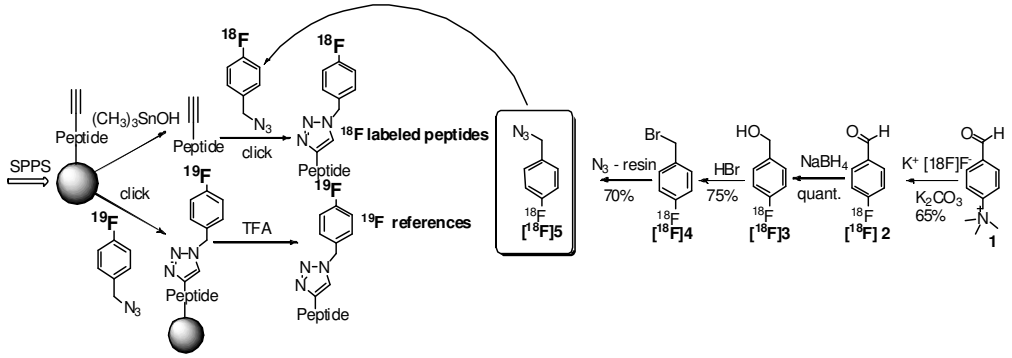
PEPTIDE CLICK LABELLING WITH 1-(AZIDOMETHYL)-4-[^{18}F]-FLUOROBENZENE AND REFERENCE COMPOUNDS SYNTHESIS ON SOLID SUPPORT

Introduction:

Huisgen 1,3 dipolar cycloaddition of alkynes with azides is well adapted to the preparation of radiopharmaceuticals as it is a fast, selective and efficient reaction that requires only benign reaction conditions, simple workup and purification procedures. For these reasons, the ^{18}F radiochemist community has recently begun to develop a library of ^{18}F prosthetic groups bearing alkyne or azide to label compounds of biological interest (peptides, oligonucleotides, lipids, …) (*1-5*). While several alkyne synthons have been reported, only one azide synthon, 2-[^{18}F]fluoroethylazide has been described (ref). Herein, we report the radiosynthesis and the bioconjugation of a new azide synthon: 1-(azidomethyl)-4-[^{18}F]-fluorobenzene **[^{18}F] 5** bearing an aromatic bound fluorine which is known to be less susceptible for *in vivo* radiodefluorination.

Results and discussion:



Azide **[^{18}F] 5** was synthetized within 75 min in 4 steps and with an overall decay-corrected radiochemical yield of 34%. These satisfying results for a four-step procedure have been obtained thanks to the exploitation of solid phase supported reactions and the absence of solvent evaporation process that allow to minimize the losses of time and radioactivity during reaction work-up and purification. This prosthetic group has been "clicked" very rapidly (10 minutes), at room temperature, with a diluted solution of a model alkyne-peptide (0.003M), in mild conditions and with an excellent yield (90%, decay corrected).

Complementarily, as small peptides are most frequently prepared by solid phase synthesis, we have developed a fast and simple procedure to prepare the reference fluorine-19 peptides on solid support by click chemistry (figure 1). This technique has been demonstrated on linear and disulfide cyclic peptides with azide **5** and with two alkyne prostethic groups reported in the literature (2, 3).

Conclusion :

In summary, an azide labeling agent (1-(azidomethyl)-4-[^{18}F]-fluorobenzene) has been produced in a four steps procedure in 75 minutes with a 34% radiochemical yield (decay corrected). Conjugation of [^{18}F]fluoroazide with a model alkyne-peptide produced the desired ^{18}F-radiolabeled peptide in less than 15 minutes with a yield of 90% and excellent radiochemical purity. Additionally, a "click" solid phase synthesis approach for the straightforward preparation of reference peptide compounds has been developed

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