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Aspects of positron emission tomography radiochemistry as relevant for food chemistry

Review Article

F. Wuest

Positron Emission Tomography Center, Institute of Bioinorganic and Radiopharmaceutical Chemistry, Research Center Rossendorf, Dresden, Germany

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Summary. Positron emission tomography (PET) is a medical imaging technique using compounds labelled with short-lived positron emitting radioisotopes to obtain functional information of physiological, biochemical and pharmacological processes *in vivo*. The need to understand the potential link between the ingestion of individual dietary agents and the effect of health promotion or health risk requires the exact metabolic characterization of food ingredients *in vivo*. This exciting but rather new research field of PET would provide new insights and perspectives on food chemistry by assessing quantitative information on pharmocokinetics and pharmacodynamics of food ingredients and dietary agents. To fully exploit PET technology in food chemistry appropriately radiolabelled compounds as relevant for food sciences are needed. The most widely used short-lived positron emitters are ^{11}C ($t_{1/2} = 20.4$ min) and ^{18}F ($t_{1/2} = 109.8$ min). Longer-lived radioisotopes are available by using ^{76}Br ($t_{1/2} = 16.2$ h) and ^{124}I ($t_{1/2} = 4.12$ d). The present review article tries to discuss some aspects for the radiolabelling of food ingredients and dietary agents either by means of isotopic labelling with ^{11}C or via prosthetic group labelling approaches using the positron emitting halogens ^{18}F, ^{76}Br and ^{124}I.

Keywords: Positron emission tomography – Radiolabelling – Prosthetic group

1 Introduction

Positron emission tomography (PET) is a functional imaging discipline using compounds labelled with short-lived positron emitting radioisotopes to obtain quantitative information of physiological, biochemical and pharmacological processes in living subjects (Phelps, 2000, 2000a; Paans et al., 2002; McCarthy et al., 1994). The interest in PET as a clinical and medical research imaging methodology has steadily grown during the last three decades. Today PET has arrived into the mainstream of clinical imaging practice in the field of oncology, cardiology and neurology. Moreover, PET is gaining more and more importance as a valuable research tool in the process of drug development and evaluation (Klimas, 2002; Fowler et al., 1999; Paans et al., 2000; Gibson et al., 2000; Maclean et al., 2003; Burns et al., 1999).

The extension of PET to the field of food science, however, represents a rather new area of application. The motivation to use PET as a novel research tool in food science stems from the need for a precise knowledge on the physiological effects of bioactive food ingredients as an essential prerequisite for an objective benefit/risk evaluation. Especially the implementation of food biotechnology and specific modified food (Functional Food) in the development of novel food with regard to health promotion or health risk will require an exact metabolic characterization of food ingredients *in vivo*. In this connection, the application of PET as molecular imaging technique with unrivalled sensitivity and specificity has great promise to provide new insights and perspectives on food chemistry by assessing quantitative information on pharmocokinetics and pharmacodynamics of food ingredients and dietary agents.

The potential of PET strongly depends on the availability of suitable PET radiotracers, compounds which are labelled with short-lived positron emitters. The most widely used PET radionuclides are ^{11}C ($t_{1/2} = 20.4$ min), ^{13}N ($t_{1/2} = 9.9$ min), ^{15}O ($t_{1/2} = 2$ min) and ^{18}F ($t_{1/2} = 109.8$ min). Longer-lived positron emitters, which can be bound covalently to organic molecules, are also available by using ^{76}Br ($t_{1/2} = 16.2$ h) and ^{124}I ($t_{1/2} = 4.12$ d).

Carbon, nitrogen and oxygen are the main constituents in most molecules of biological importance. Hence, isotopic labelling with ^{11}C, ^{13}N and ^{15}O will result in radiotracers undistinguishable from their non-labelled counterparts, with the exception of very small kinetic isotope effects. The lack of a positron-emitting isotope of hydrogen can be compensated in many cases by using ^{18}F as a bioisosteric replacement for a hydrogen atom in a molecule. Also a fluorine atom may imitate a hydroxyl group. The short half-live of PET radionuclides usually requires their in-house production, which is accomplished preferentially by means of a dedicated small biomedical cyclotron as the most frequently used production source.

Radiochemistry with positron-emitting radionuclides represents a fundamental but challenge task within the interdisciplinary research field of PET (Fowler et al., 1997; Elsinga, 2002; Pike, 1997; Langström et al., 1999; Wuest, 2003). The present survey wants to cover some important aspects for the design and synthesis of radiolabelled compounds as PET radiotracers with relevance to food chemistry. The first part will focus on potential isotopic radiolabelling routes of small molecule bioactive food ingredients, such as polyphenols and flavonoids, employing the positron emitter ^{11}C. The second part of the overview will deal with the radiolabelling of bioactive peptides and proteins as biomacromolecules with relevance to food science via prosthetic group labelling approaches using the positron-emitting halogens ^{18}F, ^{76}Br and ^{124}I. Bioactive peptides may originate from peptide degradation leading to opioid peptides such as casomorphines or ACE-inhibitors like casokinine and lactokinine. Also, several posttranslational modification processes like transglutaminase-directed peptide or protein cross-linkings, glycosylations and oxidative modifications related to nonenzymatic browning or Maillard reactions (Thorpe et al., 2003) contribute to the formation of biomacromolecules as indicators of tissue aging and pathology. An other class of biomacromolecules include macromolecule replacers in food products such as polydextrose, maltodextrins, modified starches, fibers, and protein and lipid-based replacements like fat analogs and emulsifiers (Setser et al., 1992).

2 ^{11}C–C bond forming reactions as potential tool for ^{11}C-labelling of flavonoids

Flavonoids represent a group of phytochemicals exhibiting a wide range of biological activities arising mainly from their antioxidant properties and ability to modulate several enzymes or cell receptors (Dixon et al., 1999; Rice-Evans, 2001, 2004; Birt et al., 2001; Forkmann et al., 2001). Flavonoids are the most common occurring plant polyphenols found in fruits, vegetables and grains. Their wide occurrence, complex diversity and manifold functions have made flavonoids a very attractive target for chemical, biological and medical studies.

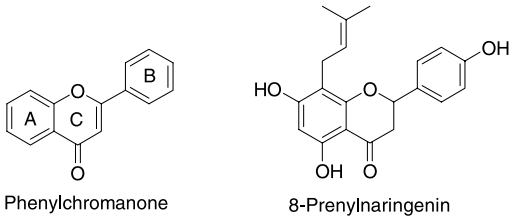

Fig. 1. Chemical structures of phenylchromanone and 8-prenylnaringenin

All flavonoids share a three-ring structure consisting of two aromatic rings A and B, and a central oxygenated heterocyclic ring C. Thus, they can be defined chemically as substances derived from phenylchromanone containing one or more hydroxyl substituents attached to the ring system. Flavonoids are classified according to the oxidation level of the central C ring. Further structural diversity results by the introduction of prenyl substituents as exemplified by the highly potent phytoestrogen 8-prenylnaringenin (Fig. 1).

The common structural features of flavonoids in general and the defined chemical structure of 8-prenylnaringenin in particular preferentially suggests isotopic labelling with ^{11}C via distinct ^{11}C–C bond forming reactions to provide radiolabelled flavonoids as molecular probes for positron emission tomography. The advantage of ^{11}C–C bond forming reactions lays in the possibility to place the ^{11}C label at a distinct position of a given molecule to form metabolically stable radiotracers. It is of great importance that the radiotracer is not rapidly metabolised during the PET measurement since PET can not discriminate between signals originating from the intact radioligand or radiolabelled metabolites.

Several routes for ^{11}C–C bond-forming reactions have been developed and successfully been applied in ^{11}C chemistry (Langström et al., 1999). The carbonation of organometallic reagents with $[^{11}C]CO_2$ is among the oldest and most commonly employed ^{11}C–C formation method for the synthesis of carboxylic acids and corresponding derivatives (Winstead et al., 1969; Matarrese et al., 2002; Oberdorfer et al., 1996). The alkylation of stabilized carbanions, like malonic esters, with ^{11}C-labelled alkyl halides is an other example for the formation of a ^{11}C–C bond (Kilbourn et al., 1984; Antoni et al., 1987). Both

methods make use of an electrophilic ^{11}C-labelling precursor ([^{11}C]CO_2 or [^{11}C]alkyl halides). On the other hand, several nucleophilic ^{11}C-labelled precursors like [^{11}C]cyanide (Hörnfeldt et al., 1994), [^{11}C]methyllithium (Bonasera et al., 2001), [^{11}C]nitromethan (Maeding et al., 1997, 1998, 2000), triphenylphosphonium [^{11}C]methylide (Kihlberg et al., 1990) or triphenylarsonium [^{11}C]methylide (Zessin et al., 1999) are also often used to form ^{11}C–C bonds by the reaction with an electrophilic carbon atom. However, the aforementioned methods often require difficult synthesis sequences, and they are not compatible with many functional groups. In order to circumvent these obstacles, novel technically simple, high-yielding and functional group tolerating synthetic methods for ^{11}C–C bond formations are of particular interest.

In recent years several transition-metal-mediated cross-coupling reactions have been shown to be effective and very innovative approaches in the development of novel ^{11}C–C bond formations. In addition to synthetic methods using cuprate- and copper-zinc-mediated coupling reactions (Kihlberg et al., 1994; Neu et al., 1997; Wuest et al., 2000), several palladium-mediated ^{11}C–C bond-forming reactions have been found to be exceptionally effective. As a result palladium-mediated aromatic cyanation (Andersson et al., 1994), Stille (Björkmann et al., 2000; Karimi et al., 2002), Suzuki (Andersson et al., 1995; Hostetler et al., 1998), and Sonogashira cross-coupling reactions (Wuest et al., 2003a) are presently very frequently used in ^{11}C-chemistry.

Also, several palladium- and selenium-promoted carbonylative coupling reactions with [^{11}C]CO have been shown to be very valuable in the synthesis of a broad range of carbonyl group-containing biologically active compounds like amides, esters and ureas (Karimi et al., 2001; Kihlberg et al., 1999, 2002; Nader et al., 2002; Hostetler et al., 2002). The handling of [^{11}C]CO as a labelling precursor is accompanied by the difficulty to ensure its sufficient trapping in an appropriate organic solvent. However, recent technical developments have facilitated to make this labelling route an exceptional useful approach for the incorporation of a ^{11}C label into a broad variety of compounds (Audrain et al., 2004).

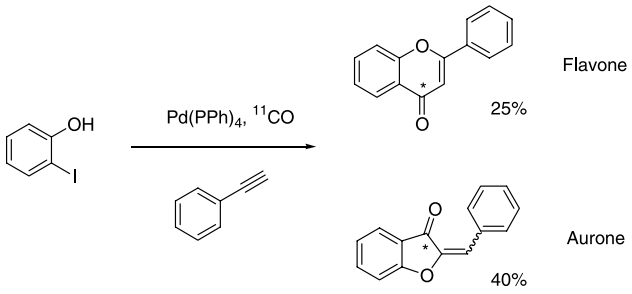

Fig. 2. Carbonylative cross-coupling with [^{11}C]CO

A first attempt to adapt transition metal-mediated ^{11}C–C bond formations to the ^{11}C-labelling of flavanoids was exemplified by the radiosynthesis of flavone (Kihlberg et al., 1999a) (Fig. 2).

The radiolabelling was accomplished by means of a palladium-mediated carbonylative coupling reaction using [^{11}C]CO as the labelling precursor. This labelling route allows the defined incorporation of a ^{11}C carbonyl group into the chromanone subunit typically found in flavonoids. However, cross-coupling of *o*-iodophenol with phenylacetylene in the presence of [^{11}C]CO predominantly led to the formation of aurone rather than to flavone. Moreover, this methodology has not been applied for the radiosynthesis of ^{11}C-labelled naturally occurring flavonoids containing different patterns of OH-groups.

Alternative synthesis routes for the ^{11}C-labelling of flavanoids can be envisaged when prenylated compounds such as 8-prenylnaringenin are used. Thus, the isotopic substitution of one of the two methyl groups present in the prenyl group with a [^{11}C]methyl group represents a promising approach to form a ^{11}C-labelled prenyl group.

A commonly employed strategy to form α,α'-disubstituted alkenes comprises the formation of alkenylzirconium complexes by the cis-insertion of a C–C triple bond into the Zr–H bond of Schwartz's reagent [$Cp_2Zr(H)Cl$] followed by metal-mediated C–C bond formation with electrophiles under retention of the configuration of the C–C douple bond (Wipf et al., 1996).

The principle feasibility of the approach was elaborated by the synthesis of 2-[^{11}C]methylpropenyl benzene via

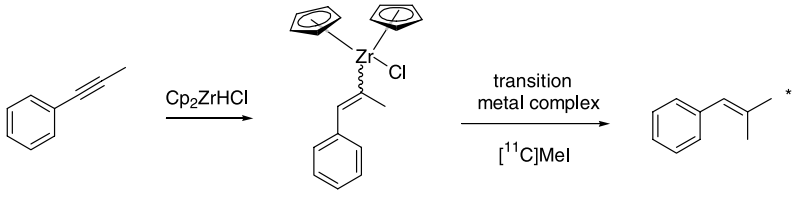

Fig. 3. ^{11}C-labelling via hydrozirconation/^{11}C-methylation reaction

Table 1. Radiochemical yields of transition metal-mediated cross-coupling reaction

Transition metal complex	Radiochemical yield
$Ni(PPh_3)_4$	4%
$Pd(PPh_3)_4$	70%
$Pt(PPh_3)_4$	11%

hydrozirconation/^{11}C-methylation of prop-1-ynyl-benzene with [^{11}C]MeI as a model reaction (Wuest and Maeding, 2004) (Fig. 3).

The reaction conditions were optimised by the variation of different group 10 transition metal complexes. The results are summarized in Table 1.

The radiochemical yield was determined by radio-HPLC representing the percentage of radioactivity area of ^{11}C-labelled product related to the total radioactivity area. The results clearly show that the use transition metal complex $Pd(PPh_3)_4$ is superior to $Ni(PPh_3)_4$ and $Pt(PPh_3)_4$, respectively.

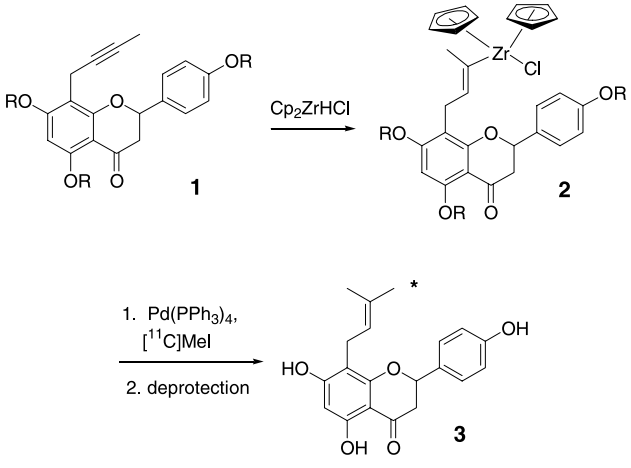

Fig. 4. ^{11}C-labelling of 8-prenylnaringenin via hydrozirconation/^{11}C-methylation

A potential radiosynthesis route involving a hydrozirconation/^{11}C-methylation reaction sequence for the synthesis of ^{11}C-labelled 8-prenylnaringenin is given in Fig. 4.

Alkyne-substituted naringenin **1** is treated with Schwartz reagent to give the corresponding alkenylzirconium derivative **2**, which can be cross-coupled with [^{11}C]MeI in the presence of $Pd(PPh_3)_4$ to afford the desired ^{11}C-labelled 8-prenyl-naringenin **3** after acetyl protecting group cleavage by means of potassium carbonate.

An additional radiolabelling route for the synthesis of ^{11}C-labelled 8-prenylnaringenin **3** may also exploit the well known Stille reaction with [^{11}C]MeI (Björkmann et al., 2000; Karimi et al., 2002). A synthesis scheme is depicted in Fig. 5.

Gester et al. have developed an efficient synthesis of 8-prenylnaringenin via a tandem Claisen/Cope rearrangement (Gester et al., 2001). Thus, using alkenylhalide **4** instead of prenyl alcohol while subjected to reaction condition described by Gester et al. will lead to the formation of compound **5**. The required stannane labelling precursor **6** can easily be prepared via a Pd-catalysed cross-coupling reaction between alkenylhalide and hexamethylditin. Reaction of stannane **6** according to standard Stille reaction conditions with [^{11}C]MeI will provide ^{11}C-labelled 8-prenyl-naringenin **3**.

The advantage of the presented radiolabelling techniques employing [^{11}C]MeI as the coupling partner in the cross-coupling reactions is their relatively broad functional group compatibility. Especially the Stille reaction with [^{11}C]MeI was shown to be very effective while tolerating a broad range of functional groups such as OH-groups as typically present in flavonoids.

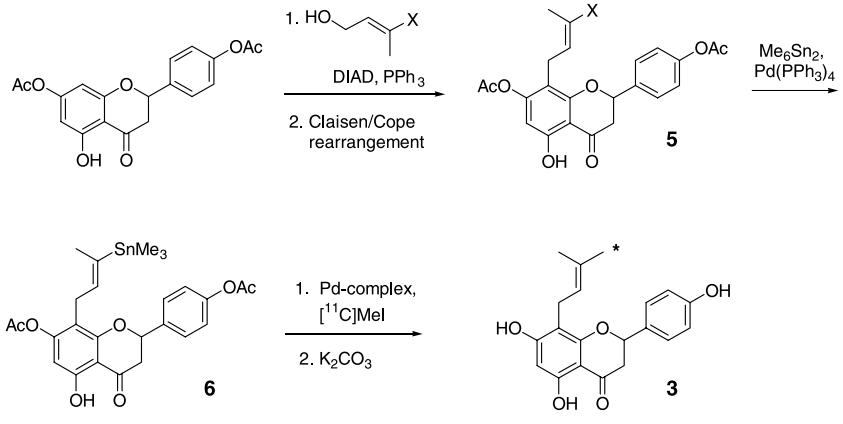

Fig. 5. Synthesis of ^{11}C-labelled 8-prenylnaringenin via Stille reaction with [^{11}C]MeI

3 The use of prosthetic groups for labelling biomacromolecules with the positron emitting halogens ^{18}F, ^{76}Br and ^{124}I

The interest in suitable radiolabelling methods of biomacromolecules with relevance to food science stems from the importance that bioactive peptides derived from peptide degradation, and posttranslational peptide and protein modifications play as food ingredients. However, only little is known about their exact biological and metabolic pathways. Thus, radiolabelling and metabolic characterization of peptides and proteins as food ingredients *in vivo* will provide helpful information in terms of an objective risk/benefit evaluation of food items.

For this purpose especially radiohalogens are particularly useful radionuclides because their chemistry is well-understood, they can form stable covalent bonds, their steric and electronic character causes only minimal alterations to the biomolecule, and the radiolabelling can be accomplished at high specific radioactivity. As a consequence of these benefits, the interest in the radiolabelling of biomacromolecules via radiohalogenation methods has been in the focus of radiopharmaceutical chemistry for several decades.

The positron emitter ^{18}F is an almost ideal radionuclide for PET thanks to its ease of production, favourable physical properties of a 109.8 min half live and the low β^+-energy (0.64 MeV) (Lasne et al., 2002). However, radiochemistry with ^{18}F implies special challenges, and direct incorporation of ^{18}F at high specific radioactivity as [^{18}F]fluoride into biomolecules like proteins and peptides is not possible due to the harsh reaction conditions occurring during [^{18}F]fluoride labelling reactions. In order to circumvent this obstacle peptide and protein labelling with ^{18}F has to be accomplished by means of prosthetic groups, also referred as bifunctional labelling agents. This approach comprises ^{18}F incorporation into a small organic molecule capable of being linked to peptides, proteins, oligonucleotides and antibodies under mild conditions.

The positron-emitting halogens ^{76}Br ($t_{1/2} = 16.2$ h) and ^{124}I ($t_{1/2} = 4.12$ d) represent interesting medium half-life and longer half-life alternatives to the short-lived ^{18}F ($t_{1/2} = 109.8$ min), respectively. The production mode of ^{76}Br and ^{124}I in cyclotrons is based on solid target techniques. Comprehensive overviews on the production of ^{76}Br and ^{124}I have been published recently (Glaser et al., 2003a; Rowland et al., 2003; Finn, 2003). The different physical half-lives of the PET halogens ^{18}F, ^{76}Br and ^{124}I allow different study protocols in terms of the biological half-life of the process to be studied. For example, the recent advances in the use of monoclonal antibodies and other high molecular weight biomolecules in tumour diagnosis and therapy favour the use of long-lived radioisotopes.

The present survey will deal with peptide and protein labelling by means of radiohalogenated small bifunctional molecules capable of being linked to amine or sulfhydryl groups present in the biomacromolecule, or by photochemical conjunction. The direct labelling of biomacromolecules such as proteins and peptides with *in situ* generated electrophilic radioiodine species as the most commonly employed radiohalogenation procedure (Seevers et al., 1982; Wilbur, 1992) will not be discussed.

3.1 ^{18}F-labelled prosthetic groups

Efficient labelling of peptides and proteins with the positron emitter ^{18}F should preferentially occur by the use of prosthetic groups. Approaches involving direct nucleophilic incorporation of [^{18}F]fluoride fail due to the lack of functional groups in the biomolecule required for a nucleophilic ^{18}F-fluorination and, more important, the harsh reaction conditions (high temperature, strongly basic) of radiofluorinations with [^{18}F]fluoride cause denaturation and decomposition of the sensitive biomolecule. On the other hand, direct electrophilc radiofluorination reactions of peptides with [^{18}F]F_2 or [^{18}F]AcOF are in principle possible when tyrosine residues are present (Hebel et al., 1990; Ogawa et al., 2003). However, this approach is accompanied with regioselectivity problems and the resulting ^{18}F-labelled peptides can only be obtained at low specific activity, which may limit their use when saturable biological processes are to be studied (e.g., receptor binding, enzyme binding, specific transport processes etc.).

As a consequence and to overcome the aforementioned problems, several prosthetic groups have been developed and successfully been applied for the mild and site-specific incorporation of ^{18}F into peptides, proteins and other biomacromolecules. ^{18}F incorporation into biomacromolecules via prosthetic groups generally can be accomplished via amine-reactive conjugates, sulfhydryl-reactive conjugates or photochemical reactions. The attachment is achieved either by acylation, amidation, imidation, alkylation, thiourea-forming and oxime-forming reactions, or by photochemistry. In the following section prosthetic groups for ^{18}F-labelling will be presented with respect to their conjugation mode, being amine-reactive, sulfhydryl-reactive and photochemical conjugations.

3.1.1 ^{18}F-labelling of peptides and proteins via amine-reactive conjugates

The most commonly exploited functional group for conjugation of small ^{18}F-labelled prosthetic groups to peptides and proteins is the amine group, which generally represents ε-amino groups of lysine or the *N*-terminus of peptides. Numerous small molecules containing an amine-reactive functionality have been labelled with ^{18}F and conjugated to amine groups.

^{18}F-labelled active esters

The formation of stable amide linkages between an amino group of the biomacromolecule and the prosthetic group belongs to the most prominent reactions for ^{18}F-labelling of peptides and proteins. Hence, a large number of compounds based on small [^{18}F]fluorocarboxylic acids have been developed and tested as suitable bifunctional reagents for fluoroacylation reactions with amines. The amide formation can either be accomplished by *in-situ* activation of small [^{18}F]fluorocarboxylic acids with dicyclohexylcarbodiimide (Müller-Platz et al., 1982; Guhlke et al., 1994; Hostetler et al., 1999b) or, more prominent, by direct aminolysis of several ^{18}F-labelled active esters. Figure 6 depicts the most frequently used ^{18}F-labelled active esters as prosthetic groups for peptide and protein labelling capable of being linked to terminal amine groups via acylation reactions.

Every prosthetic group used for [^{18}F]fluoroacylation reaction has its own advantages and limitations, but the use of *N*-succinimidyl-4-[^{18}F]fluorobenzoate ([^{18}F]SFB) was shown to be the most suitable ^{18}F-labelled active esters in terms of radiochemical yield and *in vivo* stability of the corresponding 4-[^{18}F]fluorobenzoylated peptide or protein conjugate. Moreover, the coupling of [^{18}F]SFB to amine groups via acylation can be performed under mild conditions of pH and temperature compatible with peptides and proteins. Thus, numerous proteins, peptides and other biomacromolecules have successfully been labelled with ^{18}F by conjugation with [^{18}F]SFB (Bergmann et al., 2002; Fredriksson et al., 2001; Page et al., 1994; Vaidyanathan et al., 1994, 1995, 1997; Wester et al., 1996; Wuest et al., 2003b). Optimal reaction conditions for acylation reactions with [^{18}F]SFB were elaborated, being room temperature or slightly elevated temperatures at a pH of 8.2 to 8.6 (Bergmann et al., 2002; Wuest et al., 2003b; Wester et al., 1996). However, a major drawback of the [^{18}F]SFB synthesis is its laborious three-step radiosynthesis, which general outline is shown in Fig. 7. A simple single-step radiosynthesis by direct nucleophilic substitution with [^{18}F]fluoride is not possible.

The [^{18}F]SFB synthesis starts with (1) the nucleophilic aromatic ^{18}F-fluorination of the triflate salt of a

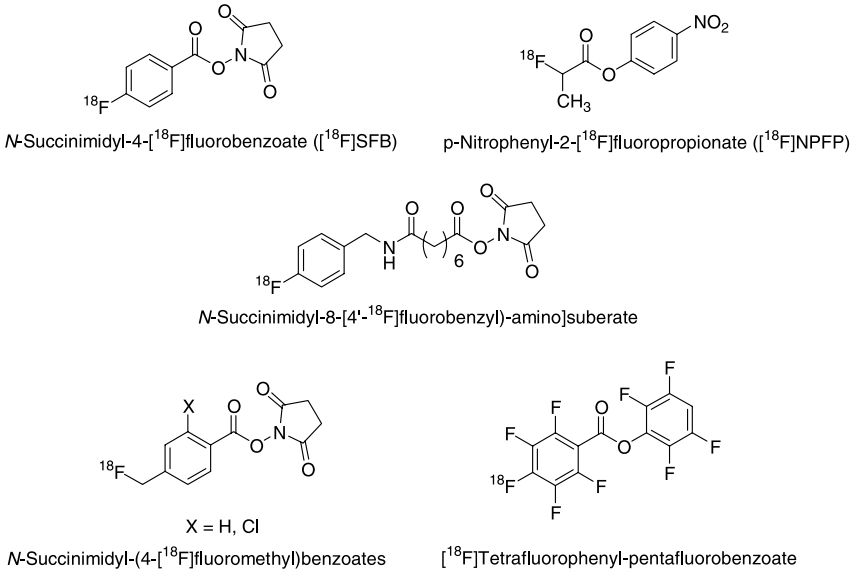

Fig. 6. Frequently used ^{18}F-labelled active esters for peptide and protein labelling via acylation – *N*-Succinimidyl-4-[^{18}F]fluorobenzoate ([^{18}F]SFB): (Vaidyanathan et al., 1992, 1994; Page et al., 1994; Guhlke et al., 1994a; Wester et al., 1996; Wuest et al., 2003). p-Nitrophenyl-2-[^{18}F]fluoropropionate ([^{18}F]NPFP): (Guhlke et al., 1994a, b). *N*-Succinimidyl-8-[4′-^{18}F]fluorobenzyl)-amino]suberate: (Garg et al., 1991; Page et al., 1994). Pentafluorobenzoate esters (Herman et al., 1994). *N*-Succinimidyl-(4-[^{18}F]fluoromethyl)benzoate and 2-chloro-*N*-succinimidyl-(4-[^{18}F]fluoromethyl)-benzoate (Lang et al., 1994, 1997; Moody et al., 1998; Wuest et al., 2003a)

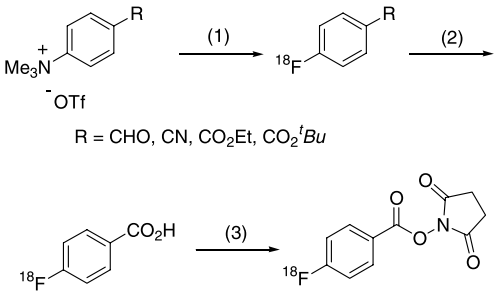

Fig. 7. General three-step reaction pathway of [^{18}F]SFB synthesis

4-trimethylammonium benzaldehyde or benzoic acid derivative followed by (2) the formation of 4-[^{18}F]fluorobenzoic acid as the key intermediate by means of a oxidation or saponification step, and final (3) conversion of 4-[^{18}F]fluorobenzoic acid into its *N*-succinimidyl ester in the presence of several carboxyl group activating agents.

Dependent on the reaction condition, the radiosynthesis of [^{18}F]SFB was accomplished in 25–75% radiochemical yield within 35–100 min. A major improvement in the [^{18}F]SFB synthesis was the introduction of *O*-(*N*-succinimidyl) N,N,N′,N′,-tetramethyluronium tetrafluoroborate (TSTU) as carboxyl group activating agent instead of employing dicyclohexyl carbodiimide (DCC)/*N*-hydroxy-succinimide- or di-(*N*-succinimidyl) carbonate-(DSC) mediated *N*-succinimidyl ester formations. TSTU enables purification of [^{18}F]SFB by SPE filtration rather than a time consuming HPLC separation when DCC/*N*-hydroxy-succinimide and DSC are used. Moreover, the reaction of TSTU with 4-[^{18}F]fluorobenzoic acid proceeds very rapidly compared to the approaches using DCC/*N*-hydroxy-succinimide and DSC. To facilitate the laborious three-step synthesis and to reduce radiation exposure automation of the [^{18}F]SFB synthesis was successfully developed (Zijlstra et al., 2003; Maeding et al., 2004). A strategy for a solid phase synthesis of ^{18}F-labelled peptides via an acylation reaction with 4-[^{18}F]fluorobenzoic acid using *N*-[(dimethylamino)-1H-1,2,3-triazolo[4,5-b] pyridin-1-ylmethylene]-*N*-methylmethanaminium hexa fluorophosphate *N*-oxide (HATU) as the activating agent was also developed (Sutcliffe-Goulden et al., 2000, 2002) (Fig. 8).

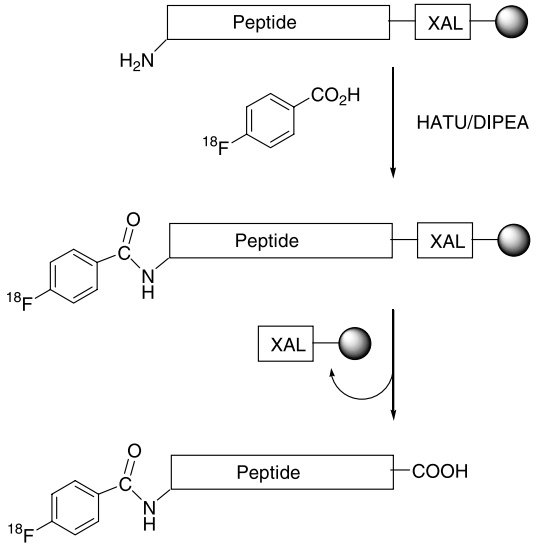

Fig. 8. Solid phase synthesis of ^{18}F-labelled peptides

The solid phase attached peptides could be acylated with 4-[^{18}F]fluorobenzoic acid in radiochemical yields >95% within 3 min, and the labelled peptide could be released from the solid support matrix within 7 min.

The formation of [^{18}F]fluoroacylated peptides can also be accomplished by using 4-nitrophenyl-2-[^{18}F]fluoropropionate ([^{18}F]NPFP) as prosthetic group. Several peptides could successfully be conjugated with [^{18}F]NPFP to give the corresponding 2-[^{18}F]fluoropropionylated peptides such as RDG peptides and octreotide in good radiochemical yields of 65–85% (Guhlke et al., 1994; Haubner et al., 2004; Wester et al., 1996, 1997). The efficiency for ^{18}F-labelling of peptides using [^{18}F]NPFP can considerably be improved when a catalytic amount of HOBt is used during the aminolysis reaction. However, the use of [^{18}F]NPFP as prosthetic group seems not to be suitable when proteins and other higher molecular weight biomolecules like antibodies with a high content of tyrosine and histidine residues should be labelled due to competitive *O*-acylation through tyrosine or hydrolysis of [^{18}F]NPFP through histidine (Wester et al., 1996).

N-Succinimidyl-8-[4′-^{18}F]fluorobenzyl)-amino]suberate as acylation agent was used for the radiofluorination of antibodies and antibody fragments. The radiosynthesis comprises a three step procedure involving the formation of 4-[^{18}F]fluorobenzylamine, which was reacted with disuccinimidyl suberate to form the radiofluorinating agent in radiochemical yields of 25–40% within 55–60 min. The coupling yields of *N*-succinimidyl-8-[4′-^{18}F]fluorobenzyl)-amino]suberate with biomolecules could reach up to 52% when the prosthetic group was purified by HPLC prior its subjection to aminolysis.

The use of ^{18}F-labelled tetrafluorophenyl-pentafluorobenzoate as prosthetic group for radiofluorinations of proteins via acylation has also been reported (Herman et al., 1994). 2,3,5,6-tetrafluorophenyl-pentafluorobenzoate readily incorporated ^{18}F in a single-step procedure to form the desired ^{18}F-labelled acylation agent, which reacted quickly with HAS to give 15% ^{18}F-labelled HAS within

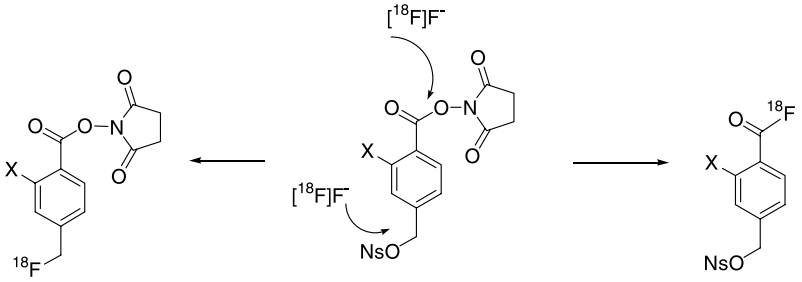

Fig. 9. Competitive reactions during the radiofluorination

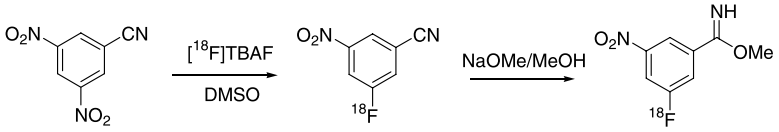

Fig. 10. Radiosynthesis of ^{18}F-labelled imidate ester methyl 3-[^{18}F]fluoro-5-nitrobenzimidate

72 min, based on [^{18}F]fluoride. Due to the ^{19}F to ^{18}F exchange, however, this procedure only provides the prosthetic group at low specific radioactivity. Other prosthetic groups for amino group acylation, which can be synthesized in a single-step radiofluorination, comprise several ^{18}F-labelled benzylfluorides. In a series of reports several ^{18}F-labelled benzylfluoride derivatives containing a *N*-hydroxysuccinimide active ester functional group could be synthesized in low radiochemical yields of 10–18% starting from the corresponding benzyl nosylate precursors in a single-step procedure (Lang et al., 1994, 1997; Moody et al., 1998; Wuest et al., 2003c). The low radiochemical yield can be explained by an acid fluoride formation as competitive reaction of [^{18}F]fluoride with the NHS active ester group (Fig. 9).

Moreover, the single-step preparation advantage is compensated by the low stability of the ^{18}F-labelled benzylfluoride peptide and protein conjugates with regard to a rapid *in vivo* defluorination resulting in high bone accumulation.

^{18}F-labelled imidate esters

Imidates or imido esters have been used for protein modification. The reaction of imidates with proteins proceeds specifically with ε-amino groups of lysine residues to form stable amidine bonds. A suitable ^{18}F-labelled imidate (methyl 3-[^{18}F]fluoro-5-nitrobenzimidate) was prepared in a two-step reaction sequence involving nucleophilic aromatic radiofluorination of 3,5-dinitrobenzonitrile as labelling precursor and subsequent conversion of the nitrile group into the imido ester by treatment with an excess of sodium methoxide (Kilbourn et al., 1987) (Fig. 10). The total radiochemical yield was about 20% in an overall synthesis time less than 1 h.

The stability of ^{18}F-labelled imido ester was investigated in borate buffer at room temperature and pH 8.0. The ^{18}F-labelled imidate undergoes a <10% hydrolysis over a two-hour period. Labelling studies of human serum albumin (HAS) with methyl 3-[^{18}F]fluoro-5-nitrobenzimidate revealed that the amidation reaction (Fig. 11) is pH independent above pH 7.5, but very dependent on the protein concentration.

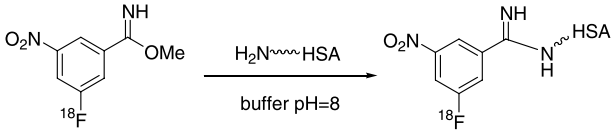

Fig. 11. Labelling of HAS with methyl 3-[^{18}F]fluoro-5-nitrobenzimidate

^{18}F-labelled isothiocyanates

Amines readily react with isothiocyanates to form thioureas, which are fairly stable towards hydrolysis. Many metal chelates have used isothiocyanates for conjugation with biomacromolecules, but only two ^{18}F-labelled benzylfluorides as prosthetic groups have been reported using this functionality (Hedberg et al., 1997; Wuest et al., 2004a). The ^{18}F-labelling was accomplished by the single-step reaction of a benzyliodide or benzylnosylate labelling

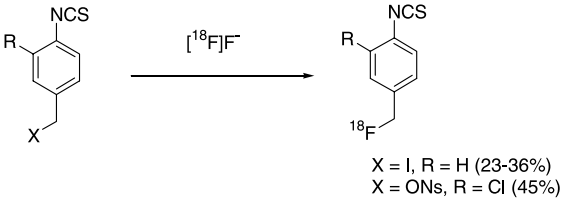

Fig. 12. Radiolabelling of isothiocyanates

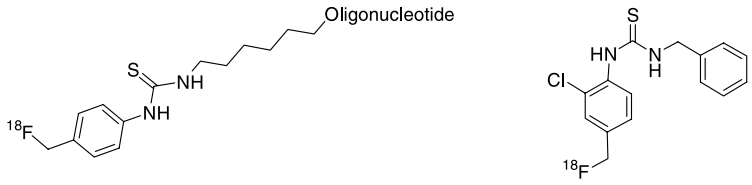

Fig. 13. ^{18}F-labelled thiourea oligonucleotide and benzylamine conjugates

precursor with [^{18}F]fluoride in moderate radiochemical yields (Fig. 12).

^{18}F-labelled isothiocyanates were conjugated to oligonucleotides or to benzyl amine (Fig. 13).

The resulting thiourea oligonucleotide conjugates showed very low *in vitro* stability in different buffers expressed by a high rate of radiodefluorination (Hedberg et al., 1997). The benzyl amine-thiourea conjugate showed appreciable buffer stability at pH 7.4, whereas significant radiodefluorination was observed when the conjugate was studies *in vivo*. Preliminary dynamic PET studies with ^{18}F-labelled thiourea in Wistar rats showed high bone accumulation of radioactivity, which is indicative of a high *in vivo* radiodefluorination rate (Wuest et al., 2004a). These findings are in agreement with the low stabilities reported for other ^{18}F-labelled benzylfluorides containing a NHS functional group.

^{18}F-labelled benzaldehyde

In order to provide a simple single-step, high yield synthesis of an ^{18}F-labelled prosthetic group with sufficient *in vivo* stability and capability of being coupled chemoselectively to biomacromolecules under mild conditions a novel and innovative approach was developed by the group of Wester (Poethko et al., 2003; Poethko et al., 2004). Based on the known efficient and chemoselective oxime formation between an aminooxy and aldehyde group several unprotected aminooxy-functionalized peptides were efficiently coupled with [^{18}F]fluorobenzaldehyde as an easy accessible and stable against *in vivo* radiodefluorination ^{18}F-labelled prosthetic group (Fig. 14).

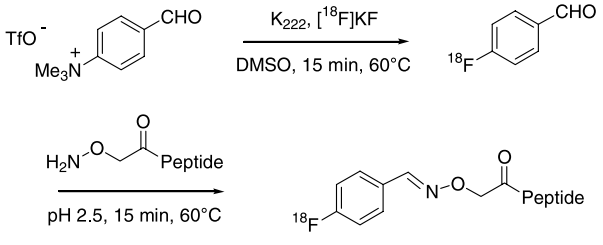

Fig. 14. Radiosynthesis of [^{18}F]fluorobenzaldehyde and oxime formation with aminooxy-functionalized peptides

The method was investigated and applied to various analogs of minigastrin, RGD-peptides and octreotates functionalized with aminooxyacetic acid. Optimal labelling efficiencies of 60–80% were obtained within 15 min at 60°C and a pH between 2 to 4, independent from the peptide used. The major advantages of this approach combine the single-step, high-yield radiosynthesis of an ^{18}F-labelled prosthetic group with a straightforward single-step chemoselective conjugation to unprotected peptides under mild conditions. However, this approach seems to exclude more sensitive biomacromolecules such as proteins and antibodies, which are not generally compatible with the low pH (2–4) and elevated temperatures (60°C) necessary for efficient coupling.

3.1.2 ^{18}F-labelling of peptides and proteins via sulfhydryl-reactive conjugates

Another widely used functional group on biomacromolecules capable of forming conjugates with prosthetic groups is the sulfhydryl or thiol group. As very good nucleophiles sulfhydryl groups can be reacted selectively via alkylation reactions with activated halides and maleimides even in the presence of other functional groups like amino and hydroxyl groups. Thus, sulfhydryl groups can be radiolabelled by means of prosthetic groups very efficiently with usually high radiochemical yield. Cysteine residues as present in proteins and other biomacromolecules are the most prominent source of sulfhydryl groups for formation of conjugates. Biomacromolecules lacking a free sulfhydryl group but containing disulfides as found in cystine disulfide bridges can be treated with 2-mercaptoethanol and dithiothreitol as reducing agents to generate a free sulfhydryl group. Alternatively, biomacromolecules can be reacted with compounds to produce sulfhydryl groups. The most prominent example is the reaction of amino groups in proteins with 2-iminothiolane to form stable amidine conjugates bearing a terminal sulfhydryl group (Fig. 15).

^{18}F-labelled activated α-halo ketones

Activated halides such as α-halo ketones can readily be reacted with soft nucleophiles like the thiolate group to give the corresponding α-keto thioethers. Moreover, this

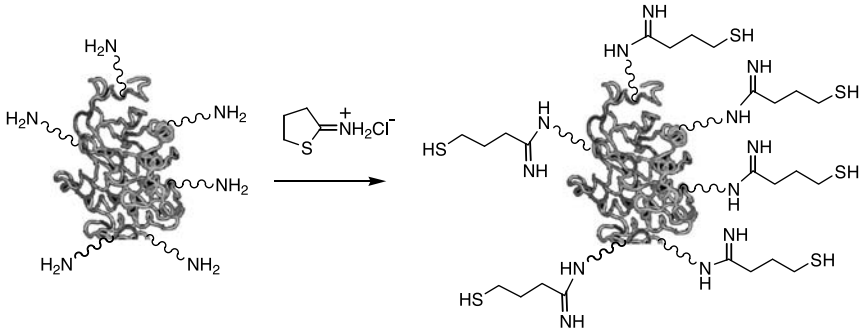

Fig. 15. Generation of free sulfhydryl groups by reaction of protein with 2-imino-thiolane

reaction is quite thiolselective. Thus, several ^{18}F-labelled α-bromo ketones have been developed as important prosthetic groups for conjugation with thiol-group bearing biomacromolecules. One of the first alkylating ^{18}F-labelled prosthetic groups for thiol-group conjugation was 4-[^{18}F]fluorophenacyl bromide ([^{18}F]FPB). This ^{18}F-labelled prosthetic group can be obtained via two different synthesis routes, involving a three-step or two-step radiosynthesis, respectively, as depicted in Fig. 16 (Kilbourn et al., 1987; Dence et al., 1993).

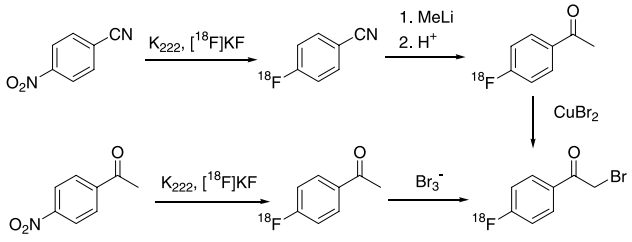

Fig. 16. Two different routes for the synthesis of [^{18}F]FPB

The three-step radiosynthesis commences with the nucleophilic aromatic radiofluorination of 4-nitrobenzonitrile followed by conversion of 4-[^{18}F]fluorobenzo-nitrile into 4-[^{18}F]fluoroacetophenone. Bromination of the methyl ketone was performed with cupric bromide to give the desired [^{18}F]FPB in 85–90% radiochemical purity after SPE-purification. The overall radiochemical yield of [^{18}F]FPB was 28–40%, and the entire synthesis was accomplished within 75 min. The simplified two-step synthesis involves conversion of 4-nitroacetophenone into 4-[^{18}F]fluoro-acetophenone, which was treated with polymer supported bromination with perbromide on Amberlyst® A-26 resin to provide [^{18}F]FPB in 39% radiochemical yield within 15 min.

[^{18}F]FPB was successfully used in the radiolabelling of HAS. The labelling efficiency was shown to be only slightly pH dependent but it was strongly influenced by the protein concentration. Pre-treatment of HSA with 2-iminothiolane to form additional sulfhydryl groups in the protein resulted in a significantly improvement of [^{18}F]FPB incorporation by the factor of 10, reaching a labelling yield of 70% (Downer et al., 1993). Other alkylating ^{18}F-labelled prosthetic groups based on α-halo ketones comprise *N*-(4-[^{18}F]fluorobenzyl)-2-bromoacetamide and 2-bromo-*N*-[3-(2-[^{18}F]fluoropyridin-3-yloxy)propyl]acetamide (Fig. 17).

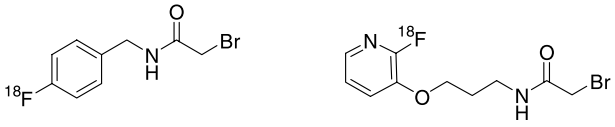

Fig. 17. ^{18}F-labelled prosthetic groups *N*-(4-[^{18}F]fluorobenzyl)-2-bromoacetamide and 2-bromo-*N*-[3-(2-[^{18}F]fluoropyridin-3-yloxy)propyl] acetamide

Both prosthetic groups can be prepared via a laborious three-step radiosynthesis with overall radiochemical yields of 40–45% within 85–95 min, and 30–34% within 80–85 min, respectively (Dolle et al., 1996; Kuhnast et al., 2000; Kuhnast et al., 2002, 2004). Both radiosyntheses could be performed in a shielded hot cell using a computer-assisted Zymate robot system. *N*-(4-[^{18}F]fluorobenzyl)-2-bromoacetamide and 2-bromo-*N*-[3-(2-[^{18}F]fluoropyridin-3-yloxy)propyl]acetamide were used for ^{18}F-labelling of several oligonucleotides bearing a phosphorothioate group at the 3′ end (Dolle et al., 1996; Kuhnast et al., 2000, 2004). *N*-(4-[^{18}F]fluorobenzyl)-2-bromoacetamide was also reacted with peptide nucleic acids employing the thiol function of cysteine attached to the C-terminus (Kuhnast et al., 2002).

^{18}F-labelled maleimides

Maleimide-containing compounds react with sulfhydryl groups according to a Michael-reaction to give thioethers as shown in Fig. 18.

This reaction is usually performed at pH 7 or below to prevent decomposition of the base-sensitive maleimide group. The reactions generally proceed clean and are complete within a few minutes. The first ^{18}F-labelled prosthetic

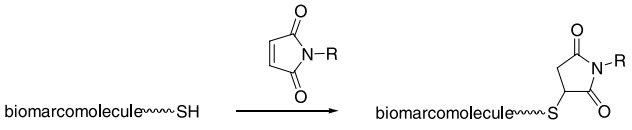

Fig. 18. Michael addition of maleimides with thiol group to form thioethers

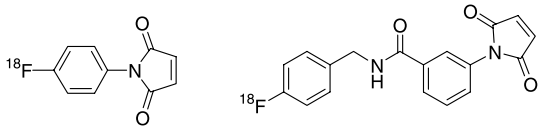

Fig. 19. *N*-(4-[^{18}F]fluorophenyl)maleimide and *m*-maleimido-*N*-(4-[^{18}F]fluoro-benzyl)-benzamide

groups containing a maleimide group synthesized were *N*-(4-[^{18}F]fluorophenyl)maleimide and *m*-maleimido-*N*-(4-[^{18}F]fluorobenzyl)-benzamide, which could be prepared in four steps and three steps in 15% and 10% radiochemical yields, respectively (Fig. 19) (Shuie et al., 1989).

A [^{18}F]fluoropyridine-based maleimide reagent related to 2-bromo-*N*-[3-(2-[^{18}F]fluoropyridin-3-yloxy)propyl] acetamide for protein labelling was developed by Dolle (Fig. 20) (Dolle et al., 2003). The three step radiosynthesis gave the ^{18}F-labelled prosthetic group in 28% radiochemical yield within 110 min including HPLC purification. The compound was used in the ^{18}F-labelling an 8 kDa mini-protein.

The innovative approach employing oxime formation by reaction of aminooxy groups with readily available 4-[^{18}F]fluorobenzaldehyde as exemplified for peptide radiolabellings (Poethko et al., 2003, 2004) was extended to aminooxy-functionalized maleimides for sulfhydryl group conjugation. In multi-step synthesis sequences a new heterobifunctional linker bearing an aldehyde-reactive aminooxy group besides a thiol-reactive maleimide group was prepared in overall yield of 18% (seven steps) or 29% (five steps) (Toyokuni et al., 2003).

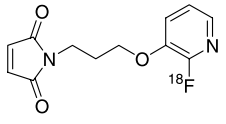

Fig. 20. [^{18}F]fluoropyridine-based maleimide as prosthetic group

The ^{18}F-labelled prosthetic group *N*-{4-[(4-[^{18}F]fluorobenzylidene)aminooxy]butyl}-maleimide was synthesized in a two step procedure involving preparation of 4-[^{18}F]fluorobenzaldehyde followed by oxime formation in overall radiochemical yield of 35% within 60 min (Fig. 21).

Initial radiolabelling experiments were carried out with thiol group-containing tripeptide glutathione and thio-functionalized oligonucleotides in phosphate buffer (pH 7.5) at room temperature. After 10 min, the corresponding ^{18}F-labelled oxime conjugates were obtained in radiochemical yields up to 70%.

3.1.3 ^{18}F-labelling of peptides and proteins via photochemical reactions

Conjugations of azides to biomacromolecules via photolysis are frequently used techniques in biochemistry and molecular biology for receptor-, enzyme-, or topological labelling. The principle of such photochemical conjunction consists of the generation of highly reactive nitrene intermediates by the treatment of azides with UV light, and subsequent reaction of the nitrene intermediates with amino groups abundant in biomacromolecules like proteins. These very fast, non-specific reactions can be of value for conjugation a radiolabelled compound to biomacromolecules. For this purpose several aryl azides were labelled with the positron emitter ^{18}F. Photolyses of the azide functionality gives the corresponding singlet nitrene, which immediately undergoes a rearrangement to form an azacycloheptatrien intermediate. This Intermediate can react with an amino group to form a 2-substituted 3*H*-azepine attached to the biomacromolecule via an amidine bound (Fig. 22) (Hashizume et al., 1995; Wester et al., 1996; Lange et al., 2002).

The radiosyntheses of ^{18}F-labelled arylazides 4-azidophenacyl-[^{18}F]fluoride ([^{18}F]APF) and 3-azido-5-nitrobenzyl-[^{18}F]fluoride ([^{18}F]ANBF) as prosthetic groups for photoconjugation of biomacromolecules were easily accomplished in a single-step reaction starting from the corresponding α-bromo ketone or benzyltosylate precursor, respectively, in 50–70% radiochemical yields. [^{18}F]APF conjugated with several proteins, being human serum albumin, transferrin, immunoglobulin G and avidin in 25–30% radiochemical yield. [^{18}F]ANBF was photochemically

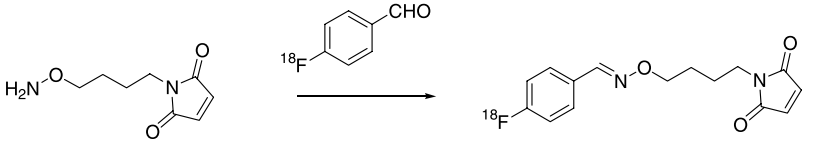

Fig. 21. Radiosynthesis of *N*-{4-[(4-[^{18}F]fluorobenzylidene)aminooxy]butyl}-maleimide

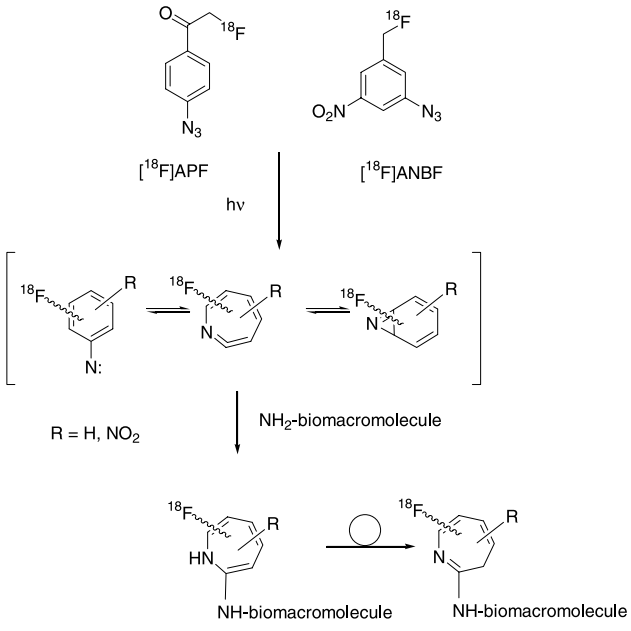

Fig. 22. Photolysis and consecutive rearrangement reactions for conjugation of [^{18}F]APF and [^{18}F]ANBF with biomacromolecules

conjugated to an amine modified 15-base, single stranded, DNA aptamer with up to 20% radiochemical yield. A reaction route for the conjugation of thiol groups with 4-[^{18}F]fluorobenzene-diazonium salts via 4-[^{18}F]fluorophenyldiazo sulfides and subsequent photolysis to form ^{18}F-labeled S-aryl-cysteine and cysteine-containing peptides was developed by Patt et al., 2002. A related approach has been utilized for substoichiometric aromatic fluorinations by silver-ion mediated decomposition of aryl diazo sulfides (Haroutounian et al., 1991).

4-[^{18}F]fluorobenzenediazonium cation was prepared in three steps starting from 1,4-dinitrobenzene in overall radiochemical yield of 60%. The 4-[^{18}F]fluorobenzenediazonium ion readily reacts with the thio group of cysteine to give *S*-4-[^{18}F]fluoro-phenyldiazocysteine, which was photochemically converted into *S*-4-[^{18}F]fluorophenylcysteine and by irradiation with 366 nm light (Fig. 23).

This method was further applied to the synthesis of *S*-4-[^{18}F]fluorophenyl-substituted tripeptide glutathione.

3.2 ^{76}Br- and ^{124}I-labelled prosthetic groups

Studies of slow biochemical processes requires access to longer-lived radionuclides than the conventional PET radionuclides such as ^{11}C, ^{13}N, ^{15}O and ^{18}F. Thus, recent advances in molecular tumour biology has prompted the application of monoclonal antibodies and other highly specific-binding biomacromolecues. This fact more and more favours long-lived radioisotopes in tumour diagnosis and therapy, especially based on radioimmunotargeting. The use of high affinity ligands labelled with long-lived radionuclides would also allow more accurate studies of receptor sites. Late images of these compounds will reflect the domination of receptor-bound radiotracers rather than non-specific binding, which may be considerable when short-lived radionuclides are used.

The medium- and long-lived positron emitting radiohalogens ^{76}Br ($t_{1/2} = 16.2$ h) and ^{124}I ($t_{1/2} = 4.12$ d) are interesting candidates when slow biochemical kinetics of brominated and iodinated compounds should be studied via positron emission tomography. Moreover, their convenient half lives also allow transport to several other research site (satellite concept). Many methods for their production has been developed, but especially recent advances in solid target technique using small biomedical cyclotrons has significantly improved access to these radionuclides (Beyer et al., 2000; Finn et al., 2003; Glaser et al., 2003; McCarthy et al., 2001; Nickles et al., 2003; Pagani et al., 1997; Qaim et al., 2003; Rowland et al., 2003; Schlyer 2003).

The radiochemistry of bromine and iodine is very similar, and basic considerations of radiobromine and radioiodine chemistry has extensively been reviewed in the literature (Coenen et al., 1983; Maziere et al., 1986, 2001; Seevers et al., 1982; Wilbur et al., 1992). In contrast to ^{18}F, radiobromine and radioiodine can very readily introduced directly into compounds via electrophilic substitution reaction by means of various chemical oxidising agents such as H_2O_2, CH_3CO_3H, HOCl, chloamine T, iodobead® or iodogen®. The direct labelling of proteins with electrophilic radioiodine and radiobromine can be accomplished when highly activated aromatics such as phenolic rings of tyrosine residues and imidazole rings

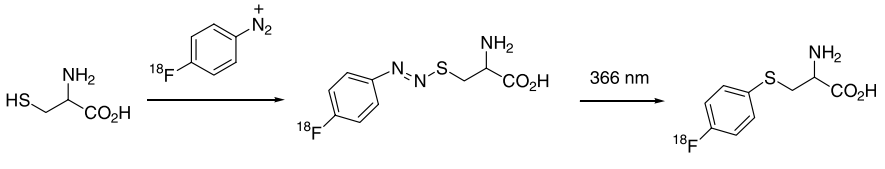

Fig. 23. Photochemical conjuction of thiol groups with 4-[^{18}F]fluorobenzene-diazonium ions

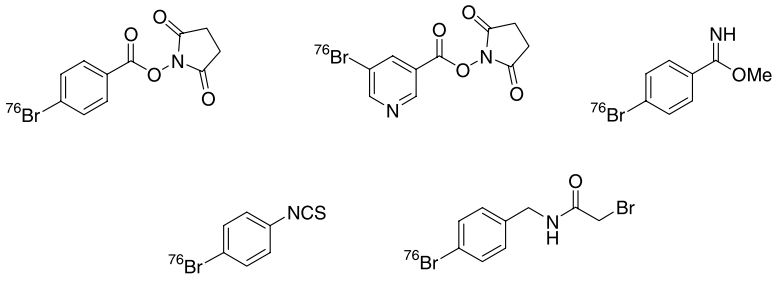

Fig. 24. Structures of ^{76}Br-labelled prosthetic groups

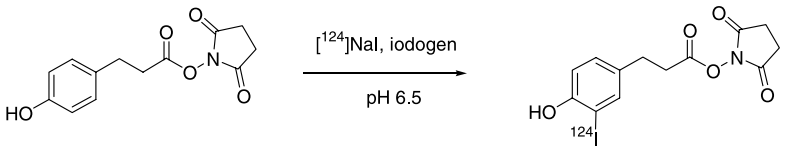

Fig. 25. Radiosynthesis of ^{124}I-labelled Bolton-Hunter reagent [^{124}I]SHPP

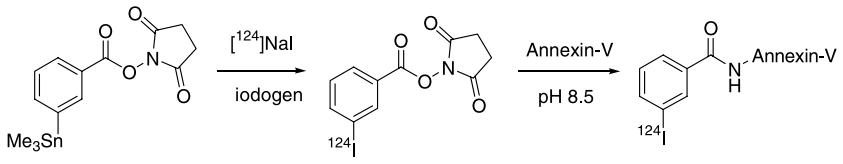

Fig. 26. Preparation of [^{124}I]*m*-SIB and [^{124}I]*m*-IBA-annexin-V

of histidine are present. However, the oxidative conditions in direct labelling may be too harsh and, therefore, may cause substantial damage to the biomacromolecule, which can result in a loss of biological activity. Thus, indirect radiolabelling of biomacromolecules with ^{76}Br and ^{124}I via small radiolabelled prosthetic groups would provide much milder labelling conditions. For this purpose several prosthetic groups were synthesized employing a halodestannylation as key step for the introduction of the radiohalogens ^{76}Br and ^{124}I.

^{76}Br-labelled prosthetic groups

Several ^{76}Br-labelled prosthetic groups for conjugation to peptides, oligonucleotides and antibodies have been developed (Fig. 24).

The prosthetic groups were prepared in a single radiolabelling step using a bromodestannylation (Yngve et al., 2001; Höglund et al., 2000, 2001; Sundin et al., 1999) or bromodesilation reaction (Kuhnast et al., 2000b) with an electrophilic radiobromine species. The use of polyhedral boron anions as linkers for attachment of radiobromine to antibodies was reported recently (Winberg et al., 2004; Bruskin et al., 2004). These compounds were shown to form strong boron-bromine bond. Moreover, an enzymatic debromination is very unlikely to occur due to the unique chemical character of this endogeneous compounds.

^{124}I-labelled prosthetic groups

^{124}I-labelled prosthetic groups were conjugated to antibodies, the MDR probing compounds doxorubicin and daunorubicine, and Annexin-V (Glaser et al., 2002, 2003; McGarry et al., 1988; Sosabowski et al., 1997). The preparation of the ^{124}I-labelled Bolton-Hunter reagent was accomplished in 25–58% radiochemical yield by direct radioiodination of N-succinimidyl-3-(4-hydroxyphenyl)-propionate with [^{124}I]NaI, which was oxidised with iodogen® (Fig. 25). Conjugation of [^{124}I]SHPP with VG76e succeeded in 17–28% labelling efficiency.

Another ^{124}I-labelled prosthetic group ([^{124}I]*m*-SIB) was prepared via a radioiodo-destannylation reaction in 22% radiochemical yield (Fig. 26). After incubation of [^{124}I]*m*-SIB with Annexin-V, 14-25% of radiolabelled annexin-V could be obtained after gel-filtration.

4 Summary and conclusion

In the last decades positron emission tomography (PET) was mainly focused on applications in clinical and biomedical routine and research. PET was also shown to be a valuable tool within the complex process of drug development and evaluation. The extension of the PET methodology to the field of food science as rather new field of application opens novel and innovative ways for a more precise and accurate benefit/risk evaluation of food

ingredients. The rapid implementation of food biotechnology and specific modified food requires a precise assessment of pharmacokinetics and pharmacodynamics of bioactive food ingredients.

Bioactive food ingredients and other dietary agents may comprise small molecules such as flavonoids and other polyphenols, or biomacromolecules such as peptides or proteins. Small molecules suggest isotopic labelling with ^{11}C to provide PET radiotracers exhibiting the same chemical and biochemical properties like their non-radioactive counterparts. For that purpose, ^{11}C–C bond forming reactions are of particular value to introduce the radiolabel into a defined position of a given molecule. The development of novel radiochemical tools for ^{11}C labelling has made tremendous progress in the last years, and especially transition metal-mediated reactions can now be used for the mild and effective incorporation of an ^{11}C label.

On the other hand, many compounds with relevance to food chemistry comprise biomacromolecules, such as peptides or proteins. Here, the radiolabelling should occur under especially mild conditions compatible with the sensitive nature of proteins and peptides. Consequently, several prosthetic group approaches using positron-emitting halogens will become more and more important. The use of ^{18}F as the most prominent positron-emitting halogen has prompted the development of numerous prosthetic groups capable of being linked to biomacromolecules. However, [^{18}F]SFB was shown to be one of the most suitable ones, and automation of [^{18}F]SFB synthesis will further promote the application of this prosthetic group for effective protein and peptide labelling under mild conditions. An extension of the time window of the biological process to be studied can be achieved when ^{76}Br or ^{124}I are used.

The availability of suitable radionuclides (^{11}C, ^{18}F, ^{76}Br and ^{124}I) and radiolabelling techniques (^{11}C–C bond forming reactions, prosthetic groups) are important prerequisites that will accelerate and assist PET to enter the field of food science.

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References

Andersson Y, Langström B (1994) Transition metal-mediated reactions using [^{11}C]cyanide in the synthesis of ^{11}C-labelled aromatic compounds. J Chem Soc, Perkin Trans 1 1994: 1395–1400

Andersson Y, Cheng A, Langström B (1995) Palladium-promoted coupling reactions of [^{11}C]methyl iodide with organotin and or ganoboron compounds. Acta Chem Scand 49: 683–691

Antoni G, Langström B (1987) Asymmetric synthesis of L-2-amino[3-^{11}C]butyric acid, L-[3-^{11}C]norvaline and L-[3-^{11}C]valine. Acta Chem Scand B 41: 511–517

Audrain H, Martarello L, Gee A, Bender D (2004) Utilisation of [^{11}C]-labelled boron carbonyl complexes in palladium carbonylation reaction. Chem Commun 7: 558–559

Bergmann R, Scheunemann M, Heichert C, Maeding P, Wittrich H, Kretzschmar M, Rodig H, Tourwé D, Iterbeke K, Chavatte K, Zips D, Reubi JC, Johannsen B (2002) Biodistribution and catabolism of ^{18}F-labeled neurotensin (8–13) analogs. Nucl Med Biol 29: 61–72

Beyer GJ, Pimentel-Gonzales G (2000) Physicochemical and radiochemical aspects of separation of radioiodine from TeO_2-targets. Radiochim Acta 88: 175–178

Birt DF, Hendrich S, Wang W (2001) Dietary agents in cancer prevention: flavonoids and isoflavonoids. Pharmacol Ther 90: 157–177

Björkman M, Doi H, Resul B, Suzuki M, Noyori R, Watanabe Y, Langström B (2000) Synthesis of a ^{11}C-labelled Prostaglandin F2α analogue using an improved method for stille reactions with [^{11}C]methyljodide. J Labelled Compd Radiopharm 43: 1327–1334

Bonasera TA, Grue-Sorensen G, Ortu G, Binderup E, Bergstrom M, Bjorkling F, Langström B (2001) The synthesis of [26,27-^{11}C]dihydroxyvitamin D(3), a tracer for positron emission tomography (PET). Bioorg Med Chem 9: 3123–3128

Bruskin A, Sivaev I, Persson M, Lundqvist H, Carlsson J, Sjoberg S, Tolmachev V (2004) Radiobromination of monoclonal antibody using potassium [^{76}Br] (4 isothiocyanatobenzyl-ammonio)-bromodecahydro-closo-dodecaborate (Bromo-DABI). Nucl Med Biol 31: 205–211

Burns HD, Hamill TG, Eng WS, Francis B, Fioravanti C, Gibson RE (1999) Positron emission tomography neuroreceptor imaging as a tool in drug discovery, research and development. Curr Opin Chem Biol 3: 388–394

Coenen HH, Moerlein SM, Stöcklin G (1983) No-carrier-added radiohalogenation methods with heavy halogens. Radiochim Acta 34: 47–68

Dence CS, McCarthy TJ, Welch MJ (1993) Improved synthesis of [^{18}F]4-fluorophenacyl bromide: the use of polymer supported perbromide. Appl Radiat Isot 44: 981–983

Dixon RA, Steele CL (1999) Flavonoids and isoflavonoids – a gold mine for metabolic engineering. Trends Plant Sci 4: 394–400

Dolle F, Hinnen F, Vaufrey F, Tavitian B, Crouzel C (1996) A general method for labelling oligonucleotides with ^{18}F for *in vivo* PET imaging. J Labelled Compd Radiopharm 39: 319–329

Dolle F, Hinnen F, Lagnel B, Boisgard R, Sanson A, Russo-Marie F, Tavitian B (2003) Radiosynthesis of a [^{18}F]fluoropyridine-based maleimide reagent for protein labelling. J Labelled Compd Radiopharm 46: S15

Downer JB, McCarthy TJ, Edwards WB, Anderson CJ, Welch MJ (1993) Reactivity of p-[^{18}F]fluorophenacyl bromide for radiolabeling of proteins and peptides. Appl Radiat Isot 48: 907–916

Elsinga PH (2002) Radiopharmaceutical chemistry for positron emission tomography. Methods 27: 208–127

Finn R (2003) Chemistry applied to iodine radionuclides. In: Welch MJ, Redvanly CS (eds) Handbook of radiopharmaceuticals. John Wiley & Sons, New York, pp 423–440

Forkmann G, Martens S (2001) Metabolic engineering and applications of flavonoids. Curr Opin Biotechnol 12: 155–160

Fowler JS, Wolf AP (1997) Working against time: rapid radiotracer synthesis and imaging the human brain. Acc Chem Res 30: 181–188

Fowler JS, Volkow ND, Wang GJ, Ding YS, Dewey SL (1999) PET and drug research and development. J Nucl Med 40: 1154–1163

Fredrickson A, Johnström P, Stone-Elander S, Jonasson P, Nygren PÅ, Ekberg K (2001) Labeling of human C-peptide by conjugation with N-succinimidyl-4-[^{18}F]fluorobenzoate. J Labelled Compd Radiopharm 44: 509–519

Garg PK, Garg S, Zalutsky MR (1991) Fluorine-18 labeling of monoclonal antibodies and fragments with preservation of immunoreactivity. Bioconjug Chem 2: 44–49

Gester S, Metz P, Zierau O, Vollmer G (2001) An efficient syntheis of the potent phytoestrogens 8-prenylnaringenin and 6-(1,1-dimethylallyl) naringenin by europium(III)-catalyzed Claisen rearrangement. Tetrahedron 57: 1015–1018

Gibson RE, Burns HD, Hamill TG, Eng WS, Francis BE, Ryan C (2000) Non-invasive radiotracer imaging as a tool for drug development. Curr Pharm Des 6: 973–989

Glaser M, Carroll VA, Collingridge DR, Aboagye E, Price P, Bicknell R, Harris AL, Luthra SK, Brady F (2002) Preparation of the iodine-124 derivative of the Bolton-Hunter reagent ([^{124}I]I-SHPP) and its use for labelling a VEGF antibody as a PET tracer. J Labelled Compd Radiopharm 45: 1077–1090

Glaser M, Collingridge DR, Aboagye EO, Bouchier-Hayes L, Hutchinson OC, Martin SJ, Price P, Brady F, Luthra SK (2003a) Iodine-124 labelled annexin-V as a potential radiotracer to study apoptosis using positron emission tomography. Appl Radiat Isot 58: 55–62

Glaser M, Luthra SK, Brady F (2003b) Applications of positron-emitting halogens in PET oncology. Int J Oncol 22: 253–267

Guhlke S, Coenen HH, Stöcklin G (1994a) Fluoroacylation agents based on small n.c.a. [^{18}F]fluorocarboxylic acids. Appl Radiat Isot 45: 715–727

Guhlke S, Wester HJ, Bruns C, Stöcklin G (1994b) (2-[^{18}F]fluoropropionyl-(D)phe1)-octreotide, a potential radiopharmaceutical for quantitative somatostatin receptor imaging with PET: synthesis, radiolabeling, *in vitro* validation and biodistribution in mice. Nucl Med Biol 21: 819–825

Haroutounian SA, DiZio JP, Katzenellenbogen JA (1991) Aromatic fluorination by silver-ion promoted decomposition of aryl diazo sulfides: efficient utilization of substoichiometric levels of fluoride ion. J Org Chem 56: 4993–4996

Hashizume K, Hashimoto N, Miyake Y (1995) Synthesis of positron labelled photoactive compounds: ^{18}F labelled aryl azides for positron labelling of biochemical molecules. J Org Chem 60: 6680–6681

Haubner R, Kuhnast B, Mang C, Weber WA, Kessler H, Wester HJ, Schwaiger M (2004) [^{18}F]Galacto-RGD: synthesis, radiolabeling, metabolic stability, and radiation dose estimates. Bioconjug Chem 15: 61–69

Hebel D, Kirk KL, Cohen LA, Labroo VM (1990) First direct fluorination of tyrosine-containing biologically active peptides. Tetrahedron Lett 31: 619

Herman LW, Fischman AJ, Tompkins RG, Hanson RN, Byon C, Strauss HW, Elmaleh DR (1994) The use of pentafluorophenyl derivatives for the ^{18}F labelling of proteins. Nucl Med Biol 21: 1005–1010

Hedberg E, Langström B (1997) Synthesis of 4-([^{18}F]fluoromethyl)phenyl isothiocyanate and its use in labelling oligonucleotides. Acta Chim Scand 51: 1236–1240

Hoglund J, Tolmachev V, Orlova A, Lundqvist H, Sundin A (2000) Optimized indirect (76)Br-bromination of antibodies using N-succinimidyl para-[^{76}Br]bromobenzoate for radioimmuno PET. Nucl Med Biol 27: 837–843

Hoglund J, Tolmachev V, Orlova A, Lundqvist H, Sundin A (2001) Cellular uptake and processing of directly and indirectly ^{125}I-iodinated and ^{76}Br-brominated monoclonal antibody A33. J Labelled Compd Radiopharm 44: S712–S714

Hörnfeldt K, Langström B (1994) Synthesis of [^{11}C]cyanoalkyltriphenylphosphoranes via [^{11}C]cyanide substitution on haloalkyl-phosphonium salts. J Labelled Compd Radiopharm 34: 707–715

Hostetler ED, Burns HD (2002) A remote-controlled high pressure reactor for radiotracer synthesis with [^{11}C]carbon monoxide. Nucl Med Biol 29: 845–848

Hostetler ED, Jonson SD, Welch MJ, Katzenellenbogen JA (1999a) Synthesis of 2-[^{18}F]fluoroestradiol, a potential diagnostic imaging agent for breast cancer: strategies to achieve nucleophilic substitution of an electron-rich aromatic ring with [^{18}F]F^{-}. J Org Chem 64: 178–185

Hostetler ED, Edwards WB, Anderson CJ, Welch MJ (1999b) Synthesis of 4-[^{18}F]fluorobenzoyl octreotide and biodistribution in tumour-bearing Lewis rats. J Labelled Compd Radiopharm 42: S720–S722

Karimi F, Langström B (2002) Synthesis of 3-[(2S)-azetidin-2-ylmethoxy] 5-[^{11}C]methylpyridine, an analogue of A-85380, via a Stille coupling. J Labelled Compd Radiopharm 45: 423–434

Karimi F, Kihlberg T, Langström B (2001) [^{11}C]/(^{13}C)Carbon monoxide in palladium-mediated synthesis of imides. J Chem Soc Perkin Trans 1 2001: 1528–1531

Kihlberg T, Langström B (1994) Cuprate mediated ^{11}C–C coupling reactions using Grignard reagents and ^{11}C-alkyl iodides. Acta Chem Scand 48: 570–576

Kihlberg T, Langström B (1999) Biologially active ^{11}C-labeled amides using palladium-mediated reactions with acryl halides and [^{11}C]carbon monoxide. J Org Chem 64: 9201–9205

Kihlberg T, Gullberg P, Langström B (1990) [^{11}C]Methyltriphenylphosphorane, a new ^{11}C-precursor, used in a one pot Wittig synthesis of [β-^{11}C]styrene. J Labelled Compd Radiopharm 28: 1115–1120

Kihlberg T, Karimi F, Langström B (1999) [^{11}C]Carbon monoxide in the synthesis of carbonyl compounds using palladium or selenium mediated reactions. J Labelled Compd Radiopharm 42: S86–S88

Kihlberg T, Karimi F, Langström B (2002) [^{11}C] Carbon monoxide in selenium-mediated synthesis of ^{11}C-carbamoyl compounds. J Org Chem 67: 3687–3692

Kilbourn MR, Dischino DD, Welch MJ (1984) Synthesis of DL-[3-^{11}C]phenylalanine. Int J Appl Radiat Isot 35: 603–605

Kilbourn MR, Dence CS, Welch MJ, Mathias CJ (1987) Fluorine-18 labeling of proteins. J Nucl Med 28: 462–470

Klimas MT (2002) Positron emission tomography and drug discovery: contributions to the understanding of pharmacokinetics, mechanism of action and disease state characterization. Mol Imaging Biol 4: 311–337

Kuhnast B, Dolle F, Vaufrey F, Hinnen F, Crouzel C, Tavitian B (2000a) Fluorine-18 labeling of oligonucleotides bearing chemically-modified ribose-phosphate backbones. J Labelled Compd Radiopharm 43: 837–848

Kuhnast B, Dolle F, Terrazzino S, Rousseau B, Loc'h C, Vaufrey F, Hinnen F, Doignon I, Pillon F, David C, Crouzel C, Tavitian B (2000b) General method to label antisense oligonucleotides with radioactive halogens for pharmacological and imaging studies. Bioconjug Chem 11: 627–636

Kuhnast B, Dolle F, Tavitian B (2002) Fluorine-18 labeling of peptide nucleic acids. J Labelled Compd Radiopharm 45: 1–11

Kuhnast B, de Bruin B, Hinnen F, Tavitian B, Dolle F (2004) Design and synthesis of a new [^{18}F]fluoropyridine-based haloacetamide reagent for the labeling of oligonucleotides: 2-bromo-N-[3-(2-[^{18}F]fluoropyridin-3-yloxy)propyl]acetamide. Bioconjug Chem 15: 617–627

Lang L, Eckelman WC (1994) One-step synthesis of ^{18}F labelled [^{18}F]-N-succinimidyl 4-(fluoromethyl)benzoate for protein labelling. Appl Radiat Isot 45: 1155–1163

Lang L, Eckelman WC (1997) Labeling proteins at high specific activity using N-succinimidyl 4-[^{18}F](fluoromethyl) benzoate. Appl Radiat Isot 48: 169–173

Lange CW, VanBrocklin HF, Taylor SE (2002) Photoconjugation of 3-azido-5-nitrobenzyl-[^{18}F]fluoride to an oligonucleotide aptamer. J Labelled Compd Radiopharm 45: 257–268

Langström B, Kihlberg T, Bergstrom M, Antoni G, Bjorkman M, Forngren BH, Forngren T, Hartvig P, Markides K, Yngve U, Ogren M (1999) Compounds labelled with short-lived beta(+)-emitting radionuclides and some applications in life sciences. The importance of time as a parameter. Acta Chem Scand 53: 651–669

Lasne M-C, Perrio C, Rouden J, Barré L, Roeda D, Dolle F, Crouzel C (2002) Chemistry of beta(+)-emitting compounds based on fluorine-18. Topics Curr Chem 222: 201–258

Maclean D, Northrop JP, Padgett HC, Walsh JC (2003) Drugs and probes: the symbiotic relationship between pharmaceutical discovery and imaging science. Mol Imaging Biol 5: 304–311

Maeding P, Steinbach J (1998) N.c.a. ^{11}C-labelling of benzoid compounds in ring positrons: synthesis of 3-nitro-[3-^{11}C]toluene and 4-nitro-[4-^{11}C]toluene and their corresponding toluidines. J Labelled Compd Radiopharm 41: 647–656

Maeding P, Steinbach J (2000) Synthesis of [1-^{11}C]phenol. J Labelled Compd Radiopharm 43: 557–563

Maeding P, Steinbach J, Johannsen B (1997) N.c.a. ^{11}C-labelling of benzoid compounds in ring positrons: [^{11}C]anisole derivates. J Labelled Compd Radiopharm 39: 585–599

Matarrese M, Sudati F, Soloviev D, Todde S, Turolla EA, Kienle MG, Fazio F (2002) Automation of [^{11}C]acyl chloride syntheses using commercially available ^{11}C-modules. Appl Radiat Isot 57: 675–679

Maziere B, Loc'h C (1986) Bromine radiopharmaceuticals. Radiopharmaceuticals labelled with bromine isotopes. Appl Radiat Isot 37: 703–713

McCarthy TJ, Schwarz SW, Welch MJ (1994) Nuclear medicine and positron emission tomography: an overview. J Chem Edu 71: 830–836

McCarthy TJ, McCarthy D, Laforest R, Bigott HM, Wuest F, Reichert DE, Lewis MR, Welch MJ (2001) Non-standard isotope production and applications at Washington University. In: Duggan JL, Morgan IL (eds) Application of accelerators in research and industry: sixteenth international conference. American Institute of Physics, Melville, NY, pp 841–844 (AIP conference proceedings, vol 576)

Moody TW, Leyton J, Unsworth E, John C, Lang L, Eckelman WC (1998) (Arg15, Arg21) VIP: evaluation of biological activity and localization to breast cancer tumors. Peptides 19: 585–592

Müller-Platz CM, Kloster G, Legler G, StöckIin G (1982) ^{18}F-Fluoroacetate: an agent for introducing n.c.a. fluorine-18 into urokinase without loss of biological activity. J Labelled Compd Radiopharm 19: 1645

Nader MW, Oberdorfer F (2002) Syntheses of [carbonyl-^{11}C]2-(2-benzoylphenoxy)-N-phenylacetamide from [^{11}C]carbon monoxide by the Suzuki and the Stille reactions. Appl Radiat Isot 57: 681–685

Neu H, Kihlberg T, Langström B (1997) Synthesis of saturated fatty acids ^{11}C(^{13}C)-labelled in the ω-methyl position. J Labelled Compd Radiopharm 39: 509–524

Nickles RJ (2003) The production of a broader palette of PET tracers. J Labelled Compd Radiopharm 46: 1–27

Oberdorfer F, Theobald A, Prenant C (1996) Simple production of [1-carbon-^{11}]acetate. J Nucl Med 37: 341–342

Ogawa M, Hatano K, Oishi S, Kawasumi Y, Fujii N, Kawaguchi M, Doi R, Imamura M, Yamamoto M, Ajito K, Mukai T, Saji H, Ito K (2003) Direct electrophilic radiofluorination of a cyclic RGD peptide for *in vivo* alpha(v)beta3 integrin related tumor imaging. Nucl Med Biol 30: 1–9

Paans AM, Vaalburg W (2000) Positron emission tomography in drug development and drug evaluation. Curr Pharm Des 6: 1583–1591

Paans AM, van Waarde A, Elsinga PH, Willemsen AT, Vaalburg W (2002) Positron emission tomography: the conceptual idea using a multidisciplinary approach. Methods 27: 195–207

Pagani M, Stone-Elander S, Larsson SA (1997) Alternative positron emission tomography with non-conventional positron emitters: effects of their physical properties on image quality and potential clinical applications. Eur J Nucl Med 24: 1301–1327

Page RL, Garg PK, Vaidyanathan G, Zalutsky MR (1994) Preclinical evaluation and PET imaging of ^{18}F-labeled Mel-14 F(ab′)2 fragment in normal dogs. Nucl Med Biol 21: 911–919

Patt J, Patt M (2002) Reaction of [^{18}F]4-fluorobenzenediazonium cations with cystein or cycteinyl group: preparation of ^{18}F-labeled S-arylcysteine and a radiolabeled peptide. J Labelled Compd Radiopharm 45: 1229–1238

Phelps ME (2000a) Positron emission tomography provides molecular imaging of biological processes. Proc Natl Acad Sci USA 97: 9226–9233

Phelps ME (2000b) PET: the merging of biology and imaging into molecular imaging. J Nucl Med 41: 661–681

Pike VW (1997) The status of PET radiochemistry for drug development and evaluation. Drug Inf J 31: 997–1013

Poethko T, Thumshirn G, Hersel U, Schottelius M, Henriksen G, Herz M, Haubner R, Kessler H, Schwaiger M, Wester HJ (2003) Breakthrough in ^{18}F-labelling of peptides? J Labelled Compd Radiopharm 46: S17

Poethko T, Schottelius M, Thumshirn G, Hersel U, Herz M, Henriksen G, Kessler H, Schwaiger M, Wester HJ (2004) Two-step methodology for high-yield routine radiohalogenation of peptides: ^{18}F-labeled RGD and octreotide analogs. J Nucl Med 45: 892–902

Qaim SM, Hohn A, Bastian T, El-Azoney KM, Blessing G, Spellerberg S, Scholten B, Coenen HH (2003) Some optimisation studies relevant to the production of high-purity ^{124}I and ^{120g}I at a small-sized cyclotron. Appl Radiat Isot 58: 69–78

Rowland DJ, McCarthy TJ, Welch MJ (2003) Radiobromine for imaging and therapy. In: Welch MJ, Redvanly CS (eds) Handbook of radiopharmaceuticals. John Wiley & Sons, New York, pp 441–465

Rice-Evans C (2001) Flavonoid antioxidants. Curr Med Chem 8: 797–807

Rice-Evans C (2004) Flavonoids and isoflavones: absorption, metabolism, and bioactivity. Free Radic Biol Med 36: 827–828

Schlyer DJ (2003) Production of radionuclides in accelerators. In: Welch MJ, Redvanly CS (eds) Handbook of radiopharmaceuticals. John Wiley & Sons, New York, pp 1–70

Seevers RH, Counsell RE (1982) Radioiodination techniques for small organic molecules. Chem Rev 82: 575–590

Setser CS, Racette WL (1992) Macromolecule replacers in food products. Crit Rev Food Sci Nutr 32: 275–297

Shuie CY, Wolf AP, Hainfeld JF (1989) Synthesis of ^{18}F-labelled N-(p-[^{18}F]fluorophenyl)maleimide and its derivatives for labelling monoclonal antibodies with ^{18}F. J Labelled Compd Radiopharm 26: 287–289

Sosabowski J, Zweit J, Coley H, Sosabowski MH, Wilbur DS, Hamlin D, Carnochan P, Judson I (1997) Preparation and evaluation of N-acylated anthracycline analogues for radiolabelling with iodine-124 and bromine-76: potential PET radiotracers for the *in vivo* assessment of multidrug resistance. In: XIIth International Symposium on Radiopharmaceutical Chemistry, Uppsala, pp 111–113

Sundin J, Tolmachev V, Orlova A, Lundquist H, Sundin A (1999) High yield ^{76}Br-bromination of antibodies using succinimidyl para-[^{76}Br] bromobenzoate. J Labelled Compd Radiopharm 42: S768–S770

Sutcliffe-Goulden JL, O'Doherty MJ, Bansal SS (2000) Solid phase synthesis of [^{18}F]labelled peptides for positron emission tomography. Bioorg Med Chem Lett 10: 1501–1503

Sutcliffe-Goulden JL, O'Doherty MJ, Marsden PK, Hart IR, Marshall JF, Bansal SS (2002) Rapid solid phase synthesis and biodistribution of ^{18}F-labelled linear peptides. Eur J Nucl Med Mol Imaging 29: 754–759

Thorpe SR, Baynes JW (2003) Maillard reaction products in tissue proteins: new products and new perspectives. Amino Acids 25: 275–281

Toyokuni T, Walsh JC, Dominguez A, Phelps ME, Barrio JR, Gambhir SS, Satyamurthy N (2003) Synthesis of a new heterobifunctional linker, N-[4-(aminooxy)butyl]maleimide, for facile access to a thiol-reactive ^{18}F-labeling agent. Bioconjug Chem 14: 1253–1259

Vaidyanathan G, Zalutsky MR (1992) Labeling proteins with fluorine-18 using N-succinimidyl 4-[^{18}F]fluorobenzoate. Int J Rad Appl Instrum B 19: 275–281

Vaidyanathan G, Zalutsky MR (1994) Improved synthesis of N-succinimidyl 4-[^{18}F]fluorobenzoate and its application to the labeling of a monoclonal antibody fragment. Bioconjug Chem 5: 352–356

Vaidyanathan G, Zalutsky MR (1995) Fluorine-18 labeled chemotactic peptides: a potential approach for the PET imaging of bacterial infection. Nucl Med Biol 22: 759–764

Vaidyanathan G, Zalutsky MR (1997) Fluorine-18-labeled [Nle4,D-Phe7]-alpha-MSH, an alpha-melanocyte stimulating hormone analogue. Nucl Med Biol 24: 171–178

Wester HJ, Hamacher K, Stocklin G (1996) A comparative study of N.C.A. fluorine-18 labeling of proteins via acylation and photochemical conjugation. Nucl Med Biol 23: 365–372

Wester HJ, Brockmann J, Rosch F, Wutz W, Herzog H, Smith-Jones P, Stolz B, Bruns C, Stocklin G (1997) PET-pharmacokinetics of ^{18}F-octreotide: a comparison with ^{67}Ga-DFO- and ^{86}Y-DTPA-octreotide. Nucl Med Biol 24: 275–286

Wilbur DS (1992) Radiohalogenation of proteins: an overview of radionuclides, labeling methods, and reagents for conjugate labeling. Bioconjug Chem 3: 433–470

Winberg KJ, Persson M, Malmstrom PU, Sjoberg S, Tolmachev V (2004) Radiobromination of anti-HER2/neu/ErbB-2 monoclonal antibody using the p-isothiocyanatobenzene derivative of the [^{76}Br]undecahydro-bromo-7,8-dicarba-nido-undecaborate(1-) ion. Nucl Med Biol 31: 425–433

Winstead MB, Winchell HS, Fawwaz R (1969) The use of sodium ^{11}C-benzoate in renal visualization. Int J Appl Radiat Isot 20: 859–863

Wipf P, Jahn H (1996) Synthetic applications of organochlorozirconocene complexes. Tetrahedron 52: 12853–12910

Wuest F (2003) Organic chemistry with the short-lived positron emitters ^{11}C and ^{18}F. Trends Org Chem 10: 61–70

Wuest F, Maeding P (2004) A novel approach for ^{11}C–C bond formations: Hydrozirconation/^{11}C-methylation of prop-1-ynyl-benzene with [^{11}C]MeI. In: van den Hoff J, Seifert S (eds) Institute of Bioinorganic and Radiopharmaceutical Chemistry: Annual Report 2004. Research Center Rossendorf, Dresden, p 35

Wuest F, Dence S, McCarthy TJ, Welch MJ (2000) A new approach for the synthesis of [^{11}C]-labeled fatty acids. J Labelled Compd Radiopharm 43: 1289–1300

Wuest F, Zessin J, Johannsen B (2003a) A new approach for ^{11}C–C bond formation: synthesis of 17α-(3′-[^{11}C]prop-1-yn-1-yl)-3-methoxy-3,17β-estradiol. J Labelled Compd Radiopharm 46: 333–342

Wuest F, Hultsch C, Bergmann R, Johannsen B, Henle T (2003b) Radiolabelling of isopeptide N epsilon-(gamma-glutamyl)-L-lysine by conjugation with N-succinimidyl-4-[^{18}F]fluorobenzoate. Appl Radiat Isot 59: 43–48

Wuest F, Müller M, Kasper H (2003c) Synthesis of 4-[^{18}F]fluoromethyl-2-chloro-O-succinimidyl-benzoate as novel bifunctional ^{18}F-labelling agent. In: Spies H, Seifert S (eds) Institute of Bioinorganic and Radiopharmaceutical Chemistry: Annual Report 2003 (FZR-394). Research Center Rossendorf, Dresden, p 25

Wuest F, Müller M, Bergmann R (2004) Synthesis of 4-([^{18}F]fluoromethyl)-2-chlorophenylisothiocyanate: A novel bifunctional ^{18}F-labelling agent. Radiochim Acta 92: 349–353

Zessin J, Steinbach J, Johannsen B (1999) Synthesis of triphenylarsonium [^{11}C]methylide, a new ^{11}C-precurser. Application in the preparation of [2-^{11}C]indole. J Labelled Compd Radiopharm 42: 725–736

Zijlstra S, Gunawan J, Burchert W (2003) Synthesis and evaluation of a ^{18}F-labelled recombinant annexin-V derivative, for identification and quantification of apoptotic cells with PET. Appl Radiat Isot 58: 201–207

Author's address: Frank Wuest, PhD, PET Center, Institute of Bioinorganic and Radiopharmaceutical Chemistry, Research Center Rossendorf, P.O. Box 51 01 19, 01314 Dresden, Germany,
Fax: +49 351 260 2915, E-mail: f.wuest@fz-rossendorf.de