J Radioanal Nucl Chem
DOI 10.1007/s10967-010-0802-3

# 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)

**Teija Koivula · Jaana Laine · Tiina Lipponen · Outi Perhola · Eeva-Liisa Kämäräinen · Kim Bergström · Olof Solin**

Received: 10 August 2010


**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 ([M + 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*-MPPNO$_2$ proved to be challenging.

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

T. Koivula (✉)
Laboratory of Radiochemistry, University of Helsinki, PO Box 55, 00014 Helsinki, Finland
e-mail: teija.s.koivula@helsinki.fi

J. Laine
Laboratory of Analytical Chemistry, University of Helsinki, PO Box 55, 00014 Helsinki, Finland

T. Lipponen · E.-L. Kämäräinen
Division of Nuclear Medicine, Helsinki University Central Hospital, PO Box 340, 00029 Helsinki, Finland

O. Perhola
Imanext Ltd, PO Box 800, 00101 Helsinki, Finland

K. Bergström
Centre for Drug Research, Faculty of Pharmacy, University of Helsinki, PO Box 56, 00014 Helsinki, Finland

O. Solin
Radiopharmaceutical Chemistry Laboratory, Turku PET Centre, Porthaninkatu 3, 20500 Turku, Finland

## 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].

Published online: 31 August 2010

Development of radiosynthesis for various 5-$HT_{1A}$ receptor ligands such as 4-[$^{18}$F]fluoro-N-[2-[1-(2-methoxyphenyl)-1-piperazinyl]ethyl-N-2-pyridinyl-benzamide (*p*-[$^{18}$F]MPPF) [6, 7], [$^{18}$F]FBWAY [8] and $^{18}$F-mefway [9] have been reported in the literature. Production of *p*-[$^{18}$F]MPPF and the desmethyl analogue *p*-[$^{18}$F]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*-[$^{18}$F]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*-[$^{18}$F]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*-[$^{18}$F]MPPF. *p*-[$^{18}$F]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*-$MPPNO_2$) 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 $^1$H-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 [$^{18}$F]fluoride

No-carrier-added (n.c.a.) [$^{18}$F]fluoride was produced with 10 MeV protons via the $^{18}O(p,n)^{18}F$ nuclear reaction using enriched [$^{18}$O]$H_2O$. Radioactivity was either added straight into a solution of Kryptofix2.2.2 (K2.2.2, 22 mg) and $K_2CO_3$ (5.5 mg) in dry acetonitrile, or it was trapped on a Chromafix cartridge (Macherey–Nagel). [$^{18}$F]Fluoride was then eluted with $K_2CO_3$-solution (11 mg/mL, 0.6 mL) to a reaction vial containing a solution of K2.2.2 (22 mg) in dry $CH_3CN$ (1 mL). The reaction mixture was dried by azeotropic distillation at 110 °C with $CH_3CN$ (2–3 portions of 1 mL) under an argon stream and vacuum. The dry fluorinating agent [K2.2.2/K]$^+$[$^{18}$F]$^-$ was thus obtained.

### Radiolabelling of *p*-[$^{18}$F]MPPF

The radiosynthesis of *p*-[$^{18}$F]MPPF was based on aromatic nucleophilic substitution of the corresponding nitro-precursor with fluorine-18 as depicted in Fig. 1. The precursor *p*-$MPPNO_2$ (10 mg) in dry DMSO (1.0 mL) was added to the K[$^{18}$F]/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*-[$^{18}$F]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 ($\lambda$ = 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*-[$^{18}$F]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 Waters $C_{18}$ Symmetry™column (7 µm, 7.8 × 300 mm) with THF/MeOH/0.05 M NaOAc

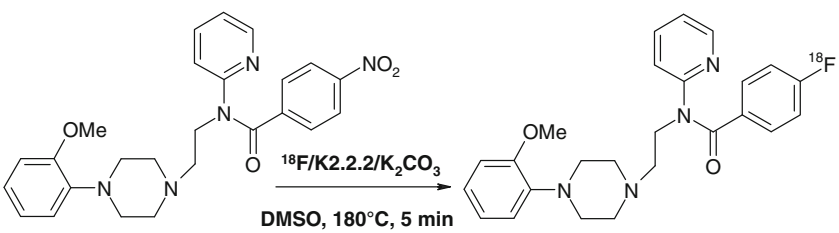


**Fig. 1** Synthesis scheme of *p*-[$^{18}$F]MPPF

(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 Symmetry™ column ($C_{18}$, 3.5 µm, 4.6 × 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 $F_{254}$, Merck) and $CH_3CN$:$H_2O$ (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 $MS^n$ System (ESI–MS). The inactive precursor *p*-$MPPNO_2$ 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 $CH_3CN$:$H_2O$ 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 × 150 mm). $CH_3CN$:$H_2O$ 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*-$MPPNO_2$ 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 ± 9.5% (mean ± SD, measured by radioHPLC). This resulted in 3.7 ± 2.4 and 2.5 ± 0.6% overall decay-corrected radiochemical yield (mean ± 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 ≥95% (by radio TLC). The highest incorporation yield of *p*-[$^{18}$F]MPPF was reached already within 5 min reaction time at 170–180 °C, prolonging the reaction time did not improve the yield. A lower reaction temperature (150 °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

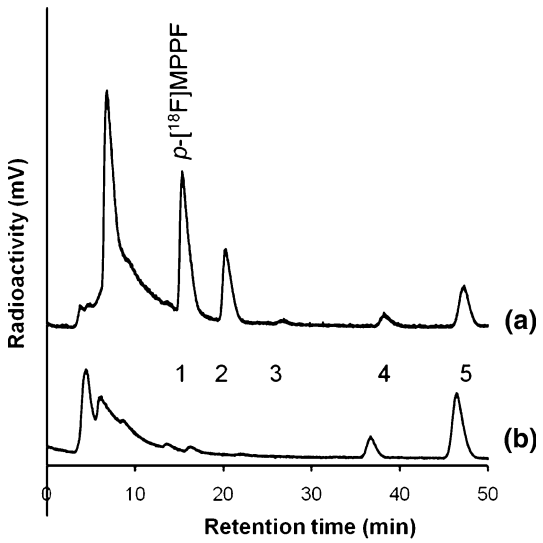


**Fig. 2** Analytical radioHPLC chromatogram of crude *p*-[$^{18}$F]MPPF. Results by labelling of (*a*) 1st batch and (*b*) 2nd batch of *p*-$MPPNO_2$ are presented together in the figure

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*-MPPNO$_2$ was used as a precursor.

Degradation of the inactive precursor *p*-MPPNO$_2$ 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*-MPPNO$_2$ [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*-MPPNO$_2$ derivative, MEM-MPPNO$_2$ 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*-MPPNO$_2$. Degradation products with similar or higher lipophilicity than *p*-MPPNO$_2$ 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 ([M + H$^+$]). The inactive product eluting from semi-preparative HPLC at 20 min was identified as the non-labelled precursor *p*-MPPNO$_2$ with *m*/*z* 462 ([M + 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

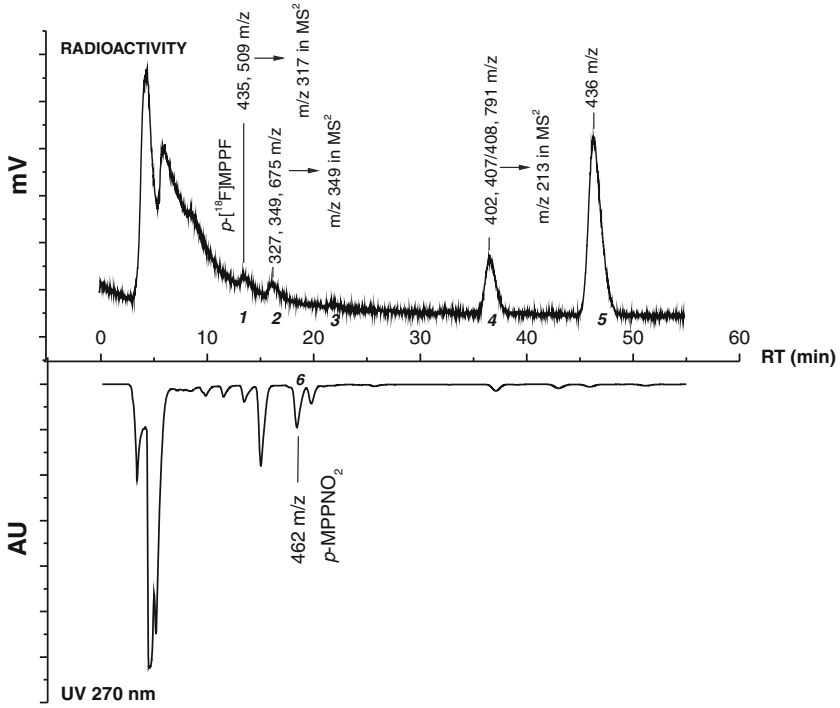


**Fig. 3** Crude *p*-[$^{18}$F]MPPF analysed by HPLC with UV (lower chromatogram) and radioactivity detection (upper chromatogram). Corresponding fractions were collected from the semi-preparative HPLC (marked with numbers 1–6) and analysed with LC–MS. The *m*/*z* ratios of the major peaks are marked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

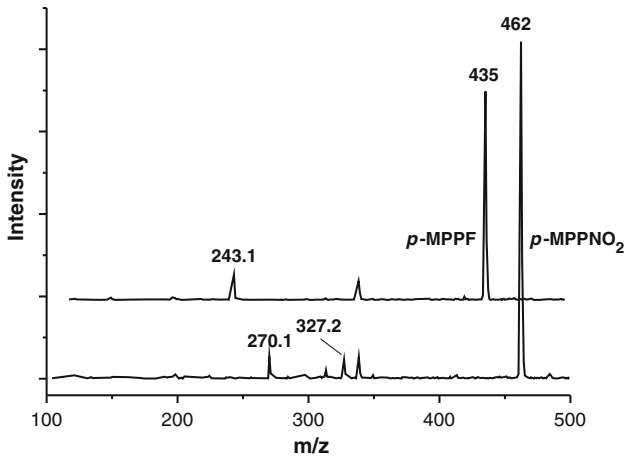


**Fig. 4** Mass spectra of *p*-$MPPNO_2$ and *p*-MPPF measured by direct infusion ESI–MS technique

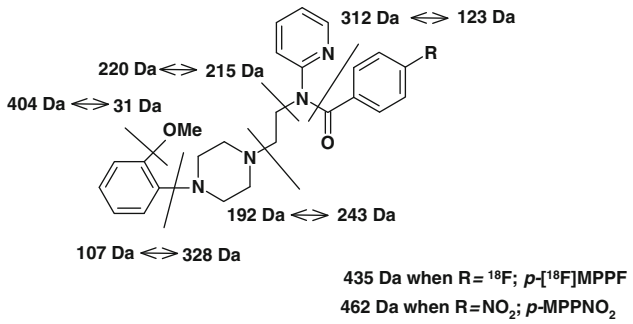


**Fig. 5** Molecular structure of *p*-[$^{18}$F]MPPF (R = $^{18}$F) and *p*-MPP $NO_2$ (R = $NO_2$). *Drawn lines* delineate considered degradation sites. Masses of the resulting fragments are calculated for decomposition of the labelled product

(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*-$MPPNO_2$ 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*-$MPPNO_2$. The molecular peak corresponding 461 u was isolated and fractionated in $MS^2$-mode and a similar major fractionated peak was found at *m*/*z* of 270. In $MS^3$ 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 $MS^2$) were measured. However, in the LC–MS analysis of *p*-[$^{18}$F]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*-[$^{18}$F]MPPF by hydrolysis is also unlikely to happen as it was shown in the experiments of Defraiteur et al. However, sensitivity to radiolysis was reported for the desmethyl analogue *p*-D[$^{18}$F]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*-[$^{18}$F]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 $CH_3CN$:0.01 M $H_3PO_4$ (in ratio of 10:90) *p*-$MPPNO_2$ eluted from the reverse-phase column before *p*-MPPF until the pH (adjusted with different ratios of $NaH_2PO_4$:$Na_2HPO_4$) was raised (from 2.7) to 5.3. Although neutralizing *p*-MPPF and *p*-$MPPNO_2$ by increasing the pH of the phosphate buffer seemed to improve their separation, with pH close to p$K_a$ values even a small pH change affected the retention and caused variation in retention times. The p$K_a$ values of *p*-$MPPNO_2$ and *p*-MPPF (6.67 and 6.68,

**Table 1** The average retention times (RT) of *p*-MPPF and *p*-$MPPNO_2$ 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) (mL/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:$CH_3CN$: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 |
| $CH_3CN$:0.01 M $H_3PO_4$ | 10:90 | 6.7 | 1 | 4.0 | 5.0 | 4 | 5.5 | 7.0 |
| THF:MeOH:0.05 M $NH_4Ac$ | 19:31:50 | 6.7 | | | | 2 | 20 | 25 |

[a] Analytical, [b] semi-preparative $C_{18}$ symmetry$^{TM}$ 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*-MPPNO$_2$ 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.

**Acknowledgments** The authors wish to thank MAP Medical Technologies, Finland, for financial support. Professor Christer Halldin (Department of Clinical neuroscience, Psychiatry Section, Karolinska Hospital, Sweden) is gratefully acknowledged for supplying the inactive precursor and the product reference. We would also like to thank Dr Kerttuli Helariutta and Mr Stewart Makkonen-Craig for the fluorine-18 production, and Dr Anu J. Airaksinen for her valuable comments on this manuscript.

## References

1. Poole CF (2003) Thin layer chromatography: challenges and opprtunities. J Chromatogr A 1000:963–984
2. Kämäräinen E-L, Haaparanta M, Siitari-Kauppi M, Koivula T, Lipponen T, Solin O (2006) Analysis of $^{18}$F-labelled synthesis products on TLC plates: comparison of radioactivity scanning, film autoradiography, and a phosphoimaging tecnique. Appl Radiat Isot 64:1043–1047
3. Hyllbrant B, Tyrefors N, Markides KE, Långström B (1999) On the use of liquid chromatography with radio- and ultraviolet absorbance detection coupled to mass spectrometry for improved sensitivity and selectivity in determination of spesific radioactivity of radiopharmaceuticals. J Pharm Biomed Anal 20:493–501
4. Ma Y, Kiesewetter D, Lang L, Eckelman W (2003) Application of LC-MS to the analysis of new radiopharmaceuticals. Mol Imaging Biol 5:397–403
5. Lavén M, Itsenko O, Markides K, Långström B (2006) Determination of metabolic stability of positron emission tomography tracers by LC-MS/MS: an example in WAY-100635 and two analogues. J Pharm Biomed Anal 40:943–951
6. Shiue CY, Shiue GG, Mozley PD, Kung M-P, Zhuang Z-P, Kim H-J, Kung HF (1997) *p*-[$^{18}$F]MPPF: a potential radioligand for PET studies of 5-HT$_{1A}$ receptors in humans. Synapse 25:147–154
7. Le Bars D, Lemaire C, Ginovart N, Plenevaux J, Aerts J, Brihaye C, Hassoun W, Leviel V, Mekhsian P, Weissmann D, Pujol JF, Luxen A, Comar C (1998) High-yield radiosynthesis and preliminary in vivo evaluation of *p*-[$^{18}$F]MPPF, a Fluoro Analog of WAY-100635. Nucl Med Biol 25:343–350
8. Lang L, Jagoda E, Scmall B, Vuong B-K, Adams HR, Nelson DL, Carson RE, Eckelman WC (1999) Development of fluorine-18-labeled HT$_{1A}$ antagonists. J Med Chem 42:1576–1586
9. Saigal N, Pichika R, Easwaramoorthy B, Collins D, Christian BT, Shi B, Narayanan TK, Potkin SG, Mukherjee L (2006) Synthesis and biologic evaluation of a novel serotonin 5-HT$_{1A}$ receptor radioligand $^{18}$F-labeled mefway, in rodents and imaging by PET in a nonhuman primate. J Nucl Med 47:1697–1706
10. Defraiteur C, Lemaire C, Luxen A, Plenevaux A (2006) Radiochemical synthesis and tissue distribution of *p*-[$^{18}$F]DMPPF, a new 5-HT$_{1A}$ ligand for PET, in rats. Nucl Med Biol 33:667–675
11. Ginovart N, Hassoun W, Le Bars D, Weissmann D, Leviel V (2000) In vivo characterization of *p*-[$^{18}$F]MPPF, a fluoro analog of WAY-100635 for visualization of 5-HT$_{1A}$ receptors. Synapse 35:192–200
12. Kyllönen T, Kämäräinen E-L, Björk H, Bergström K, Tarkiainen J, Halldin C, Solin O (2003) Study on reaction mechanisms and kinetics of *p*-[$^{18}$F]MPPF radiosynthesis. J Label Compd Radiopharm 46(Suppl 1):199
13. Zhuang Z, Kung M-P, Kung HF (1994) Synthesis and evaluation of 4-(2′-methoxyphenyl)-1-[2′-(2″-pyridinyl)-p-iodobenzamido]ethyl]piperazine (p-MPPI): a new iodinated 5-HT$_{1A}$ ligand. J Med Chem 37:1406–1407
14. Vandecapelle M, Dumont F, De Vos F, Strijckmans K, Leysen D, Audenaert K, Dierckx RA, Slegers G (2004) Synthesis and preliminary in vivo evaluation of 4-[$^{18}$F]fluoro-*N*-{2-[4-(6-trifluoromethylpyridin-2-yl)-1-piperazin-1-yl]ethyl}benzamide, a potential PET radioligand for the 5-HT$_{1A}$ receptor. J Label Compd Radiopharm 47:531–542
15. Passhier J, van Waarde A, Pieterman RM, Elsinga PH, Pruim J, Hedrikse HN, Willemsen ATM, Vaalburg W (2000) In vivo delineation of HT$_{1A}$ receptors in human brain with [$^{18}$F]MPPF. J Nucl Med 41:1830–1834
16. CAS Database (2010) American Chemical Society, Washington. https://scifinder.cas.org. Accessed 27 Aug 2010