^{18}F LABELING OF BIOMOLECULES USING CLICK CHEMISTRY FOR PET APPLICATIONS : SYNTHETIC DEVELOPMENTS

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Molecular imaging has been defined as the in vivo characterization and measurement of biological process at the cellular and molecular level. By example, molecular imaging creates the possibility of in vivo imaging of gene expression, optimizing drug therapy and imaging drug effect at molecular and cellular level or detecting pathology at a « predisease » state[1].

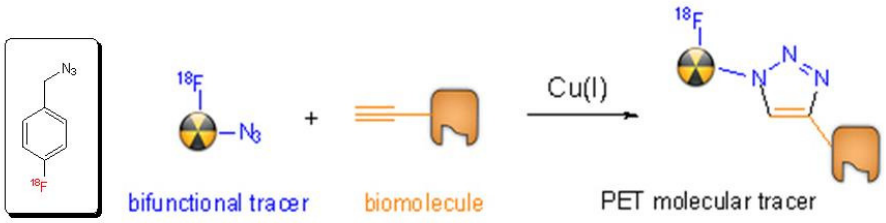
Thanks to its high sensitivity (10^{-9} -10^{-12}M) and "quantitativety", positron emission tomography (PET) is ideally suited to image molecular processes. Among a number of positron-emitting nuclides, fluorine-18 appears to be the best candidate for labeling biomolecules in regards of its favourable physical and nuclear properties.

The challenge for the radiochemist is to introduce a short half-life radioisotope (18-fluorine, $t_{1/2}$ 109.7 min) onto biomolecules which are specific to the biological process studied. In this context, the goal of our work is to develop a general and simple method that permit to label a large library of biological compounds.To achieve this aim, we have selected a fast, selective and efficient reaction that permits to graft ^{18}F tagged molecules onto compounds of biological interest (peptides, oligonucleotides, lipids, …). « Click » reactions and more particularly Huisgen 1,3 dipolar cycloaddition of alkynes with azides are well adapted to the preparation of radiopharmaceuticals as they require only benign reaction conditions, simple workup and purification procedures [2,3]. This strategy implies the introduction of either alkyne or azide groups onto the biomolecules and to prepare a bifunctional tracer featuring the complementary function.

Two ways of functionalization used in the laboratory will be presented:

- Direct peptide functionalization at the N terminal position
- Multi-step procedure based on aromatic amino acids alkynated through Sonogashira reaction

In the other hand, an original four steps, fully automated radiosynthesis of an ^{18}F labeled azide has been developed. Final functionalization is obtained by means of nucleophilic substitution using an azide reagent supported on an anionic resin. At last, preliminary results obtained in « Click » chemistry will be demonstrated. These results confirm that « Click » chemistry for fluorine-18 labeling in well selected conditions has the potential to develop into a general labeling tool thanks to its rapidity and selectivity. The next step must be in vivo studies to determine both stability and toxicity.



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