SYNTHESIS OF C^1-[^{18}F]FLUOROETHYLAMNINO ASPARAGINE FOR IMAGING CANCER

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Summary:
C^1-[^{18}F]fluoroethylamino asparagine was synthesised from N^1-t-boc C^1-p-nitrophenol asparagine and the radiolabelled precursor [^{18}F]flouroethylamine in a one-pot-synthesis. The yield of this synthesis was 22% referring to [^{18}F]fluoride, including the removal of the protection groups. The *in vivo* tests are in progress.

Introduction:
Whereas for most of the normal cells asparagine is a non-essential amino acid, for various cancer cells asparagine is essential, i.e. some types of cancer (e.g. leucemic cancer) cannot synthesise asparagine [1]. There have been tests with asparagine-dependent L-5178Y cells *in vivo* to evaluate the anti leukemic activity of several asparagine derivatives [2]. It is therefore hoped to detect special tumours of the brain since asparagine is an amino acid which can pass the blood-brain barrier. It was the aim of this work to synthesise a fluoroethlyamine derivative of asparagine. In this case the protein synthesis rate can not be imaged, because the carboxyl group of this amino acid derivative is occupied by the ^{18}F-prosthetic group. Thus its binding to amino acid transporters could possibly be evaluated. If the ^{18}F-labelled derivative of asparagine would be accepted by proliferating cells, an increased ratio of its uptake in cancer and non-cancer cells is expected for PET-images.

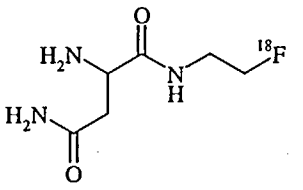

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Fig. 1: C^1-[^{18}F]fluoroethylamino asparagine

Results and Discussion:

Firstly, a fluoroethylamine derivative of asparagine, namely C^1-[^{18}F]fluoroethylamino asparagine was synthesised using [^{18}F]fluoroethylamine (3) as the labelling precursor.

The synthesis of [^{18}F]fluoroethylamine (3) was modified [3] and adapted for a one-pot-synthesis (Fig. 2).

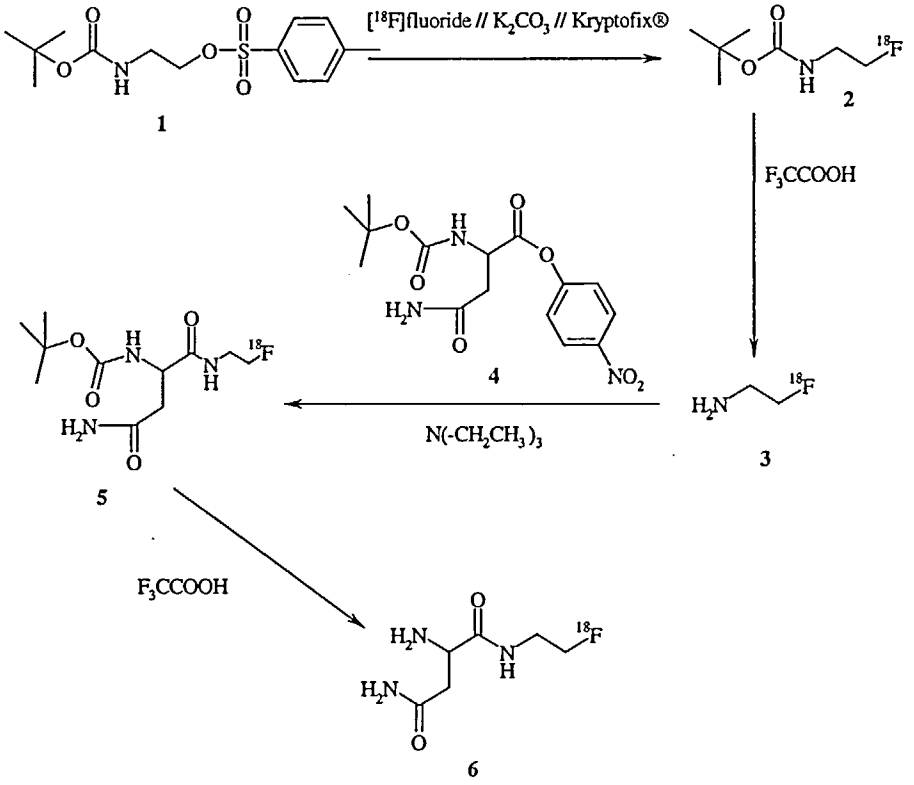

Fig. 2: Synthesis of C^1-[^{18}F]fluoroethylamino asparagine

The dried [^{18}F]flouride was added to a solution of 8 mg of N^1-t-boc C^1-p-nitrophenol asparagine (1) in 700 µl DMF. The reaction conditions of 95°C and a reaction time of 8 min were sufficient to yield (3) in 46 % radiochemical yield (in relation to the whole activity on the TLC plate). The hydrolysis of the t-boc group was completed within 8 min at room temperature using trifluoroacetic acid. This solution was basified with triethylamine and 15 mg of N^1-t-boc C^1-p-nitrophenol asparagine (4), which is commercially available, was added in 700 µl of DMF. N^1-t-boc C^1-[^{18}F]fluoroethylamino asparagine (5) was formed with >98% radiochemical yield within 6 min at a temperature of 80 °C (Fig. 3). The

removal of the t-boc group is quantitative within 8 min using trifluoroacetic acid at room temperature. The product was isolated by means of HPLC with 64 H_2O : 36 ethanol as eluent.

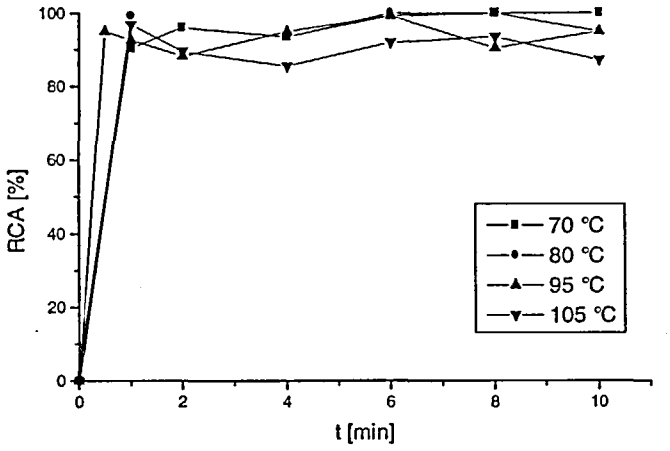

Fig. 3: Yields of C^1-[^{18}F]fluoroethylamino asparagine (in relation to the [^{18}F]fluoroethylamine activity) at several temperatures

It is therefore possible to synthesise a radiolabelled derivative of asparagine in less than one hour with radiochemical yields higher than 20%.
All ^{19}F standard compounds were synthesised and analysed with common spectroscopic methods such as ^{1}H-NMR and mass spectroscopy.

Conclusions:
C^1-[^{18}F]fluoroethylamino asparagine (6) was successfully synthesised in a "one pot synthesis" with a radiochemical yield of 22% (with respect to the initial [^{18}F]fluoride activity). First *in vitro* studies in relation to 2-[^{18}F]FDG and O-(2-[^{18}F]flouroethyl)-L-tyrosine are in progress.

References:
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