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Review

Oxime formation for fluorine-18 labeling of peptides and proteins for positron emission tomography (PET) imaging: A review

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ABSTRACT

Positron emission tomography (PET) is a powerful technology for medical and biological imaging and the scope of PET applications is expanding rapidly. The development of suitable PET tracers is at a central position in PET technology. An increasing number of peptides and proteins have been developed for the clinic due to their special properties which small molecule drugs do not have. These advances have provoked interest in the research community to develop radiolabeled peptides and proteins for diagnosis and therapy. Fluorine-18 is a short-lived isotope of fluorine with superior properties for PET-imaging. A majority of presently used radiopharmaceuticals in PET are labeled with fluorine-18. This review focuses on a promising strategy, oxime formation of aminooxy-functionalized peptides with ^{18}F-containing aldehydes, for fluorine-18 labeling of peptides/proteins. At present only a few ^{18}F-containing prosthetic groups are available for oxime formation. The radiosynthesis of the ^{18}F-containing aldehydes and key factors influencing conjugation efficiency of ^{18}F-containing aldehydes with peptides are addressed.

Contents

1. Introduction

The element fluorine has had a profound impact on the pharmaceutical industry, with a significant proportion of the drugs on the market and in research pipelines containing fluorine. Ten of the top 30 best selling medicines in the US in 2008 contained at least one fluorine atom [1]. Fluorine-18 (^{18}F) is a radioactive isotope of fluorine and of major importance in nuclear pharmacy [2,3]. The half-life of ^{18}F is 109.7 min and ^{18}F has a very clean positron decay process (97% β^+ emission) [4]. ^{18}F is the most often used radionuclide for clinical positron emission tomography (PET) imaging and 2-[^{18}F]fluoro-2-deoxy-D-glucose ([^{18}F]FDG) is the most used PET tracer. PET is a sensitive, noninvasive, and quantitative technology for medical and biological imaging. The prerequisite for carrying out PET imaging is to inject a PET tracer to the patient before scanning [5]. Therefore the development of suitable PET tracers has a central position in medical PET applications.

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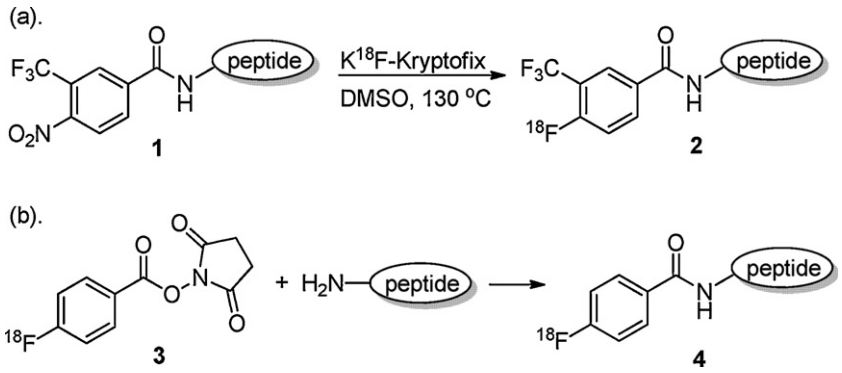


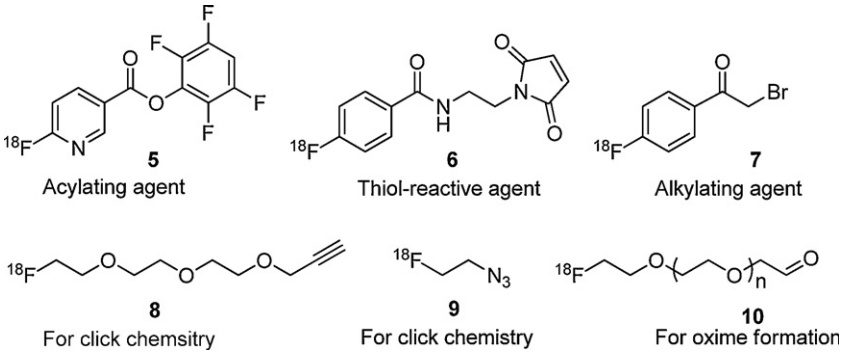
Scheme 1. (a) Direct approach for ^{18}F-fluorination of peptides [13] and (b) labeling of peptides with prosthetic groups (indirect approach for ^{18}F-fluorination of peptides).

Since each organ expresses its unique peptide receptors both in health and in disease, the corresponding peptide ligand (sometimes called the homing peptide) may act as a probe for specific targeting [6]. Numerous peptide drugs are in widespread clinical use, e.g., Exendin and Octreotide analogues. Radiolabeled natural peptides are considered to be promising tracers for diagnosis of major diseases and for monitoring physiological changes [7,8]. There are both direct and indirect approaches for fluorine-18 labeling of peptides. In a direct approach, a covalent C–F bond is formed between the peptide and ^{18}F-fluoride. In an indirect approach, a prosthetic group is produced by incorporation of ^{18}F-fluoride into a bifunctional agent and is subsequently conjugated to a peptide. Albeit it is a less commonly used method than indirect labeling, direct labeling methods have been continuously developed and some exciting results have appeared (Scheme 1a) [9–13]. For example, nucleophilic substitution of a nitro group with K^{18}F-Kryptofix complex was successfully used for the labeling of peptide **1** [13]. The nitro group is a well known leaving group used for aromatic nucleophilic substitution and the *ortho*-trifluoromethyl group facilitates the substitution by decreasing electron density in the aromatic ring [14]. The synthesis was achieved in 40 min and the specific activity of labeled peptide **2** was 79 ± 13 GBq/μmol.

So far, in a majority of cases peptide labeling is achieved by using ^{18}F-containing prosthetic groups (indirect labeling approach, Scheme 1b). Several types of prosthetic groups based on different chemical reactions are available (Scheme 2) [8]. Among acylation agents, *N*-succinimidyl 4-[^{18}F]fluorobenzoate (SFB, **3**) is frequently used to acylate free amino groups in peptides [15–18]. Recently Olberg et al. developed the acylating agent, nicotinic acid tetrafluorophenyl ester **5** (Scheme 2), and the radiosynthesis of prosthetic group **5** is straightforward [19]. When an acylating agent will react with any/all free amino groups available, the peptide precursor should bear only one amino group in order to label the peptide in a specific position. The prosthetic group bearing a maleimide (e.g., compound **6**) is highly thiol-reactive and thus is a commonly used reagent for site-specific labeling of cysteine-containing peptides [20]. 4-[^{18}F]Fluorophenacyl bromide (compound **7**) and 2-bromoketone represent an alternative methodology for peptide labeling based on thiol chemistry, albeit to a lesser extent compared to maleimide-thiol chemistry [21]. Click chemistry (1,3-dipolar cycloaddition) is a very attractive method for bioconjugations, as it is highly compatible with biomolecules and the reactions can be carried out under physiological conditions with high efficiency [22]. In PET applications, it is possible to employ either an alkyne (e.g., compound **8**) or an azide (e.g., compound **9**) as the ^{18}F-prosthetic group for peptide labeling [23,24].

Oxime formation between an aldehyde or a ketone and an aminooxy-bearing compound **11** is widely used for conjugation of biomolecules, as it is a highly chemoselective reaction which can be carried out in aqueous media (Scheme 3a) [25]. In oxime bond formation reactions, other functional groups in biomolecules are tolerated without a need for protection/deprotection processes. Similar to other types of imine formation, oxime formation is a reversible reaction [26,27]. However, due to α-effect nitrogen in the aminoxy group [28], reaction equilibrium favors oxime bond formation and in many cases the reactions can reach completion. The reaction efficiency of oxime bond formation can be dramatically enhanced by a number of catalysts (e.g. aniline, Scheme 3b) [25,26,29]. Aniline forms a Schiff base **12** with an aldehyde or ketone, and **12** undergoes rapid transimination to oxime via the formation of intermediate **13**. The formed oxime exists in *E*- and *Z*-forms in solution and is stable under physiological conditions. The ratio of *E*- to *Z*-form of an oxime partially depends on the size of substitutes at the C=N double bond. Because the two isomers equilibrate quickly in solution, it is not practically useful to isolate *E*- and *Z*-forms from each other [30].

Oxime formation is useful in PET tracers synthesis, because it has high chemoselectivity, straightforward reaction protocol and it



Scheme 2. Examples of prosthetic groups for peptide labeling with fluorine-18.