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Carbohydrate-Based Molecules for Molecular Imaging in Nuclear Medicine

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This review covers published literature describing the synthesis of labeled carbohydrates for use in molecular imaging, with a particular focus on the use of nuclear techniques (PET, SPECT). Recent advances in the radiosynthesis of [^{18}F]FDG (electrophilic vs. nucleophilic radiofluorinations), a PET radiotracer based on glucose and the most widely PET tracer currently in use for cancer and inflammatory disease diagnosis, is considered. The powerful impact of [^{18}F]FDG in the clinic has prompted intensive research efforts into glucose-based radiotracers for PET and SPECT imaging. These achievements are also reviewed, along with the use of glycopeptides for nuclear molecular imaging. Finally, recent work on the radionuclide labeling of nucleosides and glycoconjugates is discussed.

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1. Introduction

Carbohydrates play important roles in biological systems, participating in cellular processes such as cell–cell recognition, cellular transport, and cell adhesion. They are found in cells in different forms, including peptido- and proteoglycans, glycoproteins, glycolipids, and lipopolysaccharides.[1] Carbohydrates are also an important source of energy for the body as the result of glucose metabolism through glycolytic pathways. Glucose is taken up by the cell through membrane proteins known as glucose transporters (GluTs). Changes in the expression of GluTs have been associated with alteration of metabolism in pathologies such as type 2 diabetes,[2] cancer,[3] and myocardial ischemia.[4] In vivo detection of carbohydrates that play major roles in molecular processes therefore warrants exploration for the diagnosis of carbohydrate-associated diseases.

Molecular imaging is a discipline that aims to visualize molecular processes in a living organism through the use of specific agents and appropriate instrumentation.[5] Among the imaging modalities (Figure 1), nuclear imaging, computed tomography (CT), and magnetic resonance (MRI) imaging have attracted particular interest for diagnostic purposes over recent years. Nuclear imaging, which includes positron emission tomography (PET) and single-photon-emission computed tomography (SPECT), is considered the most sensitive imaging modality, detecting biomolecules in the picomolar concentration range. On the other hand, the CT and MRI techniques give anatomical information. The combination of PET and CT in a single scan has revolutionalized clinical imaging, because this technique allows for co-registration of functional and anatomical information.[6] Currently, the PET/MRI modality is also being investigated.[7]

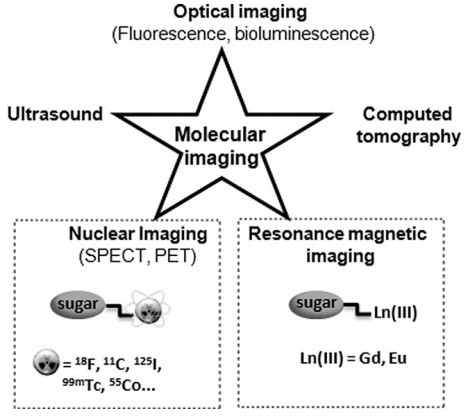


Figure 1. Examples of molecular imaging modalities[5] and a schematic representation of carbohydrate-based compounds suitable for nuclear and magnetic resonance imaging.

In nuclear imaging, molecules that target specific molecular events are tagged either with positron-emitting (e.g., ^{11}C, ^{18}F, ^{68}Ga) or with gamma-emitting (e.g., ^{99m}Tc, ^{125}I, ^{123}I) radionuclides for PET and SPECT, respectively. The most important radionuclides used in nuclear medicine are listed in Table 1.

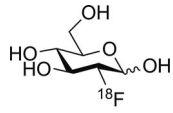
Table 1. Important radionuclides used in nuclear imaging.

Nuclide	Half-life	Mode of decay [%]	Application
^{99m}Tc	6.0 h	IT (100)	SPECT
^{123}I	13.2 h	EC[a] (100)	SPECT
^{124}I	4.18 d	EC (74.4) β+ (25.6)	PET
^{111}In	2.83 d	EC (100)	SPECT
^{67}Ga	3.27 d	EC (100)	SPECT
^{68}Ga	67.8 min	β+ (90) EC (10)	PET
^{18}F	109.8 min	β+ (97) EC (3)	PET
^{11}C	20.3 min	β+ (100)	PET
^{86}Y	14.7 h	β+ (33) EC (66)	PET
^{60}Cu	0.4 h	β+ (93) EC (7)	PET
^{62}Cu	0.16 h	β+ (98) EC (2)	PET
^{64}Cu	12.7 h	EC (43) β+ (17.8) β– (39)	PET
^{89}Zr	78.5 h	β+ (22.7) EC (77)	PET

[a] EC: electron capture.

In MRI, which give images with high spatial resolution, the image contrast is based on the differences between the water proton longitudinal ($1/T_1$) and transversal ($1/T_2$) relaxation rates in different tissues. This contrast can be enhanced by exogenous compounds, usually paramagnetic contrast agents based on lanthanides(III) (e.g., Gd^{III}) or iron oxide nanoparticles, that accelerate the magnetic relaxation process.[8] In glycobiology, MRI has found its main application in the preparation of probes based on galactosides, glucuronides, or larger glycoconjugates (Figure 1). An interesting review has been published recently,[9] so carbohydrate-based compounds developed as MRI probes are not covered here.

The carbohydrate-related molecular event that has attracted most attention in molecular imaging is the expression of the GluT glucose transporter. Several nuclear probes based on glucose have been designed and evaluated for imaging. Of these, [^{18}F]-2-fluoro-2-deoxy-D-glucose ([^{18}F]FDG, Figure 2) has emerged as the most successful.



[^{18}F]FDG

Figure 2. Chemical structure of [^{18}F]-2-fluoro-2-deoxy-D-glucose.

There are several interesting reviews on the synthesis of [^{18}F]FDG,[10] so here we only briefly address its original synthesis, while highlighting recent developments. Other carbohydrate-based radiotracers, including glucose-derived compounds developed since the advent of FDG, are also addressed. ^{3}H- and ^{14}C-labeled carbohydrates are beyond the scope of this review and are not considered.

The growing knowledge in glycobiology has opened new opportunities for exploration of carbohydrates in molecular imaging. An overview of those achievements is also covered. Although nucleosides are commonly considered a class of compounds distinct from carbohydrates, the different strategies for radiolabeling in the nucleoside pentose ring are also covered.

2. Labeling of Carbohydrate with ^{18}F and ^{11}C

2.1. [^{18}F]-2-Fluoro-2-deoxy-D-glucose

[^{18}F]FDG (Figure 2), developed almost four decades ago by Ido et al.,[11] has been used to measure glucose cellular uptake and is the most widely used PET radiopharmaceutical in oncology and neurology. In cancer cells the oxidative phosphorylation pathway, commonly used by normal cells to metabolize glucose, is down-regulated, with a shift towards the inefficient aerobic glycolysis.[12] For this reason cancer cells require higher glucose uptake than normal cells. Like glucose, [^{18}F]FDG is transported by GluTs. Once inside the cells [^{18}F]FDG is metabolized by hexokinase (HK), which is also over-expressed in carcinogenic tissues,[13] and is transformed into [^{18}F]FDG-6-phosphate. However, this molecule is not further metabolized to fructose-6-phosphate by phosphoglucose isomerase, due to the presence of the fluorine atom at the 2-position. Consequently, negatively charged [^{18}F]FDG-6-phosphate is trapped inside cells with high metabolic rates (Figure 3).[14]

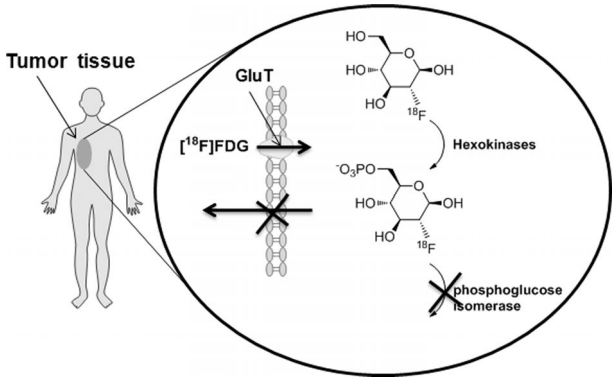
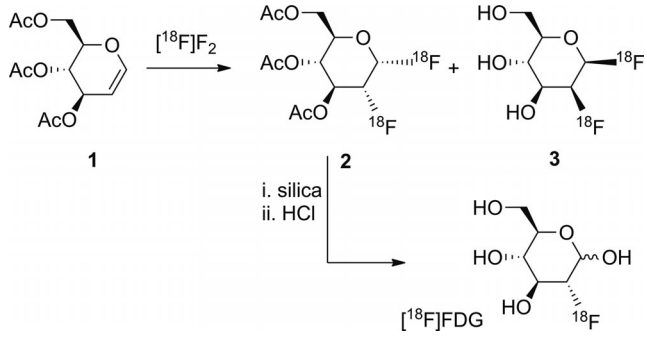


Figure 3. Schematic representation of [^{18}F]FDG cellular metabolism in cancer cells.

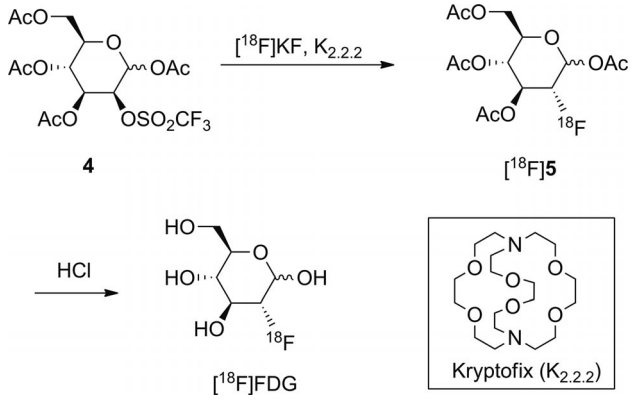
In contrast, glucose metabolism – and therefore [^{18}F]-FDG uptake – is decreased in myocardial ischemia, myocardial infarction (heart attack), and neurodegenerative diseases.

The original synthesis of [^{18}F]FDG by electrophilic addition of [^{18}F]F_2 to tri-*O*-acetyl glucal (**1**, Scheme 1)[11] was rather limited, suffering from low yields and a lack of stereoselectivity. Both glucose derivative **2** and mannose derivative **3** were produced, as a result of the unselective addition of the highly reactive [^{18}F]F_2 to both faces of the sugar ring. Alternatively, use of the less reactive acetyl [^{18}F]-hypofluorite ([^{18}F]CH_3CO_2F) as fluorinating agent improved the stereoselectivity of the reaction significantly: a 95% yield of the glucose derivative was obtained with no need for further purification.[15] In spite of the advances in stereoselectivity, which was highly dependent on the solvent,[16] however, this methodology produces [^{18}F]FDG in low radiochemical yield (RCY = 20%) and with very low specific activity.[15] The low specific activity ($<$0.40 GBq μmol^{-1}) and low RCY ($<$50%) are intrinsic drawbacks when using carrier [^{18}F]F_2 or its derivatives (e.g., [^{18}F]CH_3CO_2F) for the preparation of radiopharmaceuticals.



Scheme 1. Original synthesis of [^{18}F]FDG, as in ref.[11]

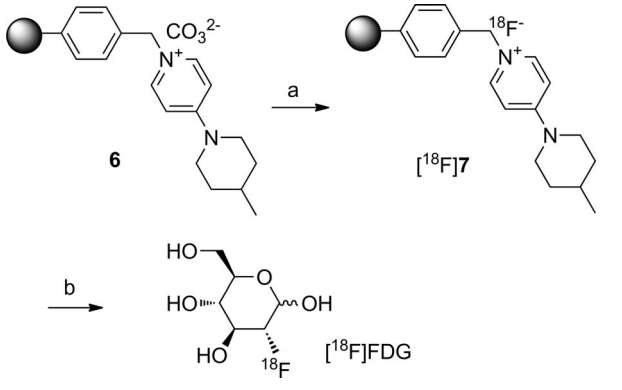
The development of the capability to use no-carrier-added (nca) [^{18}F]fluoride was an important milestone in the preparation of [^{18}F]FDG by nucleophilic substitution. [^{18}F]Fluoride is cyclotron-produced by irradiation of oxygen-18-enriched water. Although less reactive than [^{18}F]F_2, [^{18}F]fluoride is produced with higher specific activities, and its potential to achieve higher chemoselectivity leads to higher radiochemical yields and smaller amounts of radiochemical impurities. Moreover, the lack of any need for a carrier to recover aqueous [^{18}F]fluoride from the target wall produces radiolabeled compounds with very high specific activities.[17] [^{18}F]Fluoride nucleophilic substitutions follow an S_N2 mechanism, through which [^{18}F]FDG is prepared from the appropriate precursor mannose triflate. Previously, work on the synthesis of 2-fluoro-2-deoxy-D-glucose had established that only the β-anomer of the 2-triflate mannopyranoside was reactive towards the fluoride ion.[18] Only poor to fair overall yields were obtained with the use of [^{18}F]CsF[19] and [^{18}F]Et_4NF[20] as fluorinating agents, largely due to the final troublesome hydrolysis of the *O*-protecting groups. However, the use of aminopolyether potassium complex [^{18}F][K/$K_{2.2.2}$]$^+F^-$ as a fluoride source (K2.2.2. is a cryptand that captures potassium cations and increases the nucleophilicity of the fluoride ion) and per-*O*-acetylated mannose triflate **4** (Scheme 2) as precursor drastically improved the overall yield (≈60%) and enabled much shorter total reaction times.[21] This is still currently the most important method for the preparation of [^{18}F]FDG. Some variants of this method were introduced to enable basic *O*-acetate group hydrolysis;[22] the original acidic *O*-acetyl hydrolyses led to the formation of the undesired 2-chloro-2-deoxy-D-glucose, albeit in residual amounts.[23] Basic hydrolysis with sodium hydroxide overcame this problem,[22a,22c] despite the potential for epimerization at C-2, which could be minimized by control both of temperature and of reaction times.[22b]



Scheme 2. Synthesis of [^{18}F]FDG by nucleophilic radiofluorination as in ref.[21]

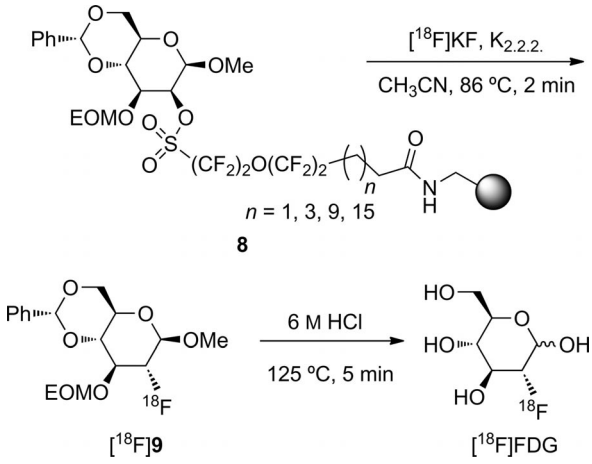
Other variants of the Hamacher method[21] include the use of tetrabutylammonium fluoride ([^{18}F]TBAF) as a strong nucleophilic fluoride source.[24] In this radiofluorination procedure, the large tetrabutylammonium cation acts as a phase-transfer catalyst, but its complete removal, like that of K2.2.2., involves multiple steps.

To facilitate the labeling procedure and purification steps, solid-phase approaches were developed. Here the [^{18}F]fluoride anion is trapped and activated either by the supported quaternary 4-aminopyridinium system **6**[25] (Scheme 3) or by tris(*n*-butyl)phosphonium[25b] salts. This procedure allows for convergent collection of [^{18}F]fluoride from target water, drying with anhydrous acetonitrile, and nucleophilic reaction with **4**.[25] More recently an alternative in which [^{18}F]fluoride anions were treated with the mannose perfluoroalkylsulfonate precursor **8** supported on polystyrene resin beads (Scheme 4) was developed.[26] Both solid-phase technologies effectively produced [^{18}F]FDG and lend themselves to automation.



Scheme 3. Synthesis of [^{18}F]FDG from resin-bound [^{18}F]fluoride anion as in ref.[25a] Reagents: a) i. $^{18}F^-/H_2{}^{18}O$; ii. anhydrous CH_3CN; b) i. **4**, CH_3CN, 100 °C, 3 min; ii. HCl (1 N), 100 °C, 15 min.

Other interesting approaches to efficient preparation of [^{18}F]FDG have involved the use either of media containing ionic liquids[27] or of microwave heating.[28] With the former process the usual azeotropic drying step was removed and a shorter radiosynthesis was possible. Microreactor technology could also be applied efficiently to the synthesis of [^{18}F]FDG (Figure 4).[29] The integrated microfluidic devices allowed for the [^{18}F]fluorination and deprotection to be carried out sequentially in a two-stage microfluidic device. This methodology has shown potential for exploitation under automated conditions in PET radiochemistry.



Scheme 4. Synthesis of [^{18}F]FDG from resin-bound precursor as in ref.[26]

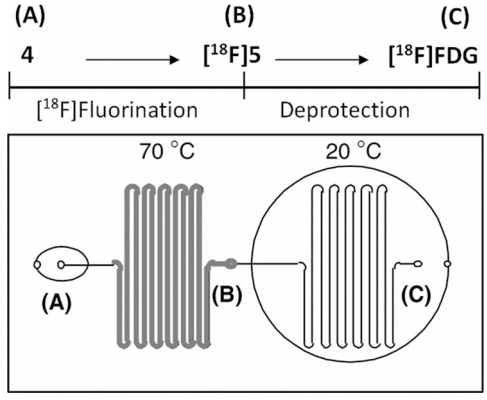


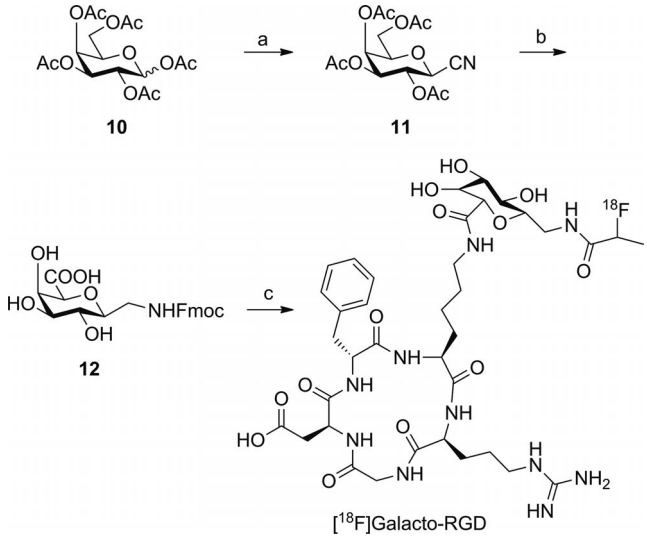
Figure 4. Overview of a two-stage microfluidic device for sequential [^{18}F]fluorination and deprotection for the synthesis of 2-[^{18}F]FDG as in ref.[29c] Reproduced by permission of John Wiley & Sons.

2.2. [^{18}F]-Fluorosugars as Prosthetic Groups

There has been growing interest in the search for selective imaging agents based on peptides or proteins.[30] However, direct radiofluorinations of those complex molecules with nca [^{18}F]fluoride is difficult because the labeling requires relatively harsh conditions (organic solvents, high temperatures, basic media) that are not compatible with these sensitive substrates. Moreover, the intrinsic H-acidic functions of biomolecules rule out the use of [^{18}F]fluoride, which shows a high proton affinity.[31] Generally, ^{18}F-labeling of peptides and proteins makes use of small ^{18}F-labeled molecules, known as prosthetic groups, that are further conjugated chemoselectively to the biomolecule. An extended survey of previously explored prosthetic groups for ^{18}F-la-

beling of peptides has been reported elsewhere,[30a,30b] and so they are not covered here.

Conjugation of sugars into small peptides has been successfully applied to improve peptide pharmacokinetics and to enhance bioavailability. A typical example was the development of a *cyclo*-RGD-containing glycopeptide, in which the coupling of galactose/amino acid conjugate **12** (Scheme 5) to *cyclo*-(Arg-Gly-Asp-D-Phe-Lys) improved its hydrophilicity and reduced its liver uptake.[32] Significantly, the sugar allowed ^{18}F-labeling of the glycopeptide through *N*-acylation of the amino methyl group at C-1 with 4-nitrophenyl 2-[^{18}F]fluoropropionate as a prosthetic group.[33] [^{18}F]Galacto-RGD has been studied as PET imaging agent for $\alpha_v\beta_3$ receptor expression.[32,34]



Scheme 5. Synthesis of [^{18}F]galacto-RGD as in ref.[33] Reagents: a) TMSCN, $BF_3{\cdot}Et_2O$, CH_3NO_2; b) i. $LiAlH_4$, THF; ii. FmocCl, $NaHCO_3$, THF/H_2O; iii. TEMPO, NaOCl, NaBr, THF/H_2O; c) i. *cyclo*-(-Arg(Pbf)-Gly-Asp(O*t*Bu)-DPhe-Lys), DIPEA, HATU, HOAt, DMF; ii. piperidine (20%), DMF; iii. TFA/H_2O/triisobutylsilane (95:2.5:2.5); iv. 4-nitrophenyl 2-[^{18}F]fluoropropionate.

Less than a decade ago, an alternative approach to ^{18}F-labeling of peptides based on the use of [^{18}F]FDG derivatives (Figure 5) as prosthetic groups was reported.[35] This strategy combines chemospecific ^{18}F-labeling and glycosylation of peptides and proteins and was pioneered by Maschauer et al.[35a,35b] These authors explored the utility of tetra-*O*-acetylated 2-[^{18}F]fluoro-2-deoxyglucopyranose (TA-[^{18}F]FDG) as an nca ^{18}F-glycosylation agent for conjugation to Fmoc-serine and Fmoc-threonine.[35a] However, this approach, which used the Lewis acid $BF_3{\cdot}Et_2O$ as promoter, was ineffective, and *O*-^{18}F-glycosylated amino acids were obtained in poor radiochemical yields (RCY = 12–25%) after complete deprotection. This *O*-^{18}F-glycosylation method was considerably improved (RCY = 67%) by using the per-*O*-acetylated 2-deoxy-[^{18}F]fluoroglycopyranosyl bromide **13** (Figure 5) under Köenings–Knorr conditions.[35b] Still, this method was only particularly useful for the ^{18}F-glycosylation of peptides that lacked potentially interfering free C termini, such as bioactive cyclic peptides. TA-[^{18}F]FDG had been used previously to prepare *N*-[^{18}F]-glycosylated 2-nitroimidiazole **18** (Figure 6), a tumor hypoxia tracer,[36] whereas fully unprotected [^{18}F]FDG participated in the synthesis of the disaccharide [^{18}F]FDL (**19**, Figure 6) through an enzymatic reaction catalyzed by a galactosyltransferase.[37] [^{18}F]FDL was developed for β-galactosidase targeting to measure in vivo enzymatic activity. As an alternative, the MacDonald synthesis of [^{18}F]FDG-1-phosphate followed by an enzymatic reaction produced the [^{18}F]-labeled glycosyl donor UDP-[^{18}F]FDG (**20**, Figure 6) as an activated precursor for enzymatic transfer of [^{18}F]FDG into biomolecules.[38]

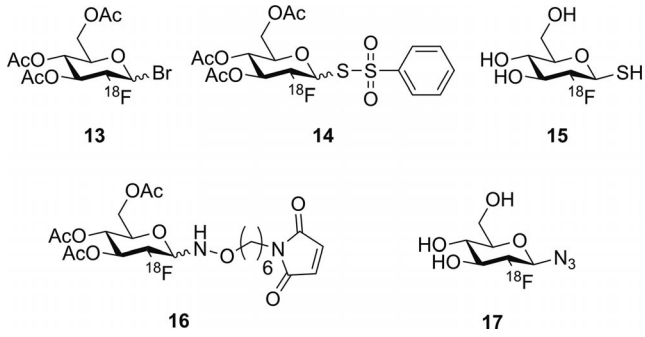


Figure 5. Chemoselective [^{18}F]FDG derivatives.

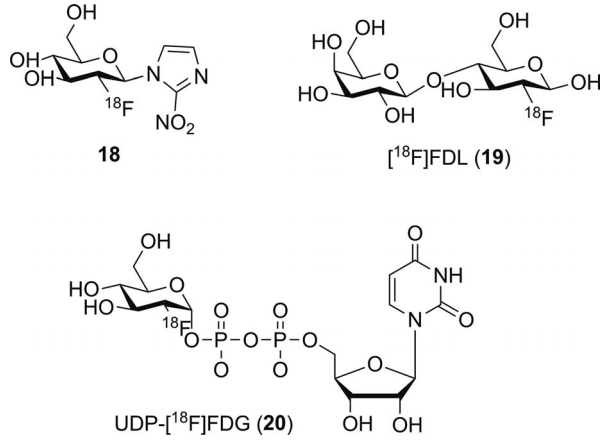
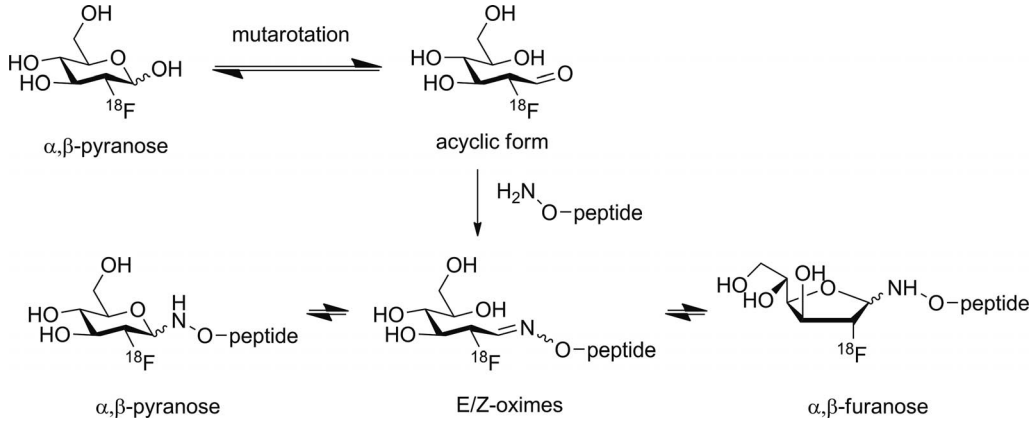


Figure 6. [^{18}F]-labeling radiotracers based on [^{18}F]FDG as building block.

In the reduced form, [^{18}F]FDG isomerizes between the α- and β-anomers through the intermediate acyclic aldehyde. This mutarotation process has been widely exploited for the direct use of [^{18}F]FDG as a prosthetic group through chemoselective oxime formation in aqueous media with unprotected aminoxy-functionalized peptides (Scheme 6).[35e–35g] The mutarotation equilibrium is favored at high temperatures (80–120 °C) and oxime formation was found to be more efficient at acidic pH (1.5–2.5).[35e–35g] However, large peptides can undergo degradation under these temperature and pH conditions.[35g] This methodology also requires the incorporation of unnatural amino acids into the peptide before treatment with the [^{18}F]fluorosugar.



Scheme 6. Mutarotation of [^{18}F]FDG and chemoselective [^{18}F]glycosylation of peptides through oxime formation.

Likewise, the successful ^{18}F-labeling of biotin with [^{18}F]-FDG through an oxime bond opened new possibilities for pre-targeted imaging of antibody-avidin conjugates.[39]

As an alternative to the direct use of [^{18}F]FDG, per-*O*-acetylated 2-deoxy-[^{18}F]fluoroglycopyranosyl 1-phenylthiosulfonate (**14**, Figure 5)[35c] and maleimidehexyloxime (**16**)[35d] were developed as chemoselective [^{18}F]-labeling reagents for cysteine-containing biomolecules. More recently, the glycosyl thiol **15** (Figure 5), obtained by treatment of [^{18}F]FDG with Lawesson's reagent, was used for [^{18}F]-labeling of proteins at cysteine and dihydroalanine residues through disulfide and sulfide bonds, respectively.[35j] Preparation of 2-deoxy-[^{18}F]fluoroglycopyranosyl 1-azide (**17**, Figure 5) from the corresponding mannosyl triflate precursor, in a manner similar to that used in the radiosynthesis of [^{18}F]FDG, allowed the [^{18}F]-glycosylation of alkyne-functionalized peptides.[35h,35i]

2.3. Other [^{18}F]-Labeled Carbohydrates

In addition to [^{18}F]FDG, other 2-deoxysugars have also been labeled with fluorine-18; these include 2-deoxy-2-[^{18}F]fluoro-D-galactose ([^{18}F]FDGal, **21**, Figure 7),[40] 2-deoxy-2-[^{18}F]-β-D-allose (**22**)[41], 2-deoxy-2-[^{18}F]fluoro-D-mannose,[42] and 2-deoxy-2-[^{18}F]fluoro-D-tallose,[43] to cite a few. The 2-deoxy-2-[^{18}F]fluorosugars have commonly been prepared by nucleophilic radiofluorination in similar manner to [^{18}F]FDG, from the corresponding C-2 epimeric sugar triflates as precursors.[40b,42,43] However, unlike in the synthesis of [^{18}F]FDG, the electrophilic addition of the radiofluorine ([^{18}F]F_2) to the galactal produced **21** in a highly stereoselective manner.[40a] 2-Deoxy-2-[^{18}F]fluorosugar **22** was also obtained through anhydrous HF-mediated electrophilic addition of [^{18}F]F_2 to the glucal **1**; it was proposed that the epimerization at C-3 proceeded through protonation of the oxygen bonded to C-3, followed by 3-*O*-acetate cleavage assisted by attack from the acyloxy group at C-4 and formation of a dioxolenium ion.[41] Electrophilic radiofluorination was also the method of choice for the preparation of *N*-acetyl-3-[^{18}F]fluoroneuraminic acid ([^{18}F]-Neu5Ac, **23**), by stereoselective addition of [^{18}F]acetyl hypofluorite to the 2-deoxy-2,3-dehydro-Neu5Ac derivative.[44] Uptake studies with [^{18}F]Neu5Ac demonstrated its unsuitability for tumor imaging, however.[44]

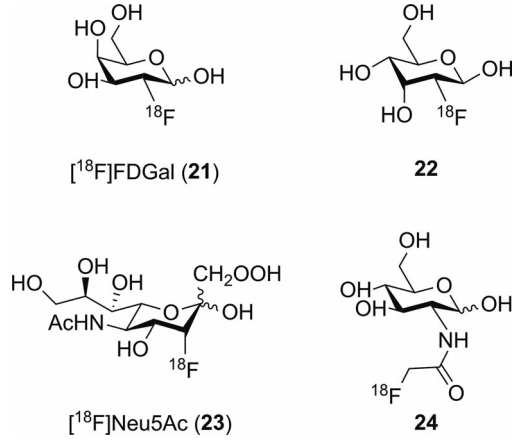
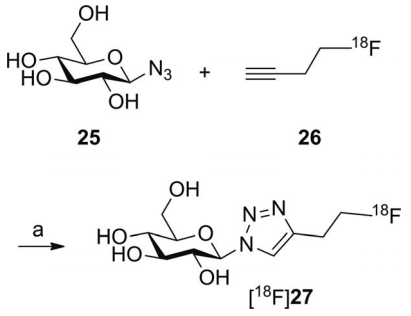


Figure 7. Examples of [^{18}F]-labeled carbohydrates.

The knowledge that 2-acetamido-2-deoxy-D-glucose is a constituent of hyaluronic acid, concentrations of which are increased in tumor environments, encouraged the preparation of the corresponding ^{18}F derivative **24** (Figure 7) as a tumor tracer. The key step for the synthesis of **24** is the preparation of [^{18}F]fluoroacetic acid, which was further conjugated to glucosamine.[45]

Compound [^{18}F]**27** constitutes another example in which ^{18}F-labeling of the glucose analogue is by means of a prosthetic group (Scheme 7). Here, the labeling proceeded by way of a Cu^{I} 1,3-cycloaddition between the unprotected sugar azide **25** and 4-[^{18}F]fluorobut-1-yne (**26**).[46] The bioorthogonal character of organic azides and phosphanes was also exploited for the labeling of galactose through the solvent- and temperature-dependent traceless Staudinger ligation.[47]

In recent decades genomic mapping has become important in the establishment of gene therapy, in the development of transgenic animal models of disease, and in targeting cells.[48] In vivo imaging of gene expression has been made possible with specific molecular imaging radiotrac-



Scheme 7. Synthesis of a glucose derivative conjugated to an ^{18}F-labeled triazole prosthetic group as in ref.[46] Reagents: a) CuI, sodium ascorbate, 2,6-lutidine, 90 °C, 10 min.

ers.[49] β-Galactosidase, encoded by the LacZ gene, is one of the most common reporter systems explored in gene expression imaging. In addition to [^{18}F]FDL (**19**, Figure 6), other agents include ^{18}F-phenyl galactopyranoside **28** (Figure 8), which was developed to assess its in vivo enzymatic activity.[50] The same authors also prepared the similar ^{11}C-based glycoconjugate **29** (Figure 8) but found that these two PET tracers were not suitable as LacZ reporter probes.[50] Related LacZ reporter molecules have been developed as MRI probes and are reviewed elsewhere.[9]

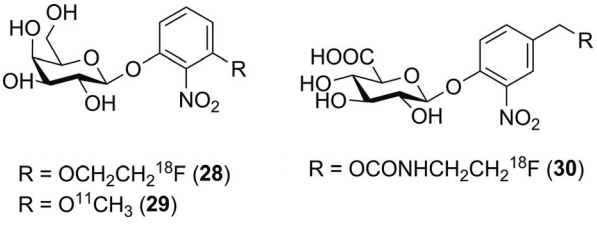
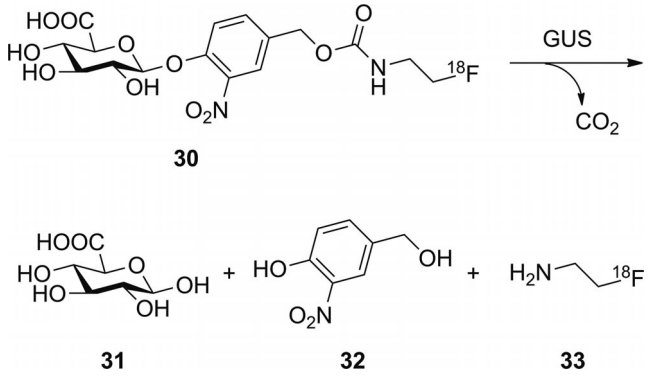


Figure 8. Examples of PET glycoconjugates.

The new ^{18}F-based substrate **30** ([^{18}F]FEAnGA, Figure 8) for β-glucuronidase (β-GUS) was also developed by Antunes et al.[51] Since in tumors the extracellular concentrations of β-GUS are increased, this enzyme has been explored for the cleavage of the cystostatics during monodrug therapy.[52] This highly hydrophilic ^{18}F-labeled *O*-linked glycoconjugate was cleaved specifically in tissues rich in β-GUS (Scheme 8) and the released [^{18}F]fluoroethylamine (**33**) remained in the target cells.[51] Further work was pursued with related ^{18}F-labeled *O*-glycoconjugates, however, to improve on the kinetics of the original tracer.[53] Previously, a similar "self-immolating" approach was explored for the preparation of glycoconjugates for MRI.[54]

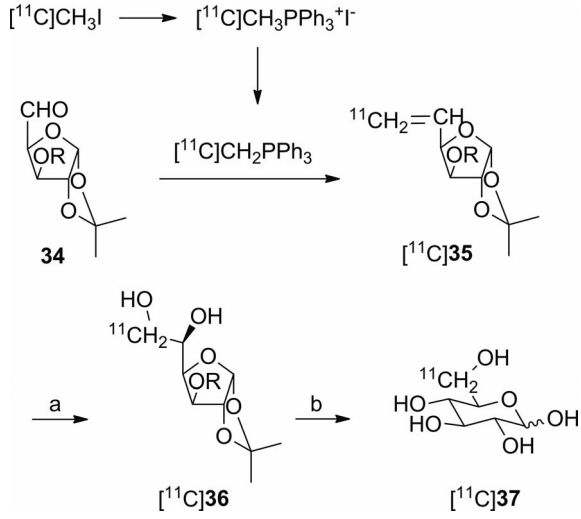


Scheme 8. General mechanism of activation of prodrug PET tracer [^{18}F]FEAn-GA (**30**) by β-glucuronidases (β-GUSs).[51]

2.4. [^{11}C]-Labeled Glucose

Assessment of the pentose phosphate shunt is important for tumor progression evaluation.[55] With this in mind, D-glucose has been labeled with the positron-emitting radioisotope carbon-11 (^{11}C), although few reports have been described. Because carbon is a constituent of biomolecules, [^{11}C]-labeled glucose is not metabolically trapped, and labeling with this radionuclide seemed very attractive. Depending on the labeling position (1-[^{11}C]- vs. 6-[^{11}C]-D-glucose) different rates of [^{11}C]CO_2 loss could be observed, revealing the proportion of glucose use for energy production and biosynthesis.

An original [^{11}C]-labeled Wittig reagent was explored for the synthesis of 6-[^{11}C]-D-glucose (Scheme 9).[55] In this approach, treatment of [^{11}C]phosphorane [^{11}C]CH_2PPh_3 with aldehyde **34** was followed by the unstereoselective asymmetric dihydroxylation of the labeled terminal olefin [^{11}C]**35** and acid deprotection of gluco-diol [^{11}C]**36**. A similar [^{11}C] labeling approach yielded 1-[^{11}C]-D-mannitol, which could be stereoselectively converted into 1-[^{11}C]-D-glucose and 1/6-[^{11}C]-D-frutose by enzymatic oxidation.[56] However, the multi-step chemical manipulation of the [^{11}C]phosphorane method is incompatible with the short half-life of ^{11}C ($t_{1/2}$ = 20.3 min) and direct ^{11}C labeling methods of carbohydrates are still needed. [^{11}C]-Carbohydrate homologation with [^{11}C]cyanide as a labeling reagent has also been achieved.[57]



Scheme 9. Radiosynthesis of 6-[^{11}C]-D-glucose as in ref.[55] Reagents: a) i. OsO_4/DHQ-PN, NMO, acetone/water 9:1; ii. HPLC separation of isomers; b) H_2SO_4 (1 M).

^{11}C-Labeling of glucose at the aglycon motif was straightforwardly accomplished by non-anomeric selective *O*-methylation of glucose with ^{11}C-methyl triflate under alkaline conditions.[58] The resulting ^{11}C-labeled α/β-methyl D-glycosides ([^{11}C]αMDG and [^{11}C]βMDG) were studied as selective tracers of sodium-dependent glucose transport (SGLT),[58] a specific glucose transporter in various human carcinomas.[59]

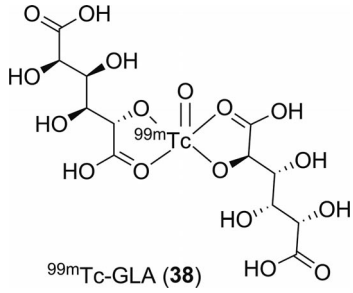


Figure 9. Chemical structure of ^{99m}Tc glucarate.

3. Gamma-Emitter Carbohydrate Derivatives

Although [^{18}F]FDG is widely accepted as an ideal radiotracer-labeled glucose in PET centers, the high costs associated with its production and the need for a cyclotron nearby are significant practical limitations. There has therefore been great clinical interest in developing γ-emitter glucose derivatives, suitable for SPECT imaging and readily available for routine use in nuclear medicine.

The radiometal technetium-99m (^{99m}Tc) is considered the workhorse radioisotope in nuclear medicine. Its almost ideal physical properties, namely a half-life of six hours and low γ-emission energy (141 keV), combined with its low cost and easy availability from ^{99}Mo/^{99m}Tc generators, have contributed to its use in about 90% of SPECT radiopharmaceuticals.[60] ^{99m}Tc^{VII} is eluted from the generator in the form of sodium pertechnetate (Na[^{99m}TcO$_4$]), which is further reduced to ^{99m}Tc^{V} or ^{99m}Tc^{I}, two chemically relevant oxidation states. One of the first ^{99m}Tc-carbohydrates was an oxo complex in which two glucuronic acid molecules were coordinated to the ^{99m}Tc^{V} (^{99m}Tc-glucurate, ^{99m}Tc-GLA, **38**, Figure 9).[61] Glucuronic acid is a six-carbon carboxylic acid analogue of glucose, and the ^{99m}Tc-GLA complex has been developed as an imaging agent for the diagnosis of acute myocardial and tumor necrosis.[61,62]

In general, saccharides by themselves are not suitable ligands for stabilizing ^{99m}Tc. To overcome this limitation, carbohydrate derivatives bearing different donor atom sets have been prepared and used to synthesize ^{99m}Tc complexes. As examples, Figure 10 shows a bifunctional chelator bearing a glucose derivative (compound **39**),[63] together with bidentate deoxyglucose thiocarbamate **40**.[64] These ligands were successfully used for the stabilization of [^{99m}TcN]$^{2+}$[64a] and [^{99m}TcO]$^{3+}$[64b] cores.

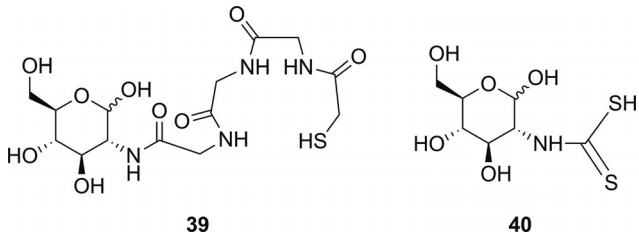


Figure 10. Examples of ligands suitable for the stabilization of the [^{99m}TcO]$^{3+}$ and [^{99m}TcN]$^{2+}$ cores.

The development, by Alberto et al.,[65] of the organometallic complex [^{99m}Tc(H$_2$O)$_3$(CO)$_3$]$^+$ as a precursor for the labeling of small biomolecules propelled research into ^{99m}Tc in a completely new direction.[66] Much of the attractiveness

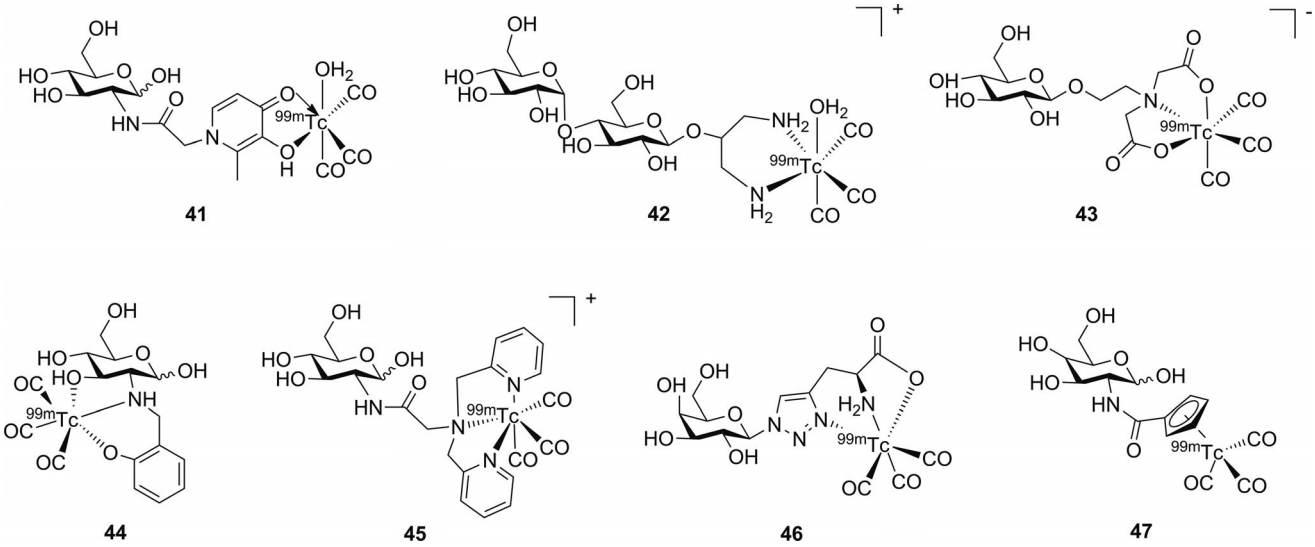
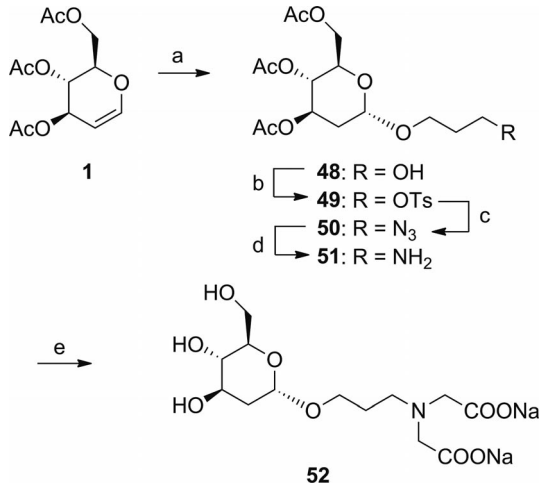


Figure 11. Examples of ^{99m}Tc^{I}-based carbohydrate complexes.

of this tricarbonyl core lies in its high kinetic inertness and stability to oxidation in biological environments. Over the last decade, a number of saccharides have been labeled with this organometallic *fac*-[^{99m}Tc(CO)$_3$]$^+$ core, with the aid of different bi- (compounds **41** and **42**, Figure 11) and tridentate (compounds **43**–**46**), Werner-type chelators,[67] cyclopentadienyl systems (e.g., **47**),[67k,68] and carborane.[69] The small size of this organometallic core means that it does not interfere with the biological activities of small molecules such as glucose.

Initially, the ^{99m}Tc^{I} complexes with pendant carbohydrates were prepared by functionalization of glucose and 2-deoxyglucose at their C-1 positions with an *O*-glycosidically linked iminodiacetic acid (IDA) chelating moiety.[67a] The primary alcohol group in the 2-deoxy-α-glucose derivative **48** (Scheme 10), obtained by acid-catalyzed *O*-glycosylation of glucal **1**, was the key intermediate for the synthesis of precursor **52**. The corresponding alcohol of the β-*O*-glucosidic analogue, which led further to the preparation of organometallic **43** (Figure 11), was achieved by standard Königs–Knorr glycosylation methodology. Originally, amine derivative **51** was obtained by a Lindlar-catalyzed reduction of azide **50** with hydrogen.[67a] A more recent chemical strategy for preparation of **51**, which required no purification, used the Staudinger reaction and polymer-bound triphenylphosphane.[67m] Related 1-*O*-glycosylations[67d,67l] and 1-*S*-glycosylations[67i,67l] were pursued for further conjugation to the ligand. Other routes to D-glucose derivatives of IDA functionalized at C-2, C-3, and C-6 have also been established.[67f,70]



Scheme 10. Functionalization of 2-deoxyglucose at C-1 with IDA as in ref.[67m] Reagents: a) diethylene glycol, H^+ resin, CH_3CN, molecular sieves; b) *p*TsCl, py, CH_2Cl_2; c) NaN_3, DMF; d) i. PPh_3 polymer-bound, CH_2Cl_2; ii. H_2O; e) i. methyl bromoacetate, Et_3N, THF; ii. NaOMe, MeOH, iii. NaOH, H_2O.

D-Glucosamine (2-amino-2-deoxy-D-glucose) provides an interesting glucosyl ligand scaffold in which the amine can act as an *N*-donor for metal coordination[67b] (e.g., **44**, Figure 11) and serve as a functionalization site either through reductive alkylation[67b,67h] or through *N*-acylation[67c,67g,67h,67j–67l] (e.g., **45** and **47**, Figure 11) with chelating units. Docking studies based on the crystal structure of hexokinase have shown that the C-2 position in a glucose derivative is indeed the best tolerated center for modifications, minimizing loss of any biological activity.[71]

The so-called "*click-to-chelate*" approach, explored in radiopharmaceutical chemistry by Schibli et al.,[67o] allows the transformation of the azido group in 1-azido galactose into a 1,2,3-triazol-4-yl alanine system, a motif structurally related to histidine. Histidine is a tridentate ligand[72] that forms stable complexes with the *fac*-[^{99m}Tc(CO)$_3$]$^+$ core, and so the 1,2,3-triazol-4-yl alanine in **46** (Figure 11) acts as a chelating unit. This approach was also extended to ^{99m}Tc-labeling of thymidine with the *fac*-[^{99m}Tc(CO)$_3$]$^+$ core. For this reaction, the deoxyribose ring was derivatized at C-3 with an azido group, followed by treatment with L-propargyl glycine.[67o]

Despite the development of these approaches to prepare carbohydrate derivatives appended to chelating units suitable for tricarbonyl systems, few biological studies directed towards GluT and HK activity have been conducted.

The suitability of pyridinone-based glycoconjugates for the formation of thermodynamically stable complexes with transition metals prompted their labeling with gallium-67[73] (^{67}Ga, $t_{1/2}$ = 78 h, gamma emitter), indium-111 (^{111}In,[73] $t_{1/2}$ = 68 h, gamma emitter) and cobalt-55 (^{55}Co,[74] $t_{1/2}$ = 17.6 h, positron emitter) for evaluation as metabolic imaging agents.

The favorable properties of iodine-123 (^{123}I, $t_{1/2}$ = 13.2, γ-emission energy = 159 keV) for SPECT imaging and its ability to replace a hydroxy group led to the preparation of radioiodinated carbohydrate derivatives. 2-Deoxy-2-[^{123}I]-iodoglucose might be expected to be the ideal SPECT analogue of [^{18}F]FDG, but this compound proved to be unstable and prone to deiodination.[75] No significant advance was achieved by introducing the iodine-123, through ^{123}I/^{127}I isotopic exchange, into the 3-, 4-, and 6-positions of the glucose molecule.[76]

4. Radiolabeled Nucleosides

Nucleosides, in which pentose units are linked to nucleobases by β-glycosidic linkages, have attracted attention in molecular imaging, thanks mainly to their involvement as building blocks in the synthesis of RNA and DNA. Several radiolabeled nucleosides have thus been developed and evaluated as nuclear imaging probes, to allow specific measurement of tumor cell proliferation, which is increased relative to normal cells. The majority of radiolabeled nucleosides are thymidine-based, because this nucleoside is incorporated only into DNA. Once taken up by cells, radiolabeled thymidine analogues are phosphorylated by thymidine-kinases (TK-1 and TK-2), resulting in negatively charged species that are trapped inside the cells. As shown in Figure 12, radioactive tags have been introduced both in the thymine base moiety (e.g., **53**–**56**)[77] and in the pentose ring component (**57** and **58**).[78] Fluorination at the 2′- and 3′-positions of the sugar led to nucleosides that were more

stable towards thymidine phosphorylase[79] – the enzyme that cleaves the *N*-glycosidic bond – so radiofluorinated thymidine analogues [^{18}F]FLT (**57**) and[^{18}F]FMAU (**58**) are considered the best suited for cell proliferation imaging. Their radiosynthesis and that of related radiolabeled nucleosides is covered here.

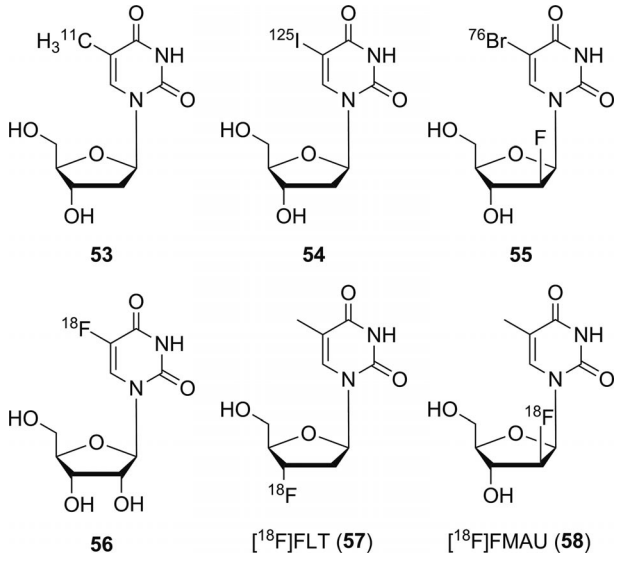
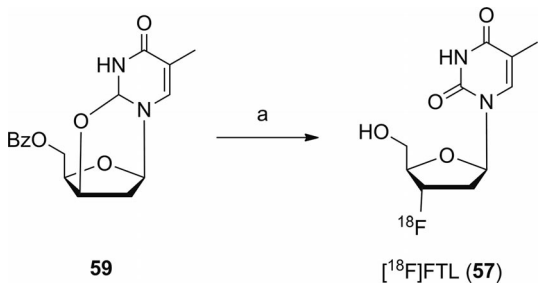
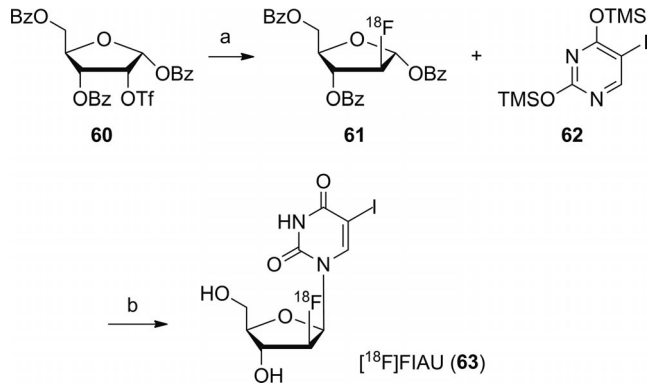


Figure 12. Examples of radiolabeled thymidine analogues.

Like in the optimized synthesis of [^{18}F]FDG, nucleophilic displacement has been the radiofluorination method most typically used to afford the five-membered flurorosugar in thymidine. Several leaving and protecting groups have been explored for the introduction of ^{18}F at the 3′-position of the deoxyribose,[78a–78c] with the most reliable radiosynthesis of [^{18}F]FLT employing the 3-*N*-Boc-protected nosylate precursor.[78c] A different route by which to prepare [^{18}F]FLT in reasonable radiochemical yields is the treatment of the anhydro derivative **59** with fluoride (Scheme 11).[80] On the other hand, preparation of [^{18}F]-FMAU was not so straightforward, because the direct introduction of ^{18}F at the 2′-position in 5-methyluridine has proved problematic. The original preparation of [^{18}F]-FMAU was accomplished in a multi-step manner, starting with the synthesis of 2-[^{18}F]fluoro-*arabino* sugar, followed by sugar bromination and coupling to the protected thymine with high β-anomeric selectivity.[78d,81] The long reaction time required for the four steps and the unavoidable corrosion in the automated equipment caused by the HBr/HOAC for the bromination step were significant drawbacks. Nevertheless, other 2′-deoxy-2′-[^{18}F]fluoro-β-D-arabinofuranosyl nucleosides have been prepared successfully in similar manner.[82] The use of trimethylsilyl trifluoromethanesulfonate (TMSOTf) as catalyst allowed the direct coupling of 2-[^{18}F]fluoro-*arabino* sugar **61** (Scheme 12) to protected thymine derivative **62** for the preparation of 2′-deoxy-2′-[^{18}F]fluoro-β-D-arabinofuranosyl-5-iodouracil (**63**, [^{18}F]-FIAU) [83] This one-pot approach has been further applied to the synthesis of [^{18}F]FMAU.[84] The use of microwave irradiation and an additional Lewis acid ($SnCl_4$) significantly enhanced the coupling efficiency of **61** with the silylated 5-substituted uracil.[85]

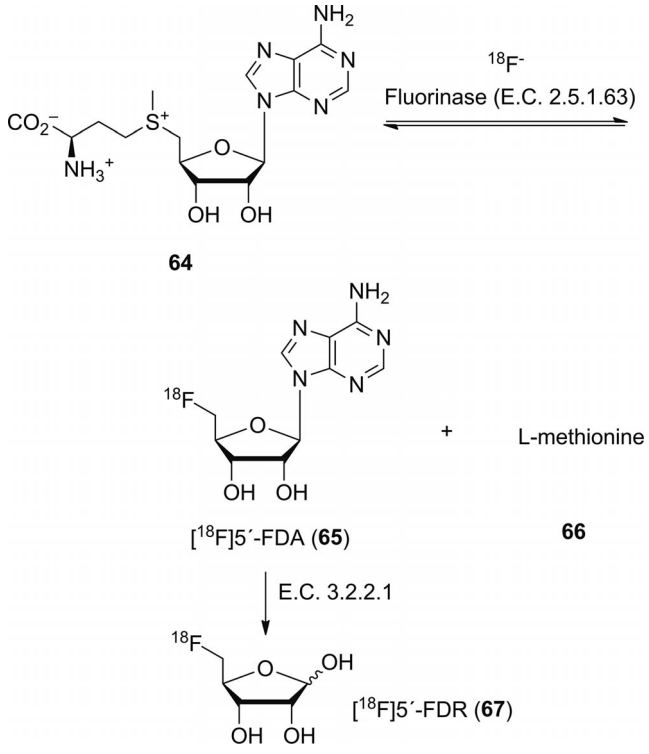


Scheme 11. Synthesis of [^{18}F]FTL as in ref.[80] Reagents: a) i. [^{18}F]KF; ii. NaOH.



Scheme 12. Synthesis of [^{18}F]FIAU as in ref.[83] Reagents: a) [^{18}F]-KF, K_2CO_3, Kryptofix; b) i. TMSOTf, $ClCH_2CH_2Cl$, 60 min, 85 °C; ii. NaOMe, MeOH, 80 °C.

An innovative approach based on the enzyme-catalyzed [^{18}F]fluorination of *S*-adenosyl-L-methionine (SAM, **64**, Scheme 13) for the radiosynthesis of [^{18}F]5′-fluoro-5-deoxyadenosine ([^{18}F]5′-FDA, **65**) was recently described.[86a] The fluorinase enzyme (E.C. 2.5.1.63), purified from the bacterium *Streptomyces cattleya*, catalyzes direct introduction of ^{18}F into organic compounds. This methodology should be particularly useful for the radiofluorination of biomolecules in aqueous media. The original radiofluorination with the wild-type enzyme proved inefficient (RCY ≈ 1%), but the use of over-expressed fluorinase (higher concentration of enzyme than nca $^{18}F^-$) in conjugation with additional enzymatic systems dramatically increased the radiosynthesis of [^{18}F]5′-FDA to 95%.[87] The coupling of L-amino acid oxidase (E.C. 1.4.3.2) with the fluorinase removes the resulting L-methionine (**66**), shifting the equilibrium towards formation of [^{18}F]5′-FDA. On the other hand, the free sugar [^{18}F]5′-fluoro-5-deoxyribose ([^{18}F]5′-FDR, **67**) could be prepared from [^{18}F]5′-FDA after combination of the fluorinase reaction with nucleoside hydrolase (E.C. 3.2.2.1).[86b] The presence of the fluorine at C-5 in **67** and the increased reactivity of five-membered aldol sugars over their six-membered counterparts with alkoxyamines encouraged its use as aldehyde source for the ^{18}F-labeling of peptides through oxime bonds.[88]



Scheme 13. Biotransformation of *S*-adenosyl-L-methionine into 5′-[^{18}F]5′-fluoro-5′-deoxyadenosine and [^{18}F]5′-fluoro-5′-deoxytibose in *S. cattleya*.[86]

A new class of nucleosides was developed from the conjugation of 2-nitroimidazole (azomycin) to sugar molecules through *N*-glycosidic bonds (Figure 13).[89] These nucleosides were designed to overcome the excessive lipophilicity of the azomycin without affecting the electron-affinity properties of the azomycin ring. Under tissue hypoxia conditions, azomycin-based radiotracers are reduced to reactive intermediates with accumulation in those sites.[90] The azomycin nucleosides, prepared mainly by Königs–Knorr reactions between the bromosugars and 2-nitroimidazole, were then radiolabeled with ^{123}I/^{125}I or ^{18}F by isotopic exchange or nucleophilic radiofluorination, respectively.[89a,89g,89h] In vitro and in vivo studies found that the radiolabeled azomycin nucleosides shown in Figure 13 were suitable for imaging of solid tumor hypoxia.[91]

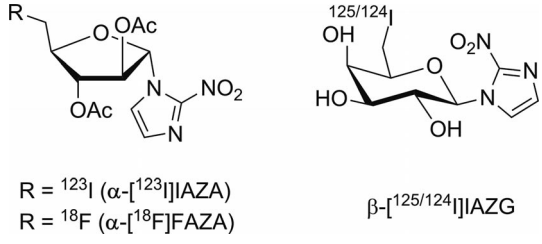


Figure 13. Examples of radiolabeled azomycin nucleosides.

5. Concluding Remarks

We have presented an overview of the most relevant radiolabeled carbohydrate derivatives for nuclear molecular imaging (PET and SPECT). A brief summary of the different methods for the preparation of [^{18}F]FDG is given, including its original synthesis by electrophilic radiofluorination and more sophisticated platform technologies exploring nucleophilic radiofluorination. The importance of [^{18}F]FDG and its derivatives as [^{18}F]-glycosylation agents of peptides and proteins is also outlined. The strong impact of [^{18}F]FDG in the clinic prompted research into alternative glucose-based radiotracers for PET and SPECT imaging. Some of these compounds have been labeled with ^{11}C or ^{18}F (PET) or with ^{123}I or ^{99m}Tc (SPECT). However, no analogue of [^{18}F]FDG is currently available.

For carbohydrate labeling ^{18}F is amongst the best options, being directly introducible onto the sugar skeleton without interfering much with the biological activity, as well as having an optimal half-life. In addition, the in vivo stabilities of radiofluorinated carbohydrates have been found to be better than those of their radioiodinated counterparts. For this reason, development of methods for radiofluorination on the sugar ring will definitely increase the number of ^{18}F-labeled carbohydrates for molecular imaging. In addition to the well established radiofluorination methods, the novel enzymatic radiofluorination approach offers new opportunities for stereoselective and cleaner ^{18}F labeling.

Acknowledgments

G. R. M. thanks the Fundação para a Ciência e Tecnologia (FCT) for the "Ciência 2008" program.

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