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Meyer, Jan-Philip, Probst, Katrin C. and Westwell, Andrew D. 2014. Radiochemical synthesis of 2'-[18F]-labelled and 3'-[18F]-labelled nucleosides for positron emission tomography imaging. *Journal of Labelled Compounds and Radiopharmaceuticals* 57 (5) , pp. 333-337. 10.1002/jlcr.3197

Publishers page: <https://doi.org/10.1002/jlcr.3197>

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# Radiochemical synthesis of 2'- and 3'-[<sup>18</sup>F]-labelled nucleosides for Positron Emission Tomography Imaging

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## Abstract

This review article considers 2'- and 3'-labelled nucleosides, which are of great importance as Positron Emission Tomography (PET) probes in clinical diagnostics and PET research. Although the radiochemical preparation of several [<sup>18</sup>F]-labelled nucleosides such as [<sup>18</sup>F]FLT or [<sup>18</sup>F]FAC has been accomplished within the last two decades, a number of potentially interesting nucleoside-based biomarkers are not yet available for automated GMP production due to the lack of fast and efficient synthetic methods for late-stage [<sup>18</sup>F]-introduction. In order to meet recent demands for new PET based biomarkers in various clinical applications, appropriate precursors that can easily be fluorinated and deprotected need to be developed.

**Keywords:** nucleoside analogues, late stage precursor, [<sup>18</sup>F]-incorporation, radiosynthesis.

## Introduction

PET (and PET-CT) imaging continues to develop as a powerful tool to quantitatively determine the *in vivo* locations of radiolabelled disease biomarkers and drugs, and is emerging as the technique of choice in the field of non-invasive imaging. This is particularly apparent in areas such as oncology where (repeat) patient scanning provides vital information on the diagnosis and grading of cancers, and on response to therapeutic intervention. The exquisite sensitivity of PET imaging tracers means that only picomolar tracer concentrations (non-pharmacological concentrations) are required for patient administration and signal detection, hence toxicological concerns become much less significant compared to use of therapeutic agents.<sup>[1]</sup> [<sup>18</sup>F] has become the radionuclide of choice amongst a variety of positron-emitting isotopes since [<sup>18</sup>F] provides an attractive balance between radioactive half-life (110 minutes) and percentage of β<sup>+</sup>-emission/sensitivity. The fluorinated glucose analogue [<sup>18</sup>F]FDG dominates the PET cancer imaging field due to both the selective uptake and trapping within “glucose-hungry” tumours<sup>[2]</sup> and its highly advanced radiochemical synthesis.<sup>[3]</sup> However, the full potential of this powerful scanning technique will only be fully realised when a wider range of [<sup>18</sup>F]-fluorinated probes representative of a variety of clinical biomarkers are

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introduced into routine clinical use.<sup>[3]</sup> This review article considers the specific case of 2'- and 3'-<sup>[18F]</sup> labelled nucleosides, considering their importance as imaging biomarkers alongside radiochemical challenges for future clinical production applications.

### **<sup>[18F]</sup>-Labelled Nucleosides as Proliferation Biomarkers**

As one of the fundamental cancer hallmarks<sup>[2]</sup>, PET imaging of proliferation within tumor tissue represents a major component of an integrated approach towards *in vivo* cancer detection and staging. <sup>[11C]</sup>Thymidine is an early example of a nucleoside based PET tracer for proliferation<sup>[4]</sup>, however, this <sup>[11C]</sup>-based tracer was later superseded by the chemical analogue <sup>[18F]</sup>fluorothymidine (<sup>[18F]</sup>FLT (**1**), Figure 1), which combined the advantages of a more stable biomarker *in vivo*<sup>[5]</sup>, with the presence of the preferred <sup>[18F]</sup> positron-emitting radiolabel. Uptake of <sup>[18F]</sup>FLT is regulated by the cytosolic S-phase specific thymidine kinase (TK1). However, <sup>[18F]</sup>FLT is not incorporated into DNA but acts as a chain terminator instead, which is why <sup>[18F]</sup>FLT is not a marker for DNA-synthesis.<sup>[6]</sup> A range of *in vivo* studies have demonstrated the utility of <sup>[18F]</sup>FLT as a proliferation biomarker, with properties complementary to the widely used clinical standard <sup>[18F]</sup>FDG. For example, in studies of C3H/HeJ mice bearing a radiation-induced fibrosarcoma tumour treated with 5-fluorouracil, the decrease in <sup>[18F]</sup>FLT uptake was more pronounced than that of <sup>[18F]</sup>FDG and correlated with the proliferating cell nuclear antigen (PCNA) index.<sup>[7]</sup> FDA (Food and Drug Administration) approval of <sup>[18F]</sup>FLT was granted in 2009 for imaging of proliferation and monitoring response to treatment.<sup>[6]</sup> <sup>[18F]</sup>FLT is nowadays accessible in high radiochemical yields using automated synthesisers in line with good manufacturing practice (GMP) guidelines.<sup>[8,9]</sup>

The 2'-<sup>[18F]</sup>-labelled arabino nucleoside analogue 2'-<sup>[18F]</sup>fluoro-2'-deoxy-1-β-D-arabinofuranosyl-5-methyluracil (<sup>[18F]</sup>FMAU (**3**), Figure 1) has been used to study cancer cell proliferation in humans<sup>[4]</sup> and animal models<sup>[10]</sup> in settings such as prostate and brain cancer. The thymidine analogue FMAU was initially developed as an antiviral and antineoplastic agent, but when labelled with <sup>[18F]</sup> it is selectively taken up and incorporated into DNA of proliferating cells.<sup>6</sup> DNA incorporation makes <sup>[18F]</sup>FMAU a powerful cell proliferation marker alongside the non DNA-incorporated <sup>[18F]</sup>FLT. Although <sup>[18F]</sup>FMAU can be synthesised in acceptable radiochemical yields and high radiochemical purity,<sup>[11]</sup> routine production for clinical studies is not yet established.

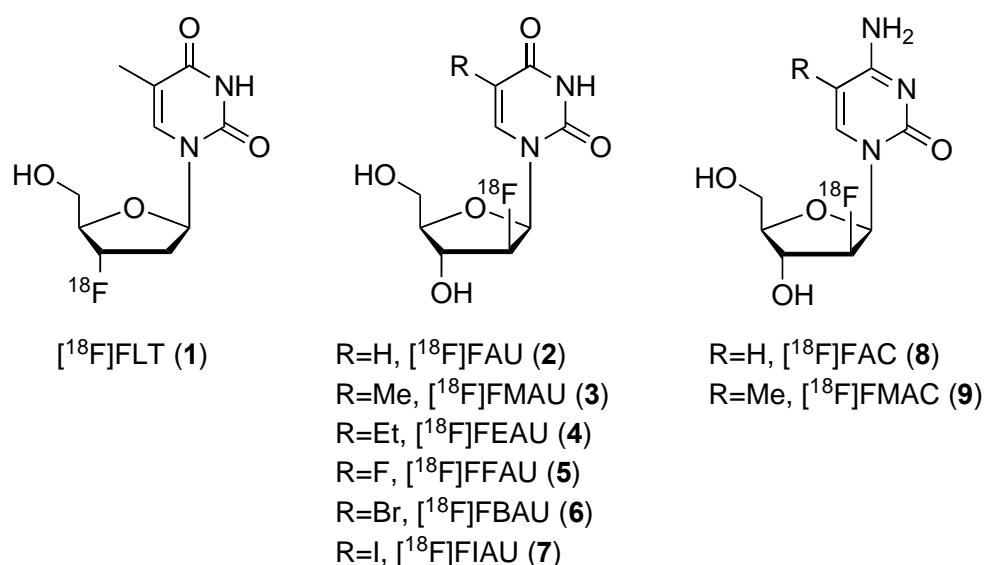
### **<sup>[18F]</sup>-Labelled Nucleosides in Prediction of Response to Nucleoside Analogue Chemotherapy**

Nucleoside analogues such as 5-fluorouracil, clofarabine and gemcitabine are used clinically in many types of cancer with variable (often low) response rates and serious dose-limiting side effects in many cases. Imaging using nucleoside PET probes is becoming established as an important tool to predict patient response and inform patient stratification, an important objective towards personalised cancer chemotherapy.<sup>[12]</sup> For example, <sup>[18F]</sup>FAU (**2**, Figure 1) can be used to identify *in vivo* expression rates of the target enzyme thymidylate synthase (TS) to potentially assess a positive outcome using TS-inhibitors such as 5-fluorouracil.<sup>[13]</sup> Gemcitabine is clinically used for treatment of pancreatic, ovarian, and lung cancers, despite being characterised by low response rates (often <20%) and frequent occurrence of grade 3 or 4 toxicity.<sup>[14]</sup> 1-(2'-deoxy-2'-<sup>[18F]</sup>fluoroarabinofuranosyl)cytosine (<sup>[18F]</sup>FAC, **8**, Figure 1) is a PET probe with a close structural relationship to gemcitabine and high affinity for deoxycytidine kinase (dCK), the rate limiting enzyme in activation of gemcitabine and related cancer drugs such as clofarabine. <sup>[18F]</sup>FAC PET has been used to identify dCK-positive and -negative tumors and predict gemcitabine response in *in vivo* models.<sup>[15]</sup> In an extension to this

work, the influence of cytidine deaminase (CDA), a determinant of gemcitabine resistance, was additionally studied using the nucleoside PET probe 1-(2'-deoxy-2'-[ $^{18}\text{F}$ ]fluoroarabinofuranosyl)-5-methylcytosine ([ $^{18}\text{F}$ ]FMAC, **9**).<sup>[16]</sup> [ $^{18}\text{F}$ ]FAC and [ $^{18}\text{F}$ ]FMAC were found to be predictive of the *in vivo* enzymatic activities of dCK and CDA further supporting the notion of using nucleoside-based [ $^{18}\text{F}$ ] PET to guide selection of nucleoside analogues for individualised cancer therapy.

### [ $^{18}\text{F}$ ]-Labelled Nucleosides in Reporter Gene Imaging – Towards Personalised Medicine

PET imaging has enormous potential for future application to personalised therapy, where binding to disease relevant drug target biomarkers provides a platform for introduction of a PET tracer for *in vivo* interrogation of reporter gene products.<sup>[17]</sup> Herpes simplex virus-1 thymidine kinase (HSV1-*tk*) represents a reporter gene product implicated in biological processes such as transcriptional regulation<sup>[18]</sup> and lymphocyte migration.<sup>[19]</sup> A number of [ $^{18}\text{F}$ ]-radiolabelled nucleosides have demonstrated promise as reporter probes for HSV1-*tk* gene expression, including [ $^{18}\text{F}$ ]FMAU<sup>[20]</sup>, and the corresponding 5-iodo- (**7**)<sup>[21]</sup> and 5-ethylpyrimidine (**4**)<sup>[22]</sup> derivatives (Figure 1).



**Figure 1.** Selected [ $^{18}\text{F}$ ]-labelled nucleosides as PET tracers.

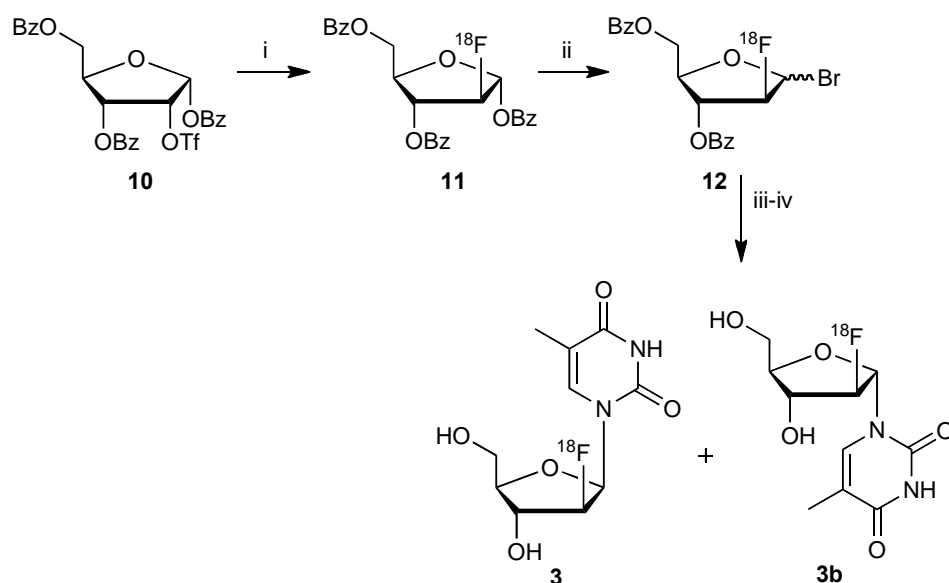
Non-invasive methods for monitoring the long term viability of transplanted stem cells *in vivo* would be of enormous benefit to therapeutic strategies involving genetically modified cells.<sup>[23]</sup> For example, the ability to measure engraftment of hematopoietic stem cell transplants non-invasively within hematopoietic tissue has been reported making use of [ $^{18}\text{F}$ ]-labelled PET nucleoside probes.<sup>[24]</sup> Studies have previously used variants of HSV1-*tk*, as described above, however HSV1-*tk* is immunogenic and therapeutic failure can result from cells expressing this enzyme being selectively cleared. The reporter gene in more recent studies is a non-immunogenic human deoxycytidine kinase containing three amino acid substitutions within the active site (hdCK3mut) in combination with [ $^{18}\text{F}$ ]FMAU, allowing *in vivo* measurements of long-term engrafted cells and maintaining hdCK3mut expression.

Altogether, 2'- and 3'-[ $^{18}\text{F}$ ]-labelled nucleoside analogues are of increasing importance in clinical PET applications and PET research.<sup>[25]</sup> The ability to introduce the weak [ $^{18}\text{F}$ ]-nucleophile into the sugar moiety, however, is the limiting factor in radiosynthetic methods. Limitations in clinical applications are therefore due to difficulties in establishing routine clinical radiosynthesis protocols. The radiosynthetic methods covered in this review focus on

the 2'- and 3'-[<sup>18</sup>F]fluorinated nucleoside analogues and are based on the current literature status which does not include unpublished in-house methods. Furthermore, the discussion will be divided into two main sections focusing on both early-stage and late-stage [<sup>18</sup>F]fluoride introduction.

### Early-stage [<sup>18</sup>F]-introduction in 2'- and 3'-[<sup>18</sup>F]-labelled nucleosides

The most common and radiochemically efficient method for the synthesis of 2'-[<sup>18</sup>F]fluorinated uridine- and cytidine-arabinonucleosides is based on an early stage radiofluorination of a protected sugar moiety in a manner similar to the radiosynthesis of [<sup>18</sup>F]FDG.<sup>[26]</sup> The radiosynthetic approach is exemplified by the formation of [<sup>18</sup>F]FMAU<sup>[27,28]</sup> (**3**, Figure 2). Moreover, a similar approach was reported for the uridine derivatives [<sup>18</sup>F]FAU (**2**), [<sup>18</sup>F]FEAU (**4**), [<sup>18</sup>F]FFAU (**5**), [<sup>18</sup>F]FBAU (**6**) and [<sup>18</sup>F]FIAU (**7**), as well as for the cytidine-based nucleosides [<sup>18</sup>F]FAC (**8**) and [<sup>18</sup>F]FMAC (**9**).<sup>[28-30]</sup>



**Reagents:** i) [<sup>18</sup>F]fluoride, K<sub>222</sub>, DMF, 150°C, 5 min; ii) HBr/AcOH, CH<sub>2</sub>Cl<sub>2</sub>, 125°C, 15 min; iii) 2,4-bis-O-(trimethylsilyl)thymine, CHCl<sub>3</sub>, 150°C, 30 min; iv) NaOMe/MeOH, MeCN, 20°C, 10 min.

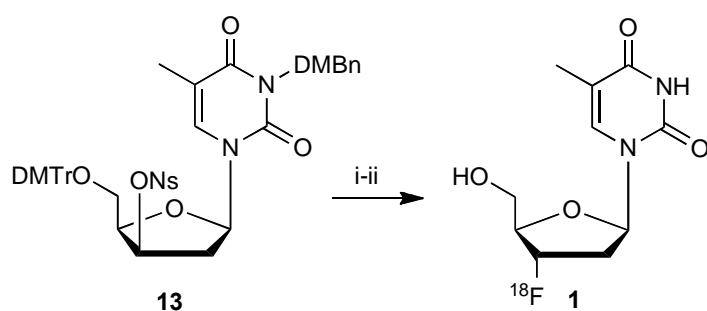
**Figure 2.** Early-step [<sup>18</sup>F] incorporation exemplified by radiosynthesis of [<sup>18</sup>F]FMAU.

Here, the protected triflate precursor **10** reacts first with an [<sup>18</sup>F]F/Kryptofix complex to perform the nucleophilic substitution reaction at high temperatures. The 2'-[<sup>18</sup>F]-labelled sugar moiety **11** contains the [<sup>18</sup>F]-substituent in the correct stereochemical orientation. Bromination and subsequent condensation of **12** with the appropriate 2,4-bis-O-(trimethylsilyl)pyrimidines followed by deprotection produced a mixture of the desired β- and α-anomers **3** and **3b** in a ratio of 3/1 to 8/1 depending on the reaction solvent, obtaining a radiochemical yield up to 45% of the correct stereoisomer.<sup>[31]</sup> Even though the nucleoside radiotracers were obtained in good radiochemical yields and high purities this synthetic approach reveals issues that inhibit these PET probes from being produced on commercially available synthesis modules for routine production and human application.<sup>[32]</sup> For instance, multiple steps after [<sup>18</sup>F]-introduction with an additional purification step due to the formation of the D- and L-isomers, as well as the use of toxic substances such as HBr, make the translation to automated synthesizers difficult. These difficulties go hand in hand with

reproducibility issues when it comes to Quality Control (QC) in clinical practice according to the British/European/American Pharmacopeia. Furthermore, as the number and space in hot cells is limited, multiple-step radiosyntheses should rather be replaced by shorter and less complex synthetic procedures.

### Late-stage [ $^{18}\text{F}$ ]-introduction in 2'- and 3'-[ $^{18}\text{F}$ ]-labelled nucleosides

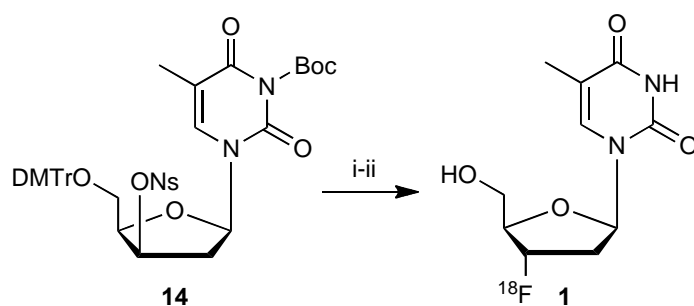
A reproducible and efficient late-stage [ $^{18}\text{F}$ ]-introduction for 2'- and 3'-labelled nucleoside analogues is potentially able to overcome these issues. However, the greatest challenge from a synthetic point of view is the rational design and synthesis of an appropriate fluorination precursor which combines an activated electrophilic position at the sugar moiety (for nucleophilic replacement by the [ $^{18}\text{F}$ ]fluoride nucleophile) with stability against decomposition and side-product formation, especially when handled at high reaction temperatures ( $>90^\circ\text{C}$ ) under basic conditions. The synthesis of [ $^{18}\text{F}$ ]FLT developed by Grierson and Shields<sup>[25]</sup> exemplifies this approach by using an N<sup>3</sup>-2,4-dimethoxybenzyl- and 5'-dimethoxytrityl-protected nosylate precursor **13** (Figure 3).



**Reagents:** i)  $\text{K}_2\text{CO}_3$ /[ $^{18}\text{F}$ ]F/ $\text{K}_{222}$ , MeCN,  $100^\circ\text{C}$ , 10 min;  
ii) CAN, EtOH/ $\text{H}_2\text{O}$ ,  $100^\circ\text{C}$ , 3min.

**Figure 3.** First reported radiochemical synthesis of [ $^{18}\text{F}$ ]FLT.

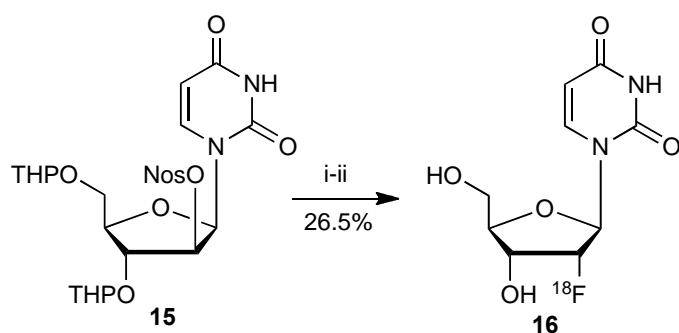
The radiochemical synthesis of [ $^{18}\text{F}$ ]FLT for clinical applications, however, is based on the approach above and makes use of the N<sup>3</sup>-Boc-group, whereas the automation was adopted from the automated [ $^{18}\text{F}$ ]FDG synthesis (Figure 4).<sup>[33,34]</sup> Hereby, the protected nosylate precursor **14** reacts with a dried [ $^{18}\text{F}$ ]/Kryptofix/ $\text{K}_2\text{CO}_3$ -mixture in anhydrous acetonitrile for 10 minutes. The subsequent deprotection step is carried out using a 1N aqueous HCl solution at  $105^\circ\text{C}$  for 5 additional minutes.



**Reagents:** i)  $\text{K}_2\text{CO}_3$ /[ $^{18}\text{F}$ ]F/ $\text{K}_{222}$ , MeCN,  $130^\circ\text{C}$ , 4 min, then cooling to  $85^\circ\text{C}$ ;  
ii) 1N HCl,  $105^\circ\text{C}$ , 5min., then 2N NaOH.

**Figure 4.** A currently used example of automated [ $^{18}\text{F}$ ]FLT synthesis.

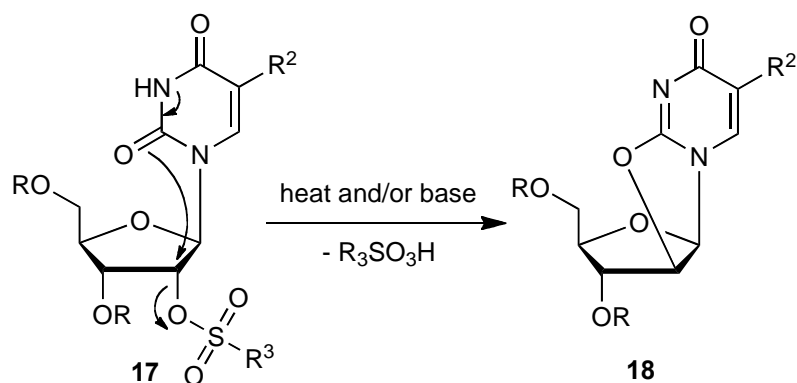
The use of the Boc-protection group simplifies the deprotection step in two ways, as both protection groups can now be removed simultaneously using acidic conditions and ceric ammonium nitrate (CAN) as an additional deprotection agent is avoided. It is worth noting that N<sup>3</sup>-Boc-protected precursors do not lead to a higher radiochemical yield than their N<sup>3</sup>-unprotected analogues. The protection of N<sup>3</sup> with an electron-withdrawing group was originally developed for preventing 2,3'-anhydro side-product formation, however, due to the unfavoured orientation of the nosyl substituent this effect seems to be unlikely. In addition the late-stage radiosynthesis of 2'-deoxy-2'-[<sup>18</sup>F]fluorouridine (2'-[<sup>18</sup>F]FU, **16**) was carried out successfully without any functionalisation at N<sup>3</sup> (Figure 5).<sup>[34]</sup> Apart from that, the formation of the 2',3'-olefinic elimination side product does in fact appear to be the main product (90%) of the labelling reaction towards [<sup>18</sup>F]FLT. Hence, a preparative HPLC purification has to be performed due to side-product formation before dispensing of the sterile product solution containing [<sup>18</sup>F]FLT.<sup>[35]</sup>



**Reagents:** i) K<sub>2</sub>CO<sub>3</sub>/[<sup>18</sup>F]F/K<sub>222</sub>, MeCN, 145°C, 15 min;  
ii) 1N HCl, 85°C, 10 min.

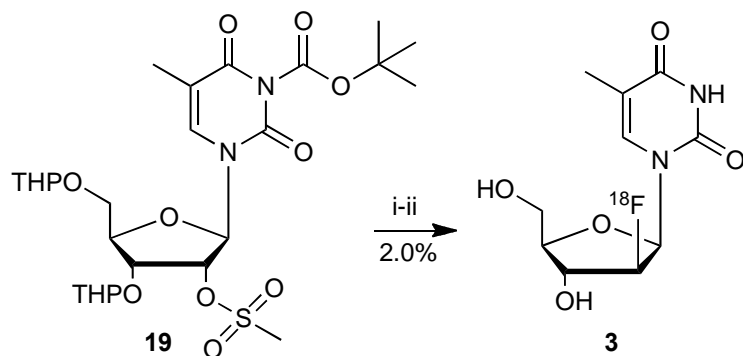
**Figure 5.** Radiosynthesis of 2'-[<sup>18</sup>F]FU without N<sup>3</sup>-protection.

At the present time the proliferation marker [<sup>18</sup>F]FLT remains the only 2'- or 3'-[<sup>18</sup>F]-labelled nucleoside which is routinely used in human clinical applications. Its synthetic accessibility is much easier to realize than for 2'-[<sup>18</sup>F]fluoro (arabino-) nucleosides. FLT only has one free 5'-hydroxy group and has a relatively stable precursor, since the leaving group is in the up position and a 6-membered ring is less likely to be formed than a 5-membered ring at the 2'-position. 2'-[<sup>18</sup>F]-labelled arabino nucleosides analogues are, however, of great interest in both clinical oncology and preclinical research mainly due to their variable applicability as described above. For instance, 2'-[<sup>18</sup>F]-labelled arabino-nucleosides have been used as reporter gene probes for targets such as HSV1-*tk* and are strong candidates for imaging other important targets within the nucleoside salvage pathway. However, introducing the [<sup>18</sup>F]fluoride substituent into the 2'-arabino position was considered to be difficult.<sup>[36]</sup> The main reason for the difficulty is the high potential of 2'-activated labelling precursors to form the anhydro side product due to the nucleophilicity of the C-2 carbonyl group of the pyrimidinone moiety (Figure 6).



**Figure 6.** Heat/base-triggered formation of the 2'-anhydro by-product **18**.

However, N<sup>3</sup>-protection with an electron-withdrawing group such as Boc could successfully prevent 2'-activated precursor molecules from forming the 2'-anhydro compounds as was recently shown by Alauddin *et al.* with an improved radiochemical synthesis of [<sup>18</sup>F]FMAU (**3**) (Figure 7).<sup>[36]</sup>



**Reagents:** i)  $K_2CO_3/[^{18}F]F/K_{222}$ , MeCN, 80°C, 20 min;  
ii) 1N HCl/MeOH, 80°C, 10 min.

**Figure 7.** Late-stage radiofluorination of precursor **19** in the synthesis of [<sup>18</sup>F]FMAU (**3**).

Further investigations<sup>[32]</sup> regarding the effect of a 2'-nosyl leaving group combined with different hydroxyl-protecting groups did not show any improvement in the radiochemical yield of [<sup>18</sup>F]FMAU, which is interesting since improved leaving group abilities would suggest a higher labelling yield. On the other hand this shows the importance of a good balance between reactivity and stability, which is needed in order to provide a high radiochemical yield while minimizing side product formation.

## Conclusion

Overall, this review demonstrates that there is a need for more efficient and less complex radiochemical syntheses using late-stage stereospecific [<sup>18</sup>F]-introduction into an intact nucleoside in order to make these syntheses suitable for automated synthesisers. Even though first attempts using stereospecific radiofluorination of intact pyrimidine nucleoside precursors have been reported, successful further investigations towards improved radiochemical yields, higher reproducibility and especially cytidine-based nucleosides such as [<sup>18</sup>F]FAC need to be accomplished. Here, the rational design and synthesis of appropriate fluorination precursors showing an improved reactivity-to-stability profile will be crucial. Moreover, as PET imaging



will consistently grow within clinical and preclinical applications in the near future, the need for highly specific radiotracers has to be addressed by developing new and efficient radiosynthetic routes. Future studies into appropriate protected nucleosides precursors that allow efficient late-stage introduction of [<sup>18</sup>F]-fluoride into the 2'- or 3'-position are certainly warranted. These developments will help to address future clinical PET imaging challenges within this field.

## Acknowledgement

We thank Cancer Research Wales for the award of a PhD studentship to Jan-Philip Meyer.

## References

- [1] M. E. Phelps, *Proc. Natl. Acad. Sci. USA* **2000**, *97*, 9226-9233.
- [2] D. Hanahan, R. A. Weinberg, *Cell* **2011**, *144*, 646-674.
- [3] S. Yu, *Biomed. Imaging Interv. J.* **2006**, *2*, e57.
- [4] J. L. Eiseman, C. Brown-Proctor, P. E. Kinahan, J. M. Collins, W. Anderson, E. Joseph, D. R. Hamburger, S. Pan, C. A. Mathis, M. J. Egorin, R. W. Klecker, *Clin. Cancer Res.* **2004**, *10*, 6669-6676.
- [5] M. Wagner, U. Seitz, A. Buck, B. Neumaier, S. Schultheiß, M. Bangerter, M. Bommer, F. Laithäuser, E. Wawra, G. Munzert, S. N. Reske, *Cancer Res.* **2003**, *63*, 2681-2687.
- [6] A. F. Shields, *J. Nucl. Med.* **2003**, *44*, 1432-1434.
- [7] K. Luthra, F. Brady, P. M. Price, E. O. Aboagye, *Cancer Res.* **2003**, *63*, 3791-3798.
- [8] J. M. Collins, R. W. Klecker, A. G. Katki, *Clin. Cancer Res.* **1999**, *5*, 1976-1981.
- [9] G. J. Kelloff, K. A. Krohn, S. M. Larson, R. Weissleder, D. A. Mankoff, J. M., Hoffman, J. M. Link, K. Z. Guyton, W. C. Eckelman, H. I. Scher, O. Shaughnessy, B. D. Cheson, C. C. Sigman, J. L. Tatum, G. Q. Mills, D. C. Sullivan, J. Woodcock, *Clin. Cancer Res.* **2005**, *11*, 7967-7985.
- [10] H. Jadvar, L. P. Yap, R. Park, Z. Li, K. Chen, L. Hughes, A. Kouhi, P. Conti, *Mol. Imaging* **2012**, *11*, 426-432.
- [11] S. J. Martin, J. A. Eisenbarth, U. Wagner-Uterman, W. Mier, M. Henze, H. Pritzkow, U. Haberkorn, M. Eisenhut, *Nucl. Med. Biol.* **2002**, *29*, 263-273.
- [12] O. S. Tehrani, O. Muzik, L. K. Heilbrun, K. A. Douglas, J. M. Lawhorn-Crews, H. Sun, T. J. Mangner, A. F. Shields, *J. Nucl. Med.* **2007**, *48*, 1436-1441.
- [13] N. Graf, K. Herrman, B. Numberger, D. Zwisler, M. Aichelr, A. Feuchtinger, T. Schuster, H. J. Wester, R. Senekowitsch-Schidtko, C. Prescheld, M. Schwaiger, U. Keller, T. Dechow, A. K. Buck, *Eur. J. Nucl. Med. Mol. Imaging* **2013**, *40*, 34-43.
- [14] V. Heinemann, D. Quietzsch, F. Gieseler, M. Gonnermann, H. Schönekas, A. Rost, H. Neuhaus, C. Haag, M. Clemens, B. Heinrich, U. Vehling-Kaiser, M. Fuchs, D. Fleckenstein, W. Gesierich, D. Uthgenannt, H. Einsele, A. Holstege, A. Hinke, A. Schalhorn, R. Wilkowski, *J. Clin. Oncol.* **2006**, *24*, 3946-3952.
- [15] R. E. Laing, M. A. Walter, D. O. Campbell, H. R. Herschman, N. Satyamurthy, M. E. Phelps, J. Czernin, O. N. Witte, C. G. Radu, *Proc. Natl. Acad. Sci. USA* **2009**, *106*, 2847-2852.
- [16] J. T. Lee, D. O. Campbell, N. Satyamurthy, J. Czernin, C. G. Radu, *J. Nucl. Med.* **2012**, *53*, 275-280.
- [17] H. Sun, T. J. Mangner, J. M. Collins, O. Muzik, K. Douglas, A. F. Shields, *J. Nucl. Med.* **2005**, *46*, 292-296.
- [18] M. Doubrovin, V. Ponomarev, T. Beresten, J. Balatoni, W. Bornmann, R. Finn, J. Humm, S. Larson, M. Sadelain, R. Blasberg, J. G. Tjuvajev, *Proc. Natl. Acad. Sci. USA* **2001**, *98*, 9300-9305.

- [19] G. Koehne, M. Doubrovin, E. Doubrovina, P. Zanzonico, H. F. Gallardo, A. Ivanova, J. Balatoni, J. Teruya-Feldstein, G. Heller, C. May, V. Ponomarev, S. Ruan, R. Finn, R. G. Blasberg, W. Bornmann, I. Riviere, M. Sadelain, R. J. O'Reilly, S. M. Larson, J. G. Tjuvajev, *Nat. Biotech.* **2003**, *21*, 405-413.
- [20] Z. Li, H. Cai, P. S. Conti, *Nucl. Med. Biol.* **2011**, *38*, 201-206.
- [21] P. C. Chan, C. Y. Wu, W. Y. Chang, W. T. Chang, M. M. Alauddin, R. S. Liu, W. J. Lin, F. D. Chen, C. L. Chen, H. E. Wang, *Nucl. Med. Biol.* **2011**, *38*, 987-995.
- [22] A. R. Buursma, V. Rutgers, G. A. Hospers, N. H. Mulder, W. Vaalburg, E. F. de Vries, *Nucl. Med. Comm.* **2006**, *27*, 25-30.
- [23] J. Sng, T. Lufkin, *Stem Cells Int.* **2012**, 521343.
- [24] M. N. McCracken, E. H. Gschweng, E. Niar-Gill, J. McLaughlin, A. R. Cooper, M. Riedinger, D. Cheng, C. Nosala, D. B. Kohn, O. N. Witte, *Proc. Natl. Acad. Sci. USA* **2013**, *110*, 1857-1862.
- [25] J. R. Grierson, A. F. Shields, *Nucl. Med. Biol.* **2000**, *27*, 143-156.
- [26] H. Sun, J. M. Collins, T. J. Mangner, O. Muzik, A. F. Shields, *Cancer Chemother. Pharmacol.* **2006**, *57*, 343-348.
- [27] T. J. Mangner, R. W. Klecker, L. Anderson, A. F. Shields, *Nucl. Med. Biol.* **2003**, *30*, 215-224.
- [28] M. M. Alauddin, P. S. Conti, J. D. Fissekis, *J. Label. Compd. Radiopharm.* **2003**, *46*, 285-289.
- [29] M. M. Alauddin, A. Shahinian, R. Park, M. Tohme, J. D. Fissekis, P. S. Conti, *J. Nucl. Med.* **2004**, *45*, 2063-2069.
- [30] C. Wu, P. Chan, W. Chang, R. Liu, M. M. Alauddin, H. Wang, *Appl. Radiat. Isotopes* **2009**, *67*, 1362-1365.
- [31] M. M. Alauddin, J. G. Gelovani, *Curr. Med. Chem.* **2010**, *17*, 101-1029.
- [32] N. Turkman, V. Paolillo, J. G. Gelovani, M. M. Alauddin, *Tetrahedron* **2012**, *68*, 10326-10332.
- [33] C. Wodarsky, J. Eisenbarth, K. Weber, M. Heinze, U. Haberkorn, M. Eisenhut, *J. Label. Compd. Radiopharm.* **2000**, *43*, 1211-1218.
- [34] S. H. Kang, S. J. Oh, M. K. Yoon, J. S. Ryu, W. K. Lee, S. J. Choi, K. P. Park, D. H. Moon, *J. Label. Compd. Radiopharm.* **2006**, *49*, 1237-1246.
- [35] M. Yuna, S. J. Oha, H.-J. Hab, J. S. Ryua, D. H. Moon, *Nucl. Med. Biol.* **2003**, *30*, 151-157.
- [36] N. Turkman, J. G. Gelovani, M. M. Alauddin, *J. Label. Compd. Radiopharm.* **2010**, *52*, 782-786.