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Review Article

The Service Hospitalier Frédéric Joliot – contributions to PET chemistry over the years†

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Abstract: The *Service Hospitalier Frédéric Joliot* (SHFJ) (CEA-Orsay, France) has been a stimulating interdisciplinary research platform in medical imaging for almost half a century and particularly in the field of positron emission tomography (PET). In this context, PET chemistry, the driving force in molecular imaging, has occupied the front stage, especially where it concerns the short-lived radioisotopes carbon-11 and fluorine-18. In this review, important marks left by the SHFJ actors over the years will be highlighted. Copyright © 2007 John Wiley & Sons, Ltd.

Keywords: carbon-11; fluorine-18; Service Hospitalier Frédéric Joliot; CEA

Introduction

In the immediate aftermath of the second world war, general Charles de Gaulle, aware of the immanent and crucial importance of nuclear energy in the new world order and eager to establish for France an independent role in its development, ordered in 1945 the creation of the *Commissariat à l'Énergie Atomique* (CEA), a central nuclear research organization under tight government control but at the same time enjoying a great freedom of action. Its mission was broad, ranging from military applications via civil nuclear energy production to biological and medical research.

The first High Commissioner and one of the founding fathers of the CEA was Frédéric Joliot, the man who, together with his wife Irène Curie, had received in 1935 the Nobel Prize for the discovery of artificial radioactivity. This discovery laid the foundation for the development of medical *in vivo* imaging which has been pushing back the frontiers of medicine ever since.

In 1958, the CEA inaugurated a research unit dedicated to nuclear medicine imaging and it was more than fitting that it was named after Frédéric Joliot, who had died the year before. The *Service Hospitalier Frédéric Joliot* (SHFJ) is a part of the nuclear research site of Saclay (CEN Saclay) near Paris and is implanted on the hospital grounds of the small town of Orsay in the midst of a relatively small territory concentrating an extraordinary number of institutions of scientific learning and research.

In 2008, the SHFJ will be 50 years. The synthesis of radiolabelled compounds and radiopharmaceuticals for positron emission tomography (PET) has been a major research line at the institute for all these years. The year 2007 sees the fiftieth anniversary of the *Journal of Labelled Compounds and Radiopharmaceuticals*. For the SHFJ, like for many others, it has been a most important platform for the publication of its radiochemistry papers, as the reference list of this article testifies.

At the occasion of the journal's milestone we would like to sketch the development of PET chemistry with the positron emitters carbon-11 and fluorine-18 over the past 35 years as reflected by the various marks left by the SHFJ during its existence, which more or less parallels that of the journal.

Radioisotope production

Carbon-11 and fluorine-18 have short half-lives and are produced using a particle accelerator, usually a cyclotron. In 1975, a French-made compact cyclotron (CGR-MeV) was installed at the SHFJ.[1] It was a variable-energy machine able to accelerate protons (3–21 MeV), deuterons (3–12 MeV) as well as helium-3

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(5–31 MeV) and helium-4 (6–24 MeV) ions. This configuration clearly reflected the wish at the time not to be restricted to the four PET radioisotopes carbon-11, nitrogen-13, oxygen-15 and fluorine-18. Indeed, initially the radioisotopes ^{43}K, ^{199}Tl, ^{197m}Hg and ^{97}Ru were produced in the spirit of the nuclear medicine research that had been carried out in the first decade of the SHFJ's existence.[1–4] With a PET camera installed in 1976, the second in Europe just after that of the Medical Research Council at Hammersmith Hospital in London, the emphasis shifted rapidly towards carbon-11 ($T_{1/2}$ = 20.4 min), oxygen-15 ($T_{1/2}$ = 2.07 min, $C^{15}O_2$ and $^{15}O_2$), fluorine-18 ($T_{1/2}$ = 109.8 min) and to a lesser extent to nitrogen-13 ($T_{1/2}$ = 9.96 min) and bromine-76 ($T_{1/2}$ = 16.1 h). Cyclotron targetry had to be developed essentially in house[5] and for many years to come Orsay was one of the reference laboratories in this field. In 2004, the CGR-MeV machine was taken out of service and was replaced by a fixed-energy two-particle machine for 18 MeV protons and 9 MeV deuterons (Cyclone 18/9, IBA, Belgium), confirming the obvious trend towards almost exclusive use of carbon-11, oxygen-15 and fluorine-18 in PET.

Carbon-11

The first SHFJ molecules: [^{11}C]chlorpromazine, [^{11}C]nicotine, [^{11}C]methionine and [^{11}C]ovine luteinizing hormone

Work at the SHFJ on the radiochemistry of carbon-11 started well before the installation of the cyclotron in 1975. In the preceding years, partly inspired by the work of Christman *et al.*[6] the syntheses of important carbon-11 alkylation agents were pioneered using the Philips cyclotron, at that time on its last legs, of the CEN-Saclay site and an improvised shielded fume hood. We are discussing here about the now well-known procedures for [^{11}C]methyl iodide and [^{11}C]formaldehyde, implying lithium aluminium hydride reduction of [^{11}C]carbon dioxide to [^{11}C]methanol followed by treatment with hot hydriodic acid or hot silver wool, respectively.[7–13] Carbon-11-labelled compounds synthesized with these precursors were transported by private car to the SHFJ for further gamma-camera experiments on animals.

[^{11}C]Chlorpromazine. The very first compound synthesized by the SHFJ group was [^{11}C]chlorpromazine[7,8,11,14] (Figure 1). The choice of this drug, used in the treatment of schizophrenia and which blocks dopaminergic receptor sites, witnesses already the coming emphasis on the brain as the target organ, a PET-research line which has been dominant at the SHFJ ever since. [^{11}C]Chlorpromazine was synthesized by reductive methylation with [^{11}C]formaldehyde using sodium cyanoborohydride. In these early days, this reductive methylation method was often chosen and not [^{11}C]methyl iodide because it was thought to give less side products in terms of double methylation (specific radioactivities were not always that high). Although HPLC separation was used from the very beginning, this technique was still in its infancy and it was felt that the side products should be avoided as much as possible. Later on it was recognized that [^{11}C]formaldehyde did, in most cases, not really have an advantage over [^{11}C]methyl iodide and the latter soon became the methylation work-horse. The cerebral distribution of [^{11}C]chlorpromazine was studied in schizophrenic patients, often on chlorpromazine treatment, as a function of treatment. It is the first example of trying to obtain *in vivo* information of a medicinal product in man using PET in a clinical context.[15] In addition, this radiopharmaceutical was used in a study of non-respiratory lung function.[16]

[^{11}C]Nicotine. Using again the reductive [^{11}C]formaldehyde methylation, now either with formic acid or with sodium borohydride, [^{11}C](–)-nicotine (Figure 1) was synthesized and its distribution was studied in animals.[11,17,18] Later, it was also labelled with [^{11}C]methyl iodide.[18] This molecule resurged in the nineties and has been generating interest continuously, mainly in other laboratories, because of its binding to the nicotinic acetylcholinergic receptor and its relation to tobacco smoking.[19–27] This, in spite of the problems of non-specific binding which makes modelling difficult. It was also proposed as a cerebral blood flow marker.[22] At

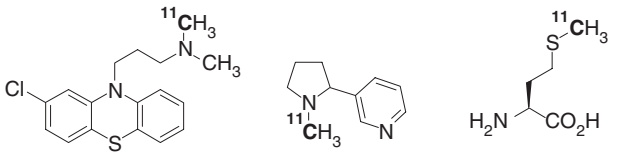

Figure 1 Some early SHFJ molecules.

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the SHFJ one stayed focused on the nicotinic receptor up to the present day, but more in favour of the development of new more selective and specific ligands, often labelled with fluorine-18.[28–35]

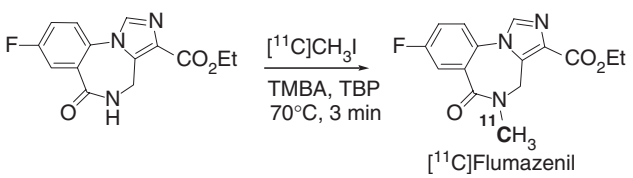
[^{11}C-methyl]L-Methionine. A star molecule in the early period was the amino acid [^{11}C-methyl]L-methionine (Figure 1). It was synthesized using the reaction of [^{11}C]methyl iodide (no expected side reactions this time !) with homocysteine.[11,36] The formulation of the final product, which was injected into human volunteers in the initial experiments, is typical for this pioneering period and unimaginable today: Taking up the crude solvent-evaporated reaction mixture in 0.1 N HCl, pH adjustment with 0.1 N NaOH, sterile filtration.[36] This tracer that measures the amino acid transport rather than protein metabolism[37] was soon put into practical use in the study of the clinical problem of phenylketonurea in young children.[14,38] In addition, work was performed on the pancreatic function[39–41] and also on the detection of brain gliomas,[42] which is the main use of [^{11}C-methyl]L-methionine today. However, this molecule stopped being synthesized at the SHFJ when the brain receptor studies had become a priority near the end of the eighties.

[^{11}C]Ovine luteinizing hormone. Today, fluorine-18 is by far preferred to carbon-11 when it concerns protein labelling, mainly because of the longer half-life, more compatible with the kinetics of protein fixation to target tissues. However, the beginnings of PET chemistry at the SHFJ were also marked by the development of a method of protein labelling with carbon-11. The reductive methylation method with [^{11}C]formaldehyde proved to be an excellent way of labelling the ε-amino groups of the lysine residues of ovine luteinizing hormone without changing the biological properties.[9] At the same time, Straatmann and Welch[43] in St Louis published a similar method labelling albumin and fibrinogen. The specific radioactivity of [^{11}C]ovine luteinizing hormone was relatively low and the same as that of [^{11}C]formaldehyde, indicating that no more than one lysine residue per protein molecule was methylated. However, since a protein usually contains a number of lysine residues, multiple labelling with accordingly high specific radioactivity is potentially possible. This was confirmed some years later at Orsay when the protein concanavalin A, containing 12 lysine groups, was labelled with the same, but improved method reaching a specific radioactivity of 2.7 Ci/μmol, six times higher than habitual for monomethylation products at that time, and 5.4 Ci/μmol for the dimer, the actual form of concanavalin A.[44]

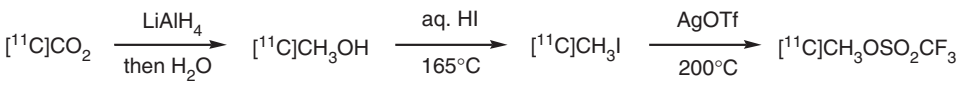
[^{11}C]Methyl iodide

[^{11}C]Methyl iodide has maintained its predominant position over the years in practically all PET laboratories in the world, either as such or more recently as its more reactive derivative [^{11}C]methyl triflate. The robust production method (Scheme 1), essentially developed in Orsay in the early years, still stands today although 'dry' production from [^{11}C]methane is becoming more and more *en vogue*. We will highlight some representative carbon-11-labelled molecules from the SHFJ as we will do also for other precursors in the following sections.

From the beginning, the study of central benzodiazepine receptors with PET[45] has been an area of intensive research at the SHFJ. After having studied benzodiazepine sites in baboons with the labelled agonist-diazepines [^{11}C]flunitrazepam and [^{11}C]diazepam, the first diazepines labelled for PET,[46,47] a breakthrough was marked in 1984 with the labelling of the imidazobenzodiazepine antagonist flumazenil also known as Ro 15-1788.[48] The radiosynthesis, outlined in Scheme 2, consisted in the typical methylation with [^{11}C]methyl iodide of a cyclic amide function in the selected solvent tributyl phosphate with trimethylbenzylammonium hydroxide as base. [^{11}C]Flumazenil had much more favourable kinetics than previous compounds and has been intensively studied,[49–53] particularly finding an important practical application in the study of epilepsy.[54–60] A solid-phase version of the synthesis was proposed recently by Krasikova *et al.*[61] Labelling of flumazenil has now also



Scheme 2



Scheme 1

been achieved with fluorine-18 at the aromatic fluorine position by Ryzhikov *et al.*[62]

The generally recognized reference PET ligand [^{11}C]PK11195 (Figure 2) for the study of the so-called peripheral benzodiazepine receptor, sometimes called the PK-site,[45] after this molecule was also a first from the SHFJ.[63] The radiosynthesis consisted in base-facilitated *N*-methylation of the amide moiety of the molecule in DMSO with [^{11}C]methyl iodide. It was rapidly shown that this radioligand could visualize the PK receptors in the heart.[64] [^{11}C]PK11195 reveals augmented PK-site concentration at damaged tissues and in tumours and has been under continuous investigation in Orsay and elsewhere.[65–70] At present, at the SHFJ the search is continuing for ligands with a similar action but with improved performance relative to PK11195, e.g. [^{11}C]DPA-713[71,72] and [^{11}C]CLINME[73] (Figure 2).

The muscarinic antagonist *N*-methylquinuclidin-3-yl benzilate, known as Me-QNB, was labelled at its quaternary ammonium position with [^{11}C]methyl iodide[74,75] (Figure 2). It has been used for the quantification of ventricular muscarinic receptors in animals and in man, for example, in heart transplant patients.[74,76–85] Recently, a largely improved synthesis using [^{11}C]methyl triflate, which was clearly superior to [^{11}C]methyl iodide, was published allowing two parallel studies on different PET cameras with one preparation.[86]

In the search for a suitable PET ligand for the dopamine reuptake receptor (DAT), an impressive number of tropane derivatives, analogues of cocaine, have been proposed by various laboratories[87] but an ultimate combination of high affinity and high selectivity relative to the serotonine and norepinephrine transporters is still being sought. A new step in this direction was our radiosynthesis[87] of a new tropane derivative, LBT-999[88] (Figure 2), which is a structural hybrid between the high affinity (*E*)-FBCINT (with instead of the *p*-methyl-a chlorine atom)[89] and PE2I[90] which exhibits excellent selectivity. The radiosynthesis was achieved by esterification of the corresponding carboxylic acid in acetone using [^{11}C]methyl triflate instead of [^{11}C]methyl iodide. The synthesis of the closely related tropane analogue [^{11}C]PE2I had been optimized before using the same reaction.[91] PET studies in baboon illustrated that LBT-999 is an excellent candidate for *in vivo* quantification of the DAT, especially in extra-striatal structures, such as the midbrain.[92]

The higher reactivity of [^{11}C]methyl triflate[93–96] relative to [^{11}C]methyl iodide incited us to a program of synthesis improvement for a number of ligands at the SHFJ often in co-operation with other laboratories. Apart from the already mentioned [^{11}C]Me-QNB and [^{11}C]PE2I, these are the D2-ligands [^{11}C]raclopide,[97] [^{11}C]FLB-457[98] and [^{11}C]epidepride,[99] the MAO-B inhibitor [^{11}C]deprenyl[100]

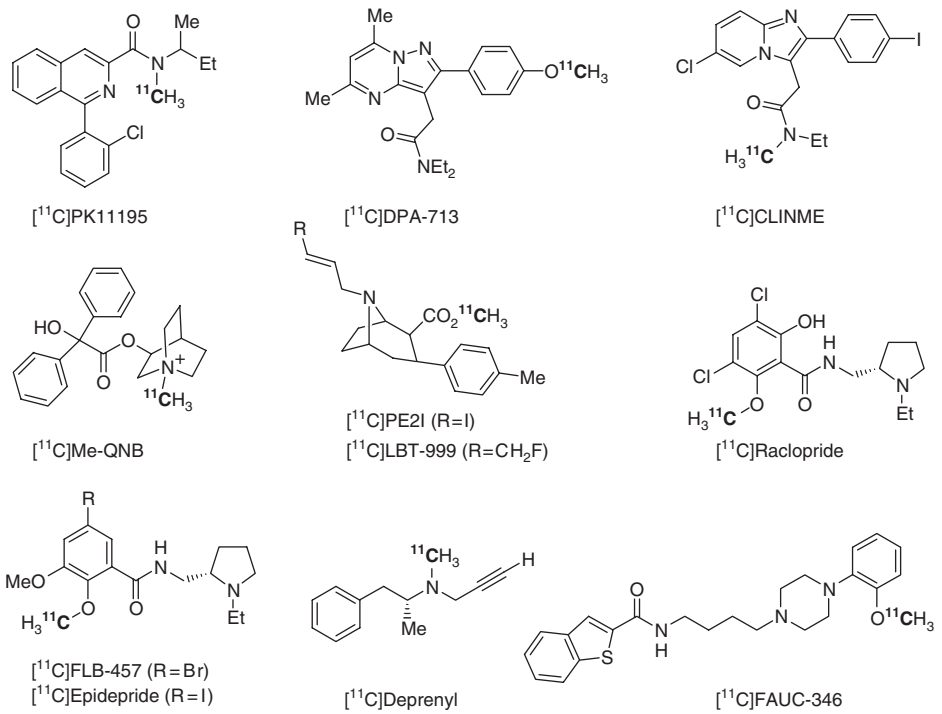


Figure 2 Selection of SHFJ ligands obtained by [^{11}C]methylation.

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and [^{11}C]FAUC-346,[101] a first compound in our current D3 receptor ligand program (Figure 2).

[^{11}C]Formaldehyde and [^{11}C]formate

Reductive methylation was the sole *raison d'être* of [^{11}C]formaldehyde in the early days. As its presumed advantage over [^{11}C]methyl iodide faded away in practice, it slowly fell into disuse. The last methylation with [^{11}C]formaldehyde at the SHFJ was published in 1985 with the synthesis of the important central benzodiazepine ligand [^{11}C]suriclone recognizing at the same time that [^{11}C]methyl iodide worked better.[102] However, towards the end of the nineties interest in this labelling agent resurged, but now for other reactions than reductive methylation. We developed a more reliable method for its production replacing the hot silver by silver ions immobilized in a ceramic material[103] (Scheme 3).

A spin-off of this research was the realization that [^{11}C]formate can be a considerable by-product in the reduction with lithium aluminium hydride of [^{11}C]carbon dioxide to [^{11}C]formaldehyde and/or [^{11}C]methanol, especially at low temperatures.[104] [^{11}C]Formate production was then optimized (Scheme 3) and used for the production of [^{11}C]chloroformate and [^{11}C]carbon monoxide.[105] Also, the reduction of [^{11}C]formate to [^{11}C]methanol using samarium diiodide was explored.[106] The new method for [^{11}C]formaldehyde production was applied in the radiosynthesis of the important α2-receptor ligand atipamezole using a previously developed general method of [^{11}C]imidazole formation from α-diketones and [^{11}C]formaldehyde.[107,108] In another laboratory, it found use in the labelling of the potential Alzheimer drug 1,1′-methylene-di-(2-naphthol).[109]

[^{11}C]Acetone

The counterpart of the reductive *N*-methylation with [^{11}C]formaldehyde is the attachment of an [^{11}C]isopropyl group to a nitrogen-containing molecule with the aid of [^{11}C]acetone. In 1980, the SHFJ-group published the first synthesis of [^{11}C]acetone, from [^{11}C]carbon dioxide and methyllithium, pointing to the importance of the stoichiometric proportions under

Scheme 4

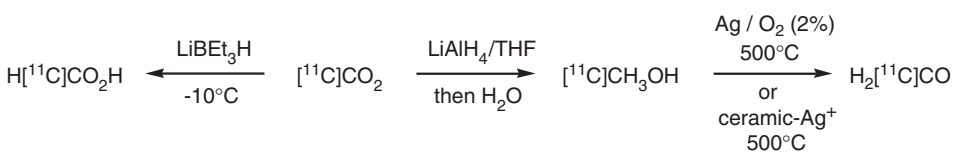
no-carrier-added conditions *vis-à-vis* [^{11}C]*t*-butanol formation (Scheme 4).[110]

Recently, Studenov *et al.*[111] addressed this problem proposing selective quenching of excess of methyllithium, suggesting that [^{11}C]*t*-butanol formation takes place during the hydrolysis step and not before. *N*-[^{11}C]Isopropylation has been very useful in labelling a family of β-adrenoceptor ligands for cardiac PET studies,[112] some of which were synthesized at Orsay, namely [^{11}C]propranolol,[113] [^{11}C]practolol[114] and [^{11}C]pindolol.[115] Reduction of [^{11}C]acetone to [^{11}C]propanol was used in the synthesis of [^{11}C]sarin,[116] a potent inhibitor of acetylcholinesterase. The latter product can be seen as the prelude to much activity to come at the SHFJ around the subject of acetylcholinesterase, focussing on [^{11}C]physostigmine (see section on [^{11}C]phosgene).

[^{11}C]Phosgene

This year it is 30 years ago that the first [^{11}C]phosgene at the SHFJ was produced, as the result of a collaboration with the Free University in Amsterdam. The method consisted of the reduction of [^{11}C]carbon dioxide to [^{11}C]carbon monoxide followed by chlorination with platinum tetrachloride.[117] This precursor proved very fertile and yielded a range of radiopharmaceuticals in a short time (Figure 3) mostly by ring-closure reactions: the antiepileptic [^{11}C]phenytoin,[118–120] the neuroleptic [^{11}C]pimozide,[119,121,122] [^{11}C]urea for the study of pulmonary oedema,[16,123] the serotonergic ligand [^{11}C]ketanserin[124–126] and, via directly from [^{11}C]phosgene-derived diethyl [^{11}C]carbonate, the antiepileptic [^{11}C]phenobarbital[127] and [^{11}C]DMO[128–130] for tissue pH measurement.

In 1987, a new, less tedious method for the production of [^{11}C]phosgene was put in place.[131] It started from [^{11}C]methane, which was produced by proton irradiation of a nitrogen/hydrogen target. This was converted in an online process with chlorine gas over a hot copper(II) chloride catalyst into [^{11}C]tetrachloromethane which was then passed over hot iron filings.



Scheme 3

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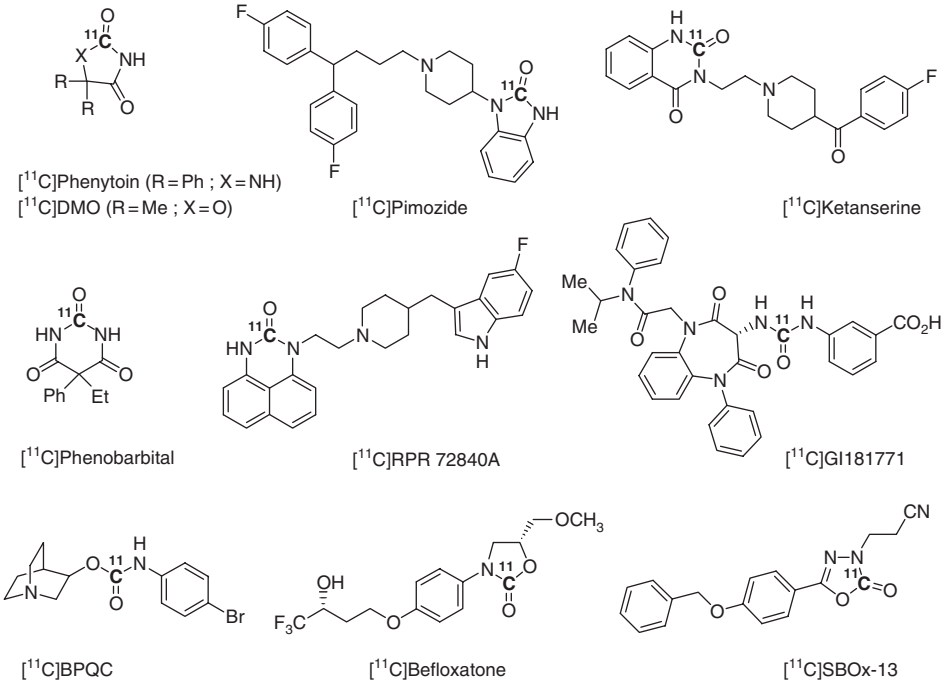
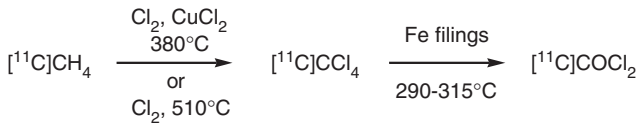
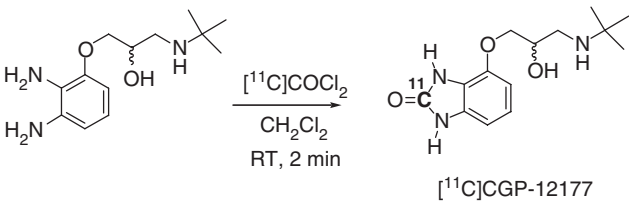


Figure 3 Selection of SHFJ ligands obtained from [^{11}C]phosgene.



Scheme 5



Scheme 6

Non-added traces of oxygen suffice to give rise to [^{11}C]phosgene. The specific radioactivity was higher than that obtained with the previous method. More recently, the copper(II) chloride catalyst was replaced by a simple hot empty glass tube according to Link and Krohn[132] and Dollé *et al.*[133,134] (Scheme 5).

Continuing the line of β-adrenoceptor research, begun in 1982 with [^{11}C]propranolol (see section on [^{11}C]acetone), the availability of [^{11}C]phosgene permitted the radiosynthesis of the ligand [^{11}C]CGP-12177, not accessible via [^{11}C]acetone unlike many other compounds of this family[135] (Scheme 6). [^{11}C]CGP-12177 proved to be highly successful and has been studied extensively at the SHFJ and elsewhere.[136–139] Later, the two enantiomers of CGP-12177 were labelled with carbon-11 separately.[140]

[^{11}C]Phosgene continued to be useful not only in ring-closure reactions,[133,135,140–145] for example, [^{11}C]RPR 72840A[142] (Figure 3), but also in the radiosynthesis of non-cyclic (unsymmetrical) ureas and carbamates such as [^{11}C]GI181771[134] and [^{11}C]BPQC[32]. Of particular interest is the carbamate [^{11}C]physostigmine, an inhibitor of acetylcholinesterase.[146–153] After having been synthesized first from [^{11}C]carbon dioxide via [^{11}C]acetyl chloride,[146] a better way was developed with [^{11}C]phosgene.[149] The first step of the latter radiosynthesis consisted in the reaction of *bis*(trimethylsilyl)methylamine with [^{11}C]phosgene to give [^{11}C]methyl isocyanate (Scheme 7). [^{11}C]Isocyanates are labelled intermediates more often encountered in [^{11}C]phosgene chemistry.[32,134] In the present case, in order to avoid *N,N'*-dimethylurea formation, the rather reactive methylamine was silylated first. In the second step, the [^{11}C]isocyanate was coupled to eseroline to give [^{11}C]physostigmine. [^{11}C]Heptastigmine was made in a similar fashion directly from the unprotected heptylamine.[149]

Befloxatone (Figure 3) is a very potent, selective and reversible inhibitor of the enzyme monoamine oxidase-A (MAO-A). It was labelled at its oxazolidinone moiety by ring closure of the corresponding aminoalcohol with [^{11}C]phosgene.[133,143] A similar ring-closure reaction had been achieved already on a hydrazinocarbonyl

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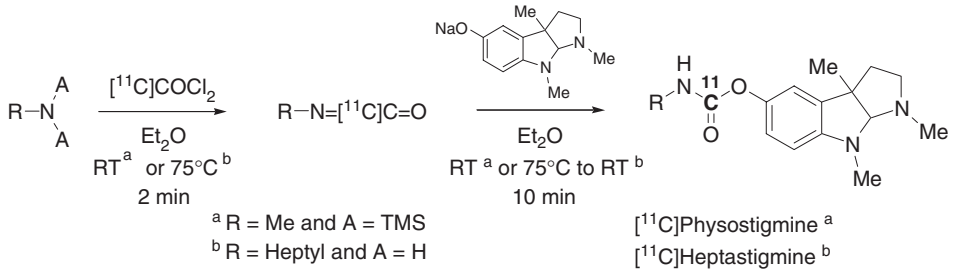
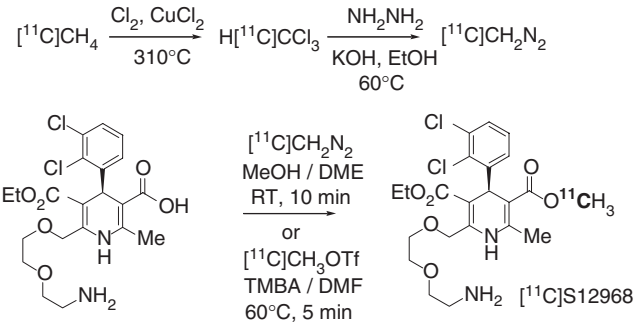
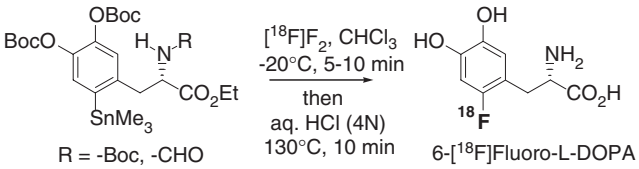


Scheme 7



Scheme 8



Scheme 9

compound to label the MAO-B inhibitor [^{11}C]SBOx-13.[141] [^{11}C]Befloxatone is currently being evaluated and used at the SHFJ.[143,154–156]

[^{11}C]Diazomethane

The existence of the [^{11}C]phosgene production apparatus facilitated the development of the interesting precursor [^{11}C]diazomethane.[157] Instead of chlorination of [^{11}C]methane to [^{11}C]tetrachloromethane as in the [^{11}C]phosgene production, [^{11}C]chloroform was made by simple adjustment of the chlorination temperature. This was then bubbled into a mixture of hydrazine, ethanol and potassium hydroxide giving [^{11}C]diazomethane, which could be distilled on line into a reaction vessel (Scheme 8). [^{11}C]Diazomethane was used for the esterification of carboxylic groups,[158–160] with the advantage that no base is required as in esterification with [^{11}C]methyl iodide. This is illustrated with the radiolabelling of the calcium-channel ligand S12968[160,161] where both [^{11}C]methyl iodide on an amino-protected precursor and [^{11}C]diazomethane on an unprotected precursor were employed (Scheme 8). Later, it was found that in this particular case [^{11}C]methyl triflate surprisingly works on the unprotected precursor.[162] [^{11}C]Diazomethane was also employed in the radiosynthesis of the labelled nitric oxide synthase inhibitor *N*(ω)-nitro-L-arginine [^{11}C]methyl ester ([^{11}C]L-NAME).[159] Interestingly, it was found that this widely used inhibitor is very rapidly demethylated *in vivo* in rats giving [^{11}C]methanol and unlabelled *N*(ω)-nitro-L-arginine, which inhibits the enzyme too.[163]

Fluorine-18

In the early years, interest in fluorine-18 lagged behind that in carbon-11 at the SHFJ as in most other laboratories. On the one hand, this was due to the relative difficulty in preparing electrophilic molecular [^{18}F]F_2 gas, which moreover cannot be obtained but in a low specific radioactivity; on the other hand, the fact that aqueous [^{18}F]fluoride is unreactive and targetry for [^{18}F]fluoride was still in its infancy. Of course, 2-[^{18}F]fluoro-2-deoxy-D-glucose ([^{18}F]FDG, made from [^{18}F]F_2) was implemented relatively early[164] and some research was performed on nucleophilic aromatic substitution with [^{18}F]fluoride in the early eighties, but only during the nineties Orsay commences to invest more and more in this radioisotope and today it is at least on an equal footing with carbon-11. Similar to the case of [^{18}F]FDG, an electrophilic routine synthesis of 6-[^{18}F]fluoro-L-DOPA was set up as soon as its importance became evident and an improvement in the synthesis of the stannylated precursor was published[165,166] (Scheme 9). However, interest in fluorine-18 has been focused almost completely on the nucleophilic form of fluorine-18.

Nucleophilic homo-aromatic substitution with [^{18}F]fluoride

Today at the SHFJ, like everywhere else, [^{18}F]fluoride is produced with the ^{18}O(p,n)^{18}F reaction on ^{18}O-enriched water and applied in nucleophilic substitution

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reactions using the cryptand Kryptofix-222®.[167,168] Before the advent of the kryptofix method, dry hydrogen [^{18}F]fluoride was used in Orsay.[169] The multiparticle cyclotron allowed for an elegant production through the reaction ^{20}Ne(^{3}He,αn)^{18}Ne on a flow-through neon–hydrogen target. ^{18}Ne has a half-life of 1.5 s decaying to fluorine-18. It is swept out of the target holder and the fluorine-18 activity is collected as hydrogen[^{18}F]fluoride in a PTFE tube where it can be solubilized in an organic solvent. It was used in studies of nucleophilic aromatic substitution on model compounds with the butyrophenone dopamine receptor ligands spiroperidol and haloperidol.[170,171] It was found necessary to add base to provide a cation for the [^{18}F]fluoride, such as potassium.

The first important ligand obtained at the SHFJ by nucleophilic aromatic substitution was [^{18}F]setoperone[172–174] (Scheme 10), a serotoninergic 5-HT$_2$ ligand. This was the result of a close collaboration project with Janssen Pharmaceuticals (Belgium), in order to replace the earlier [^{11}C]ketanserin[125] which was not selective and specific enough. The above-mentioned ^{18}F production via ^{18}Ne was used in this work and compared with the new kryptofix method. It could not stand in the latter's shadow and was definitely abandoned. Note that aqueous [^{18}F]fluoride could conveniently be made at the SHFJ also by the ^{16}O(^{3}He,p)^{18}F reaction on natural water.

The high-affinity [^{18}F]setoperone has been used mainly in psychiatry research until the present day in spite of some binding to the dopamine receptors as well.[175–184] To deal with the latter problem, [^{18}F]ritanserin (Figure 4), also from Janssen Pharmaceuticals, was labelled,[185] but no further work on this ligand was carried out, probably because the three-step synthesis is rather tedious. More recently, a systematic study was conducted on the nucleophilic aromatic substitution on 1-halo-2-nitrobenzenes with the aim to synthesize 1-[^{18}F]fluoro-2-nitrobenzene[186] as a model for the intended 5-[^{18}F]fluoro-6-nitroquipazine synthesis,[187] a putative serotonine reuptake inhibitor. The norepinephrine analogue 4-[^{18}F]fluorometaraminol (Figure 4) (as well as the 6-regioisomer) is useful in mapping adrenergic nerve terminals in the heart. In co-operation with the Stockholm and Turku PET centres, this compound was labelled via nucleophilic aromatic substitution of the appropriate benzaldehyde precursor that was subsequently converted into the desired compound.[188,189] An electrophilic approach using [^{18}F]fluorine was also developed later.[190]

Nucleophilic hetero-aromatic substitution with [^{18}F]fluoride

The interest in the nicotinic acetylcholine receptor, begun a long time ago with [^{11}C]nicotine, obtained an important new impulse at the SHFJ with the radiosynthesis of the nicotinic ligand 2-[^{18}F]fluoro-A-85380 modelled after a 3-pyridylether series of Abbott Laboratories.[29,31] The same radioligand was developed simultaneously by Horti *et al.*[191] at Johns Hopkins hospital in Baltimore. 2-[^{18}F]Fluoro-A-85380 has been extensively evaluated in animals and in man in Orsay and elsewhere.[192–201] The synthesis is delineated in Scheme 11. The key step is a nucleophilic substitution of a nitro or trimethylammonium group at the *ortho* position relative to the pyridine nitrogen atom.

Scheme 10

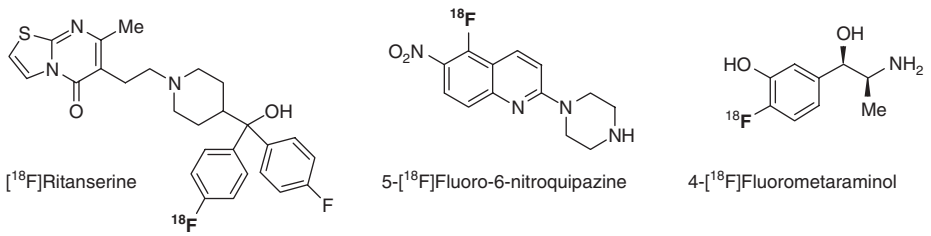

Figure 4 Selection of SHFJ ligands obtained by nucleophilic aromatic radiofluorination.

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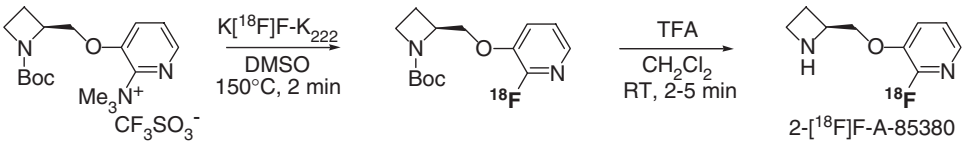

Scheme 11

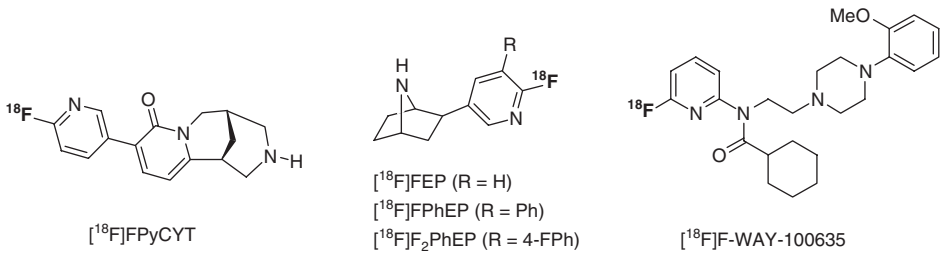

Figure 5 Selection of SHFJ ligands obtained by nucleophilic *hetero*-aromatic radiofluorination.

Having realized the attractiveness of the pyridine ring for nucleophilic substitution with [^{18}F]fluoride,[202–206] because of its intrinsic activation that absolves the need for an activating electron-withdrawing group, a systematic study of this reaction on pyridine, having a leaving group on the *ortho*, *meta* or *para* position, was carried out.[207,208] It was found that for the *ortho* position the nitro and above all the trimethylammonium group are the best, while iodine is unreactive. Substitution at the *para* position is also feasible, but the *meta* position is unreactive. Several other radioligands targeting the $\alpha_4\beta_2$ subtype of the nicotinic receptor (Figure 5) were synthesized at the SHFJ based on the concept of pyridine ring radiofluorination, namely [^{18}F]FPyCYT[33] and the epibatidine analogues [^{18}F]FEP[30], [^{18}F]FPhEP[34] and [^{18}F]F$_2$PhEP[35]. In addition, the 2-[^{18}F]fluoropyridine moiety proved useful in the design of prosthetic groups for macromolecule labelling (*vide infra*). The well-known radioligand WAY-100635 for imaging the serotoninergic 5-HT$_{1A}$ receptor in the brain contains a pyridine ring. The above-mentioned unsuitability of the *meta* position for [^{18}F]fluorination was further confirmed in efforts to make a [^{18}F]fluorinated derivative of WAY-100635 (Figure 5). As the 6-fluoro derivative was easily accessible, no labelled 5-fluoro compound could be obtained.[209]

Nucleophilic aliphatic substitution with [^{18}F]fluoride

A number of fluorine-18-labelled compounds has been synthesized through nucleophilic aliphatic radiofluorination at the SHFJ (Figure 6), namely two analogues of the NMDA antagonist MK801[210,211], the glucocorticoid ligand [^{18}F]RU-52461[212], the DAT ligands 3-[^{18}F]FMe-BTC-piperidine[213] and 4-[^{18}F]FEt-BTC-piperazine,[214,215] 3-[^{18}F]FMe-TC-piperidine for the NMDA receptor channel complex,[216] the selective serotonine uptake inhibitor [^{18}F](*S*)-fluoxetine[217] (Scheme 12) and the DAT ligand [^{18}F]LBT-999.[218,219] The last two compounds are worth mentioning in particular.

The radiosynthesis of [^{18}F](*S*)-fluoxetine is instructive in showing the difficulty of making certain labelled trifluoromethyl compounds with high specific radioactivity. This problem has also been observed by others.[220,221] The synthesis (Scheme 12) consists of two steps: first, a nucleophilic radiofluorination on α-bromo-4-chloro-α,α-difluorotoluene giving [^{18}F]4-chloro-α,α,α-trifluorotoluene, which is then coupled to (*S*)-(−)-3-(methylamino)-1-phenyl-1-propanol to give [^{18}F](*S*)-fluoxetine. The problem occurs in the first step where the precursor at a high reaction temperature can generate non-radioactive fluoride, possibly by ionization stabilized by the para chlorine atom. This fluoride causes isotopic dilution and only a few mCi/μmol of [^{18}F](*S*)-fluoxetine were obtained. However, the effect could be reduced considerably by combined reductions of precursor concentration, temperature and reaction time resulting finally in 100–150 mCi/μmol.

In the section on [^{11}C]methyl iodide we discussed the new DAT ligand [^{11}C]LBT-999. The molecule also possesses a fluorine atom suitable for labelling and the ultimate goal in this project was to make [^{18}F]LBT-999, the carbon-11 work being for preliminary evaluation. The synthesis of [^{18}F]LBT-999 consists of a typical two-step procedure[218] (Scheme 13). First, the radiolabelling step providing (*E*)-1-[^{18}F]fluoro-4-tosyloxybut-2-ene from the corresponding ditosylate followed by coupling to 3β-*p*-tolyl-8-aza-bicyclo[3.2.1]octane-2β-carboxylic acid methyl ester giving [^{18}F]LBT-999.

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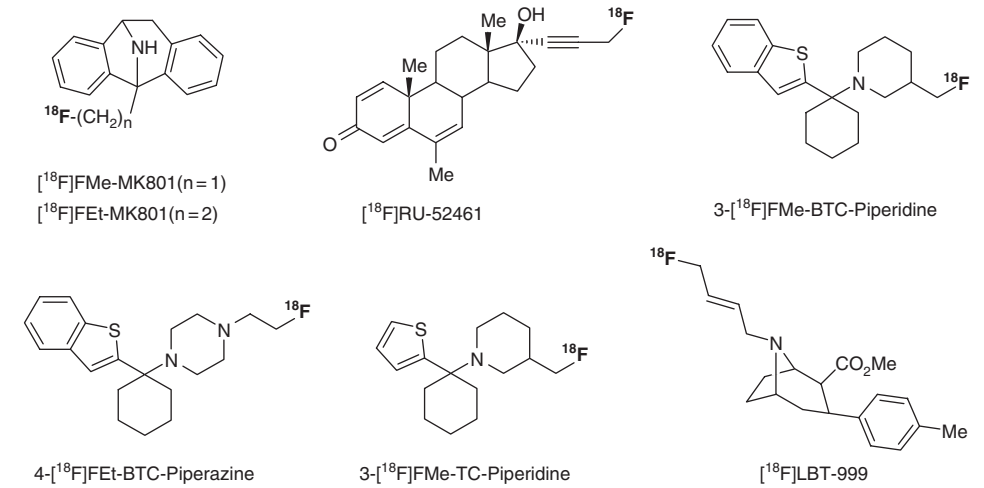
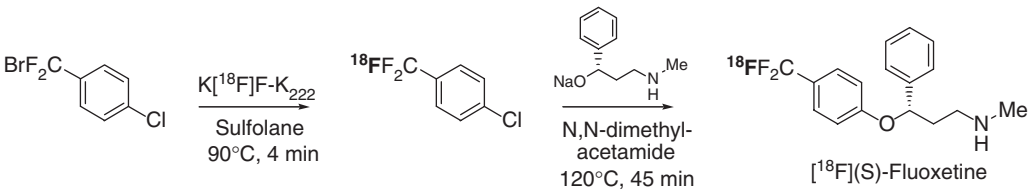
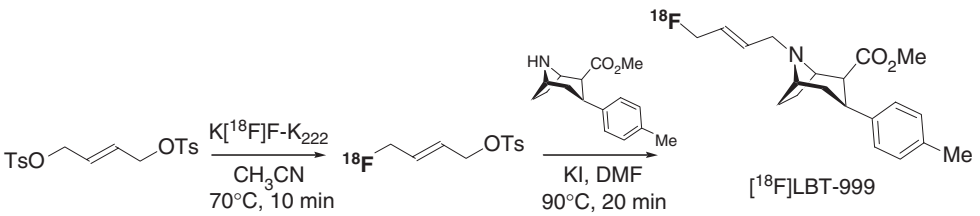


Figure 6 Selection of SHFJ ligands obtained by nucleophilic aliphatic radiofluorination.



Scheme 12



Scheme 13

Recently, this method was replaced by a single-step radioflurorination.[219] This very promising DAT ligand is currently under investigation at the SHFJ.

Macromolecule labelling with fluorine-18

During the last decade, PET applications in the field of cancer diagnosis and therapy have gained an enormous impetus. Besides the undebatable impact of [^{18}F]FDG, which also has a clear promoting effect on the dissemination of [^{18}F]chemistry in general, the demand for labelled macromolecules, such as peptides, proteins and oligonucleotides for PET, has been growing constantly. As we have seen, direct labelling of proteins with [^{11}C]formaldehyde was pioneered in Orsay.[9,44] However, because of its short half-life, carbon-11 is considered unsuitable today for most applications involving macromolecules, the kinetics of which are relatively slow. Moreover, this type of random labelling has no control over the position of labelling, risking loss of biological activity when the active site of the protein is affected by the labelling process. The latter problem also plays in the random labelling of aromatic residues with acetyl [^{18}F]hypofluorite.[37,222] Therefore, at present the generally accepted method for protein labelling involves a prosthetic group reagent in the form of a small fluorine-labelled molecule, which is then coupled regioselectively to the amino- or carboxylic end-group of the peptide or protein or to the relatively rare free thiol function.[205,206]

At the SHFJ, inspired on the one hand by the work of Shiue *et al.*[223] on certain *N*-substituted maleimides for coupling to free cysteine-SH groups of peptides and proteins, and on the other hand by our own experience

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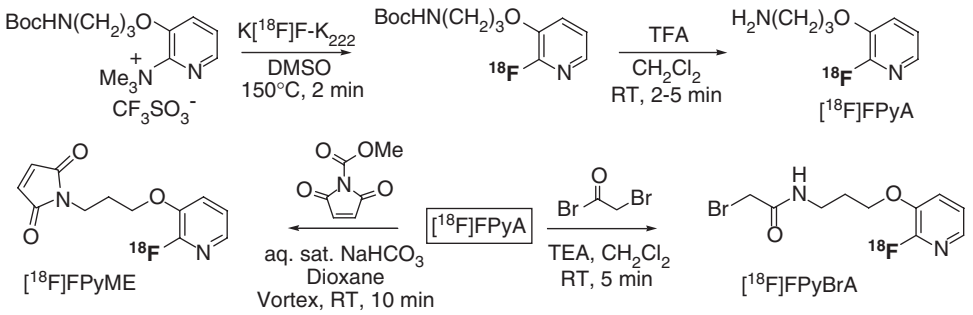
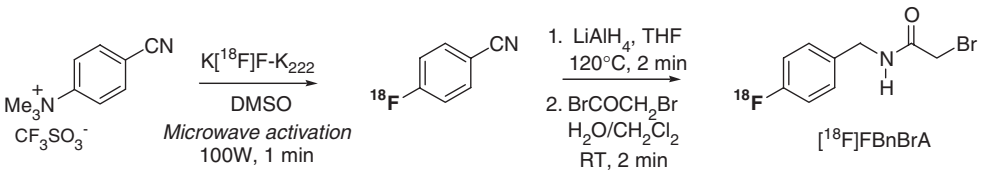
with hetero-aromatic radiofluorination initiated by the synthesis of 2-[^{18}F]fluoro-A85380,[29,31] a new *N*-substituted maleimide prosthetic group reagent, [^{18}F]FPyME[224] (Scheme 14), was developed very recently. A three-step synthesis was designed as a direct one-step radiofluorination failed, probably because of the sensitivity of the maleimide group under the fluorination conditions.[224,225] The resulting reagent was successfully coupled to a model peptide and to two proteins of interest (Scheme 16).

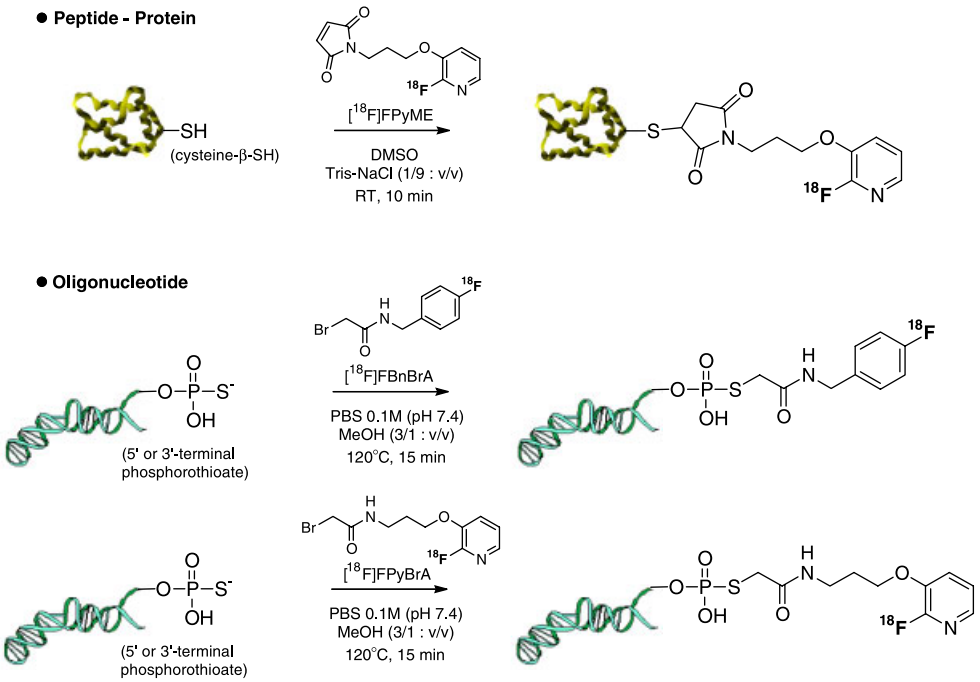
A special class of macromolecules constitutes the so-called peptide nucleic acids (PNAs). These are synthetic macromolecules where the deoxyribose phosphate backbone of DNA is replaced by the pseudo-peptide *N*-(2-aminoethyl)glycyl backbone, while retaining the nucleobases of DNA. PNAs have been labelled at a



Scheme 14



Scheme 15



Scheme 16 This Scheme is available in colour online at www.interscience.wiley/journal/jlcr

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terminal cysteine-site using *N*-(4-[^{18}F]fluorobenzyl)-2-bromoacetamide ([^{18}F]FBnBrA),[226–228] a reagent developed at Orsay originally for the labelling of oligonucleotides and which is also a thiol-selective reagent.[229] Its three-step radiosynthesis, including a *homo*-aromatic nucleophilic radiofluorination, is outlined in Scheme 15.

It has been the SHFJ's work-horse for the labelling of a whole series of oligonucleotides bearing a phosphorothioate monoester group at the 3′- or 5′-end (Scheme 16). It has been applied to all the common chemical modifications of oligonucleotides, such as full-length phosphorothioate diester internucleosidic-bond deoxyribonucleotides, hybrid methylphosphonate/phosphodiester internucleosidic-bond deoxyribonucleotides and 2′-*O*-methyl-modified oligoribonucleotides.[229–235] It was also applied to the labelling of L-RNA and L-DNA, called Spiegelmers.[236,237] Oligonucleotides have also been labelled with another bromoacetamide reagent, [^{18}F]FPyBrA[238] (Schemes 14 and 16), which is a structural hybrid of [^{18}F]FPyME and [^{18}F]FBnBrA. Notably, this reagent was recently used for the labelling of small interfering RNAs, a class of macromolecules constituted by the association of two single-stranded ribonucleic acids of short sequences.[239]

Conclusion

The *Service Hospitalier Frédéric Joliot* has been a stimulating interdisciplinary research platform over the years and remains to be so. Many scientists in the field of nuclear medicine and PET have at least once in their career found their way to Orsay for either a short visit or to work there for some time. The people who, at an early stage, were the driving force in the development of PET at Orsay were scientists with a background in pharmacology and pharmacy. They clearly saw the primordial importance of radiochemistry and even partly turned themselves into chemists. They were not satisfied with just [^{11}C]methyl iodide but stimulated active research in carbon-11 and fluorine-18 chemistry leading to new tools that were, and are, not always available in other laboratories, e.g. [^{11}C]phosgene. It was the time that labelled precursors could be developed for the sake of just making them, without having concrete applications in mind, such as [^{11}C]acetylene[240] and [^{11}C]methylamine[241]. It was this massive investment into radiochemistry development that gave the SHFJ its radiating position in the world of PET. We are confident that the future will see a continuation of this kind of radiochemical development, in Orsay and elsewhere. Molecular imaging is in a continuous and accelerating development with new vista opening up notably in oncology. It is obvious that the synthesis of labelled compounds and radiopharmaceuticals will continue to be of prime importance for a sustained development of PET.

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