Automated radiosynthesis of 2-[^{18}F]fluoroalkyltosylate as labelling synthon for ^{18}F-fluorination via prosthetic alkyl groups

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Introduction: Routine synthesis of n.c.a. radiotracers from short lived positron emitters requires time-optimised reproducible reaction conditions and minimisation of radiation exposure for radiochemists involved. Both requirements can be achieved through fully automated reaction modules which can be preloaded with all reagents, solvents and reactants, placed in shielded fumehoods (hot cells) and controlled from the outside. Included preparative HPLC and sterile-filtration allows discontinuous production of high-purity radiotracers ready for injection into patients. One distinguishes between single-vessel modules for one-step radiosynthesis (e.g. direct fluorination of precursors to the desired product) and two-(multi-)vessel modules for multi step reactions (e.g. fluorination via prosthetic groups). Labelling synthons of high chemical purity are required as well for avoiding side-products in labelling reactions for research and development of new radiotracers.
[^{18}F]Fluoroalkylation is an important tool for the incorporation of ^{18}F-fluorine into target molecules which are not suitable for direct fluorination.

Aim: The well known laboratory method for preparation of n.c.a. ω-[^{18}F]fluoroalkyltosylate had to be transferred onto a self-builded one-vessel module to provide HPLC-purified labelling synthons for ^{18}F-fluoroalkylation.

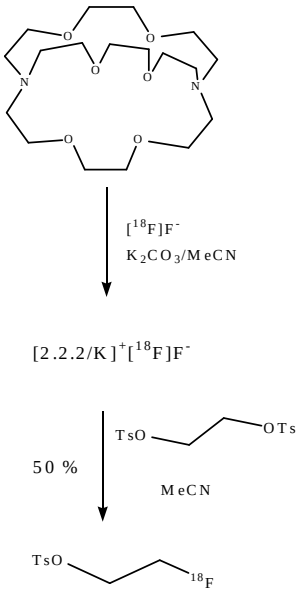

Figure 1: Synthesis scheme for the preparation of n.c.a. 2-[^{18}F]fluoroethyltosylate from ethylene-1,2-ditosylate, [^{18}F]fluoride and potassium carbonate Kryptofix® complex.

Synthesis: [^{18}F]F$^-$ is mainly produced via the ^{18}O(p,n)^{18}F nuclear reaction by irradiation of liquid [^{18}O]H_2O. [^{18}F]F$^-$ in aqueous solution was passed through an anion exchange cartridge (sepak® light QMA) to extract the [^{18}F]fluoride. The radioactivity was eluted as [$K^+ \cap 2.2.2$]^{18}F$^-$ complex directly into the reaction vessel, using a solution of potassium carbonate and Kryptofix®222 in 1 mL MeCN. After removal of residual water by azeotrope destillation at reduced pressure the [$K^+ \cap 2.2.2$]^{18}F$^-$ complex was reacted with ethylene-1,2-ditosylate at 88°C in MeCN for 3 min. The reaction mixture was quenched with eluent (MeCN:H_2O 1:1) and purified by semi-preparative reversed phase liquid chromatography. The product fraction was collected, diluted with H_2O and the product was separated by solid phase extraction on Merck® LiChrolut EN cartridges. Radioactivity was eluted with 1 mL temperated solvent to afford 2-[^{18}F]fluoroethyltosylate in good yields of 45 to 60 % after a total synthesis time of 1 h.

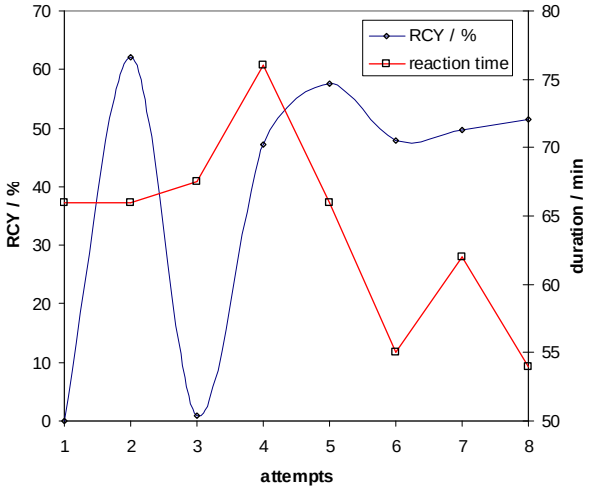

Figure 2: Plot of radiochemical yields and total synthesis duration versus synthesis attempts.

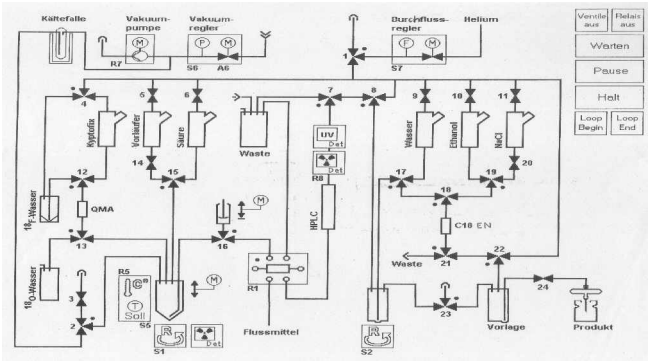

Figure 3: scheme of the synthesis module.

Results: The labelling synthon 2-[^{18}F]fluoroethyltosylate was obtained in good radiochemical yields of at least 45 %. Total synthesis time was optimized to 1 h from beginning of the synthesis till elution of the final product from the solid phase cartridge. Radiochemical purity determined by RP HPLC exceeded 98% in all syntheses. Analogue ω-[^{18}F]fluoroalkyltosylates can be produced by the same procedure without alterations except HPLC-conditions.

References:

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[2] Rösch, F.; Vértes, Nagy, Klencsár, Handbook of Nuclear Chemistry V. 4, Kluwer, Amsterdam, 2003
[3] Riss, P. et al.; Forschungsarbeit, Mainz, Okt. 2005