Use of tetrabutylammonium tosylate in conjunction with chiral Ni^{II} complex precursor for automated synthesis of [^{18}F]FET

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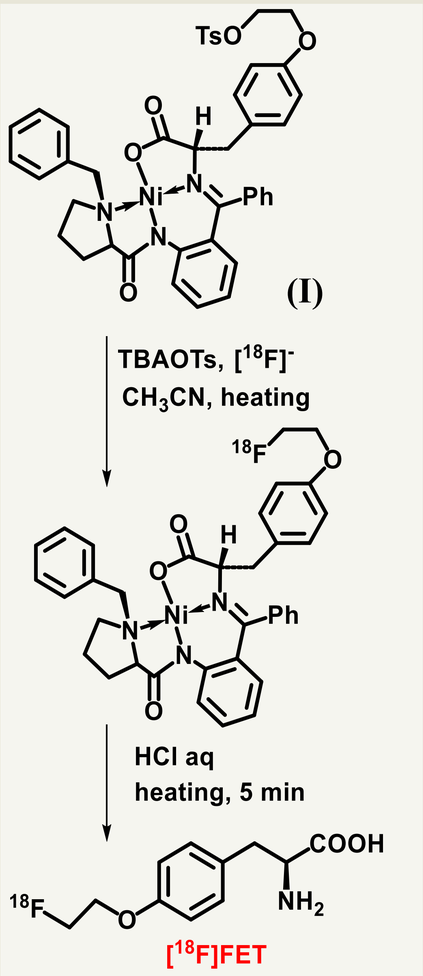
Background and objectives. Due to favorable characteristics in in vivo applications, high specificity and long half-life of ^{18}F (109.8 min), the O-(2-[^{18}F]fluoroethyl)-L-tyrosine ([^{18}F]FET) has become an important tool for molecular imaging of cerebral tumors. In our previous studies we presented a convenient synthesis of [^{18}F]FET *via* direct nucleophilic fluorination of a chiral Ni^{II} complex of an alkylated (S)-tyrosine Schiff base, Ni-(S)-BPB-(S)-Tyr-OCH_2-CH_2OTs (**I**) in the presence of $K_{2.2.2}$ and K_2CO_3 [1]. After acidic hydrolysis [^{18}F]FET was purified using reverse phase and strong cation exchange cartridges. The process was automated on the Scintomics Hotbox^{one} synthesis module. However, when transferring this procedure to TRACERlab FX N Pro, commonly used ^{18}F-radiolabeling platform, we observed two radiolabeled by-products that were not amendable to SPE purification. Their formation may be a consequence of reaction vessel design (high volume/surface *vs* small amount of reaction mixture) and possible over-heating during vacuum drying of ^{18}F-fluoride complex. As the construction of the heating block was not amendable to modification, in this work we focused on improving fluorination process, substituting $K_{2.2.2}/K_2CO_3$ with tetrabutylammonium tosylate (TBAOTs) as an inert PTC. The SPE purification protocol was adjusted to better suite TRACERlab FX N Pro.



Scheme 1. Labeling scheme for [^{18}F]FET using Ni-(S)-BPB-(S)-Tyr-OCH_2-CH_2OTs (I)

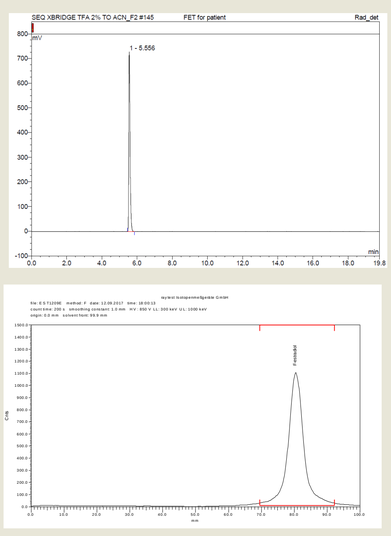


Fig. 1. Radio HPLC and radioTLC of [^{18}F]FET

Methodology. Aqueous [^{18}F]fluoride solution (1.3 ml) was loaded on Waters QMA carbonate Plus light Sep-Pak cartridge (46 mg). The cartridge was rinsed with 5 ml of MeOH and dried using gas flow; the [^{18}F]Fluoride was eluted with 4 mg of TBAOTs dissolved in 700 µl of MeOH. After solvent evaporation, 4 mg of **I** in 700 µl of MeCN was added following heating at 80^{o}C for 7 min. After acidic hydrolysis (0.5M HCl, 110^{o}C, 5 min) the crude mixture was diluted with 11 ml of water and 2.5 ml of 0.1M NaOH. Resulting basic solution (pH 8.5) was passed through small filtration column and three tC18 Light cartridges connected sequentially. [^{18}F]FET was finally eluted with 10 ml of sodium acetate solution (5 mM, pH 4) containing 3% of EtOH and further purified by passing through CM Plus cation exchange cartridge to removal any residual nickel. Radiochemical purity was determined by radio HPLC and radio TLC (Fig.1). HPLC conditions X-Bridge C18 column, 150 x 4.6 mm (Waters), eluent: mixture of trifluoroacetic acid (0,1%) with acetonitrile using gradient elution conditions: 0 - 2.0 min 2% CH_3CN isocratic; 2.0 - 13.0 min 2 - 95% CH_3CN linear increase; 13.0 - 13.5 min 95 - 2% CH_3CN linear decrease; 13.5 - 20.0 min 2% CH_3CN isocratic; flow rate 2.0 mL/min. RadioTLC was done in methanol/acetic acid (9/1).

Results and discussion Replacement of $K_{2.2.2}/K_2CO_3$ with TBAOTs allowed substantially increase radiochemical conversion (RCC > 85%, radioTLC). The radiolabeled by-products were not detected under gradient RP HPLC. [^{18}F]FET was obtained in radiochemical purity >99% and enantiomeric purity 94-95%. Noteworthy, the new protocol afforded [^{18}F]FET in high RCY (> 40%, corrected for decay) using only 2 mg of labeling precursor (Table 1, last lime).

Table 1. Radiochemical yields (RCY) of [^{18}F]FET using **I** and different PTC/base conditions

Cartridge	PTC/Base	Precursor (I), mg	Fluorination conditions	Automated module	Synthesis time, min	RCY, EOS	Reference
QMA light 130 mg	$K222/K_2CO_3$	5	80^{o}C / 5 min	Scintomics Hotbox^{one}	45	26	[1]
PS-HCO_3	Aqueous $TBAHCO_3$	10	85^{o}C / 5 min	GE TRACERlab FX FN	70	23	[2]
QMA light 130 mg	TBAOTs, MeOH 0.8 mL	5	80^{o}C / 8 min	In-house remote-controlled	65	50	This work
QMA carb. 46 mg	TBAOTs, MeOH 0.8 mL	5	100^{o}C / 5 min	GE TRACERlab FX N Pro	40	42	This work
QMA carb. 46 mg	TBAOTs, EtOH 2 mL	2	100^{o}C / 5 min	GE TRACERlab FX N Pro	35	40.6±3.4 (n = 5)	This work

Conslusion Using non-aqueous solution of TBAOTs as an inert PTC allowed for substantial increase of fluorination efficiency using minimal amounts of labeling precursor. The radioactivity loss on the inner surfaces, which is critical for the reaction vessel on the TRACERlab FX N Pro, was minimized. The proposed synthesis methodology appears to be well-suited for transfer to other automated synthesizers for nucleophilic synthesis of ^{18}F-labeled radiotracers.

[1] O.Fedorova et al., *J. Radioanal. Nucl. Chem.*, ***2014,*** 301(2):505-512
[2] N. Lakshminarayanan et al., *Appl. Rad. Isot.*, ***2017***, 127, 122-129

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