4-[¹⁸F]fluoro-N-[2-[1-(2-methoxyphenyl)-1-piperazinyl]ethyl-N-2-pyridinyl-benzamide (*p*-[¹⁸F]MPPF) [6, 7], [¹⁸F]FBWAY [8] and ¹⁸F-mefway [9] have been reported in the literature. Production of *p*-[¹⁸F]MPPF and the desmethyl analogue *p*-[¹⁸F]DMPPF [10] are examples of radiosynthesis where the labelling reaction is a straightforward nucleophilic substitution of a corresponding nitro-precursor with fluorine-18. However, separation of *p*-[¹⁸F]MPPF from its inactive precursor and labelled side-products is challenging and complex radioHPLC methods are needed for the analysis/purification of the crude product [6, 7, 11].

We have previously reported the production of *p*-[¹⁸F]MPPF with moderate radiochemical yield [12]. However, labelled side-products were not identified. The aim of this study was to estimate the effect of the labelling (heating) method on the formation of unwanted side-products and therefore the radiochemical yield of *p*-[¹⁸F]MPPF. *p*-[¹⁸F]MPPF was produced by a slightly modified method of Le Bars et al. [7] and traditional oil bath heating was compared to microwave (MW) heating. Three radioanalytical methods were used in order to identify the labelled impurities: radio-TLC, -HPLC and -MS. Various chromatographic conditions were tested in order to optimise the analytical methods.

Experimental

Materials

The inactive precursor 4-nitro-N-[2-[1-(methoxyphenyl)-1-piperazinyl]ethyl-N-2-pyridinyl-benzamide (*p*-MPPNO₂) and the fluorinated standard (*p*-MPPF) were kindly supplied by Professor Christer Halldin from the Karolinska Institute, Stockholm, Sweden. The precursor and standard were synthesised by a 3- and 4-step procedure [13], respectively, and their quality was verified by ¹H-NMR- and TOF MS ES⁺-analyses. Other reagents and chemicals were obtained from commercial sources. HPLC-solvents were of HPLC grade and other chemicals were of analytical grade.

Production of no-carrier-added [¹⁸F]fluoride

No-carrier-added (n.c.a.) [¹⁸F]fluoride was produced with 10 MeV protons via the ¹⁸O(*p,n*)¹⁸F nuclear reaction using enriched [¹⁸O]H₂O. Radioactivity was either added straight into a solution of Kryptofix2.2.2 (K2.2.2, 22 mg) and K₂CO₃ (5.5 mg) in dry acetonitrile, or it was trapped on a Chromafix cartridge (Macherey–Nagel). [¹⁸F]Fluoride was then eluted with K₂CO₃-solution (11 mg/mL, 0.6 mL) to a reaction vial containing a solution of K2.2.2 (22 mg) in dry CH₃CN (1 mL). The reaction mixture was dried by azeotropic distillation at 110 °C with CH₃CN (2–3 portions of 1 mL) under an argon stream and vacuum. The dry fluorinating agent [K2.2.2/K]⁺[¹⁸F][−] was thus obtained.

Radiolabelling of *p*-[¹⁸F]MPPF

The radiosynthesis of *p*-[¹⁸F]MPPF was based on aromatic nucleophilic substitution of the corresponding nitro-precursor with fluorine-18 as depicted in Fig. 1. The precursor *p*-MPPNO₂ (10 mg) in dry DMSO (1.0 mL) was added to the K[¹⁸F]/K2.2.2 complex and the reaction mixture was heated in a closed vial in an oil bath at 150–180 °C for 5–20 min, or in the microwave oven (Resonance Instrument, Inc., Model 520A). In the MW experiments the heating unit was placed inside a fume hood and a 5 mL vial (Wheaton or Alltech) with 1 mL solution volume was used. The reaction vial was capped with a septa (which was pierced by a venting needle) and the reaction mixture was heated with 40 W for 1 min (3 × 20 s).

Purification of *p*-[¹⁸F]MPPF

The chromatographic system consisted of a Merck-Hitachi LaChrom L-7100 HPLC pump, a Rheodyne 7010 injector with a 2 mL injection loop and a LKB Bromma 2151 UV-detector (λ = 270 nm) in series with a NaI(Tl) crystal for radioactivity detection. The crude reaction mixture was allowed to cool to room temperature. The crude *p*-[¹⁸F]MPPF was diluted with HPLC mobile phase (0.8 mL) and injected on the HPLC column. Semi-preparative HPLC was carried out on a reverse-phase C₁₈ SymmetryTM column (7 μm, 7.8 × 300 mm) with THF/MeOH/0.05 M NaOAc

Fig. 1 Synthesis scheme of *p*-[¹⁸F]MPPF

(18:27:55; v/v, acetate adjusted to pH 5 with acetic acid) as eluent at a flow rate of 3 mL/min. The collected product fraction was evaporated into dryness and the residue was then dissolved in 1.5 mL of 0.9% NaCl.

(Radio)analytical methods

Labelled products were analysed by radio TLC and -HPLC. The identity of p -[^{18}F]MPPF was confirmed by comparing the radiochromatogram with the UV-chromatogram of non-labelled reference material. In order to identify all the labelled products, five radioactive fractions were collected from the semi-preparative HPLC and were analysed also by LC-MS.

The analytical HPLC apparatus consisted of a PC-controlled system with Waters Millennium^{®32} software, a Waters 600E pump, a Rheodyne 7125 injector with a 100 μL injection loop, a Waters photodiode array detector (PDA 996, range 190–400 nm; normally set for 270 nm) and a NaI(Tl) crystal for radioactivity detection. A Waters reverse-phase SymmetryTM column (C_{18} , 3.5 μm , 4.6 $\times$ 150 mm) was used with THF/MeOH/0.05 M NaOAc (17:28:55; v/v, acetate adjusted to pH 5) as an eluent at a flow rate of 0.5 mL/min.

TLC was carried out using silica gel plates (60 F₂₅₄, Merck) and $\text{CH}_3\text{CN}:\text{H}_2\text{O}$ (90:10%) as mobile phase. UV visualisation was accomplished with a UV-lamp at 254 nm. Radioactivity was detected with a Raytest Mini-Gita TLC-scanner and/or by digital Photo Stimulated Luminescence (PSL) autoradiography using Fuji Imaging Plates (BAS-TR2025) and a Fuji Analyzer BAS-1800.

The MS studies were done using a Bruker Daltonics Esquire 3000 instrument with an electron spray ionisation-Ion trap MSⁿ System (ESI-MS). The inactive precursor p -MPPNO₂ and the product reference p -MPPF were analysed first by a direct infusion technique. The lowest detection limit for the LC-(ESI)-MS method was not determined, but even the concentration of 2 pg/ μL (4.6 nM) of p -MPPF reference was analysed easily. Samples were diluted in methanol and a solution of $\text{CH}_3\text{CN}:\text{H}_2\text{O}$ 20:80% (1% of HCOOH added for the ionisation). The concentrations of the samples were 30 μM . The preparative HPLC fractions were analysed by a LC-MS technique with an Agilent 1100 liquid chromatography system and a Waters XBridge reverse phase column (C_{18} , 3.5 μm , 2.1 $\times$ 150 mm). $\text{CH}_3\text{CN}:\text{H}_2\text{O}$ in ratio 80:20% was used as a mobile phase at a flow rate of 0.2 mL/min. All HPLC samples were diluted in water with a ratio of 1:9 (v/v). An autosampler was used for injection with the injection volume of 5 μL . The radioactivity of the measured fractions was evaluated with a dose rate meter beside the inlet of ESI.

Stability of the substituted benzamides was studied by cold synthesis tests in which either the precursor p -MPPNO₂ or the product reference p -MPPF was heated in

similar conditions as in the radiosynthetic procedure and the crude reaction mixture was injected into semi-preparative HPLC.

Results and discussion

Radiosynthesis of p -[^{18}F]MPPF

The radiochemical incorporation yield of p -[^{18}F]MPPF using oil bath heating was $27.9 \pm 9.5\%$ (mean $\pm$ SD, measured by radioHPLC). This resulted in 3.7 ± 2.4 and $2.5 \pm 0.6\%$ overall decay-corrected radiochemical yield (mean $\pm$ SD) for the purified and final, formulated p -[^{18}F]MPPF, respectively. A considerable amount of radioactivity remained in the reaction vial, the HPLC injector and on the HPLC column. The radiochemical purity of the p -[^{18}F]MPPF was $\geq 95\%$ (by radio TLC). The highest incorporation yield of p -[^{18}F]MPPF was reached already within 5 min reaction time at 170–180 $^{\circ}\text{C}$, prolonging the reaction time did not improve the yield. A lower reaction temperature (150 $^{\circ}\text{C}$) with longer heating time (20 min) was also tested resulting in similar or somewhat lower incorporation yield of p -[^{18}F]MPPF. MW heating did not increase the radiochemical yield of p -[^{18}F]MPPF either, although it has been reported to be beneficial in fluorine-18 labelling of benzamides [7, 14].

The radioHPLC analysis showed that, independent of the heating method, the crude reaction mixture consisted of p -[^{18}F]MPPF and 2–4 labelled impurities eluting after the product fraction. The results are presented in Fig. 2. The semi-preparative HPLC method [7] failed occasionally to

Fig. 2 Analytical radioHPLC chromatogram of crude p -[^{18}F]MPPF. Results by labelling of (a) 1st batch and (b) 2nd batch of p -MPPNO₂ are presented together in the figure

separate p -[^{18}F]MPPF from its radioactive by-product with close retention time. The crude p -[^{18}F]MPPF in DMSO was diluted with mobile phase and injected straight into HPLC. Changing the solvent into MeOH/THF by the reported method [7] was tested but it did not have significant effect on the purification of p -[^{18}F]MPPF by HPLC and this purification step was excluded from the synthesis procedure. The possible effect of DMSO on the stability of p -[^{18}F]MPPF was proved to be negative by cold synthesis test with p -MPPF. Specific retardation of the product in the HPLC column, which would give explanation to the late eluting radioactive peak, was not detected either. In addition, the radio TLC analysis of the HPLC-fractions collected from the radiosynthesis resulted in R_f values of 0.31 and 0.64 for p -[^{18}F]MPPF (fraction 1) and for the late eluting peak (fraction 5), respectively. The labelled impurities eluting between them showed no retention and were detected with the solvent front. RadioHPLC analyses of the separated radioactive fractions were comparable to the analysis of crude p -[^{18}F]MPPF. As expected the purified product eluted at about 13.5 min, one major by-product (fraction 2) had a 2–3 min longer retention time, and the most lipophilic by-product (fraction 5) had a retention time as long as 45 min. Unexpectedly, this by-product became a major radioactive product when a oily and a less soluble batch of p -MPPNO₂ was used as a precursor.

Degradation of the inactive precursor p -MPPNO₂ and labelling of the fragments was considered as the reason for low radiochemical yield of p -[^{18}F]MPPF and for the formation of a high number of side-products. It has been

reported that sulphonamides are susceptible for amide hydrolysis, e.g. WAY-100634 is formed from p -MPPNO₂ [15]. In the radiosynthesis of the trifluoromethyl derivative of p -[^{18}F]MPPF, acidic water was added into crude product to prevent precipitation of the nitro precursor and the reaction mixture was cooled to prevent degradation of the product in the acidic environment [14]. Defraiteur et al. [10] reported thermal sensitivity of the p -MPPNO₂ derivative, MEM-MPPNO₂ in the radiosynthesis of p -D[^{18}F]MPPF. In our stability test on the precursor, comparison of radioHPLC analyses before and after the heating showed decrease in the relative amount of p -MPPNO₂. Degradation products with similar or higher lipophilicity than p -MPPNO₂ were not detected. However, the relative amount of peak with short (4.5 min) retention time increased.

Based on the radio TLC and HPLC analyses it was difficult to draw conclusions of the formation of various labelled products during the radiosynthesis of p -[^{18}F]MPPF. Therefore characterization by MS was used. LC–MS data of the analysed fractions is shown in Fig. 3. The radiochemical yield of p -[^{18}F]MPPF in the test syntheses was low but it was shown that the mass of the isolated product fraction (RT = 14 min) corresponded the molecular mass of the p -[^{18}F]MPPF, i.e. m/z 435 ($[\text{M} + \text{H}^+]$). The inactive product eluting from semi-preparative HPLC at 20 min was identified as the non-labelled precursor p -MPPNO₂ with m/z 462 ($[\text{M} + \text{H}^+]$). However, analysis of the samples from labelled HPLC-fractions resulted in various peaks, e.g. as high as m/z of 509 was measured as an impurity together with p -[^{18}F]MPPF, suggesting that the non-labelled impurities

Fig. 3 Crude p -[^{18}F]MPPF analysed by HPLC with UV (lower chromatogram) and radioactivity detection (upper chromatogram). Corresponding fractions were collected from the semi-preparative HPLC (marked with numbers 1–6) and analysed with LC–MS. The m/z ratios of the major peaks are marked on the measured fractions

Fig. 4 Mass spectra of *p*-MPPNO₂ and *p*-MPPF measured by direct infusion ESI-MS technique

(and adduct ions formed from them) were interfering with the measurements. In order to get more information on the possible origin of the various mass peaks the inactive precursor *p*-MPPNO₂ was analysed separately and the results are shown in Fig. 4. Using a direct infusion technique *m/z* of 462 ($[M + H]^+$) was measured, as expected. However, the spectra showed also peaks at *m/z* 270 and 327. The origin of the latter peak was not identified but the loss of *m/z* 192 suggests reaction of basic nitrogen on the piperazinyl moiety of *p*-MPPNO₂. The molecular peak corresponding 461 u was isolated and fractionated in MS²-mode and a similar major fractionated peak was found at *m/z* of 270. In MS³ it has also a fractionated peak with 120 smaller *m/z* ratio, which is likely a result from cleavage of the amide bond. Similar fractionation was detected for the inactive product reference *p*-MPPF i.e. peaks with *m/z* 435 and 243 (and 123 in MS²) were measured. However, in the LC-MS analysis of *p*-[¹⁸F]MPPF mainly *m/z* ratios higher than 400 were measured for the radioactive by-products and therefore these by-products cannot arise from C-N cleavage and/or amide hydrolysis of the final product. Cleavage of methoxy group from the phenyl ring of *p*-[¹⁸F]MPPF by hydrolysis is also unlikely to happen as it was shown in the experiments of Defraiteur et al. However,

Fig. 5 Molecular structure of *p*-[¹⁸F]MPPF ($R = {}^{18}\text{F}$) and *p*-MPPNO₂ ($R = \text{NO}_2$). Drawn lines delineate considered degradation sites. Masses of the resulting fragments are calculated for decomposition of the labelled product

sensitivity to radiolysis was reported for the desmethyl analogue *p*-D[¹⁸F]MPPF [10]. In our study all analyses were done without concentration, therefore radiolysis was not considered to influence the result. The possible degradation sites that were considered for the substituted benzamides are marked in Fig. 5.

Evaluation of chromatographic methods

Optimisation of the chromatographic methods for the radiosynthesis of *p*-[¹⁸F]MPPF proved to be challenging. With radioHPLC the labelled product had to be separated from its inactive precursor as well as from various labelled by-products. Separation with the current semi-preparative method [7] was occasionally unsatisfactory and some variation was observed in retention times. Therefore various eluent conditions were tested, as presented in Table 1. With CH₃CN:0.01 M H₃PO₄ (in ratio of 10:90) *p*-MPPNO₂ eluted from the reverse-phase column before *p*-MPPF until the pH (adjusted with different ratios of NaH₂PO₄:Na₂HPO₄) was raised (from 2.7) to 5.3. Although neutralizing *p*-MPPF and *p*-MPPNO₂ by increasing the pH of the phosphate buffer seemed to improve their separation, with pH close to pK_a values even a small pH change affected the retention and caused variation in retention times. The pK_a values of *p*-MPPNO₂ and *p*-MPPF (6.67 and 6.68,

Table 1 The average retention times (RT) of *p*-MPPF and *p*-MPPNO₂ in reverse-phase column using different HPLC conditions

Eluent	Ratio	pH	Flow (mL/min) ^a	RT (MPPF) (min) ^a	RT (MPPNO ₂) (min) ^a	Flow (mL/min) ^b	RT (MPPF) (min) ^b	RT (MPPNO ₂) (min) ^b
THF:MeOH:0.05 M NaOAc	18:27:55	5	0.5	12.5	18	2	15	22
THF:CH ₃ CN:0.01 M NaOAc	6:29:65	5	1	10.5	13.5	5	18	24
	5:34:61	5	1	6.5	8.5			
	5:35:59	5	1	7.5	8.5	5	10	13
CH ₃ CN:0.01 M H ₃ PO ₄	10:90	6.7	1	4.0	5.0	4	5.5	7.0
THF:MeOH:0.05 M NH ₄ Ac	19:31:50	6.7				2	20	25

^a Analytical, ^b semi-preparative C₁₈ symmetryTM column

respectively) [16] are also very close to each other. A HPLC method/column, based on e.g. polar interactions, might therefore be appropriate for the purification of p -[^{18}F]MPPF.

Conclusions

The p -[^{18}F]MPPF was produced with moderate-low radiochemical yield and heating with MW did neither prevent the formation of radioactive by-products nor increase the yield as compared to conventional heating. Conventional radioanalytical methods (radio TLC and HPLC) without a broad reference material were inadequate in the assessment of the various labelled products, and characterisation by a more complex method, MS, was needed. The sensitivity of the ion trap MS is sufficient for the qualitative analysis of p -[^{18}F]MPPF. Degradation on the piperazinyl moiety of reference compounds p -MPPF and p -MPPNO₂ was shown in the (ESI)-MS analysis. However, LC-MS studies on p -[^{18}F]MPPF suggested decomposition of the labelled product and/or precursor through an other route.

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