Received: 14 July 2017 | Revised: 5 September 2017 | Accepted: 26 September 2017

DOI: 10.1002/jlcr.3569

RESEARCH ARTICLE

WILEY Journal of Labelled Compounds and Radiopharmaceuticals

Highly efficient solid phase supported radiosynthesis of [^{11}C]PiB using tC18 cartridge as a "3-in-1" production entity

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Pittsburgh compound B ([^{11}C]PiB) is the gold standard positron emission tomography (PET) tracer for the *in vivo* imaging of amyloid plaques. Currently, it is synthesized by either solution chemistry or using a "dry loop" approach followed by HPLC purification within 30 minutes starting from [^{11}C]CO_2. Here, we report a novel, highly efficient solid phase supported carbon-11 radiolabeling procedure using commercially available disposable tC18 cartridge as a "3-in-1" entity: reactor, purifier, and solvent replacement system. [^{11}C]PiB is synthesized by passing gaseous [^{11}C]CH_3OTf through a tC18 cartridge preloaded with a solution of precursor. Successive elution with aqueous ethanol solutions allows for nearly quantitative separation of the reaction mixture to provide chemically and radiochemically pure PET tracer. [^{11}C]PiB suitable for human injection is produced within 10 minutes starting from [^{11}C]CH_3OTf (20 min from [^{11}C]CO_2) in 22% isolated yield not corrected for decay and molar activity of 190 GBq/μmol using 0.2 mg of precursor. This technique reduces the amount of precursor and other supplies, avoids use of preparative HPLC and toxic solvents, and decreases the time between consecutive production batches. Solid phase supported technique can facilitate [^{11}C]PiB production compliant with Good Manufacturing Practice (GMP) and improve synthesis reliability.

KEYWORDS

[^{11}C]PiB, amyloid imaging, automation, carbon-11, carbon-11 methylation, labeling methods, positron emission tomography, solid phase extraction cartridge, solid phase supported synthesis

1 | INTRODUCTION

Amyloid beta protein (Aβ) accumulates in the brains of patients with Alzheimer's disease (AD),[1] and the resulting Aβ plaques are currently one of the main targets for AD diagnostic and preventive therapies.[2-4] The radiochemical synthesis of carbon-11 labeled thioflavin-T derivatives[5] resulted in development of PET radiotracer Pittsburgh compound B ([^{11}C]PiB) for Aβ imaging[6] in 2003. The results of the first trials in humans were published shortly after and revolutionized the field of AD diagnostics.[7] For the first time, the Aβ plaques were visualized in the brains of living AD patients, and the correlation between amyloid deposition and radioactivity accumulation patterns was later validated by the autopsy in postmortem studies of typical AD brains.[8,9] By highlighting Aβ deposition, [^{11}C]PiB provides earlier and more specific diagnosis in different stages of AD as well as distinguishes AD from other types of non-Aβ forms of dementia such as the frontotemporal lobar degeneration.[10] Amyloid PET for clinical diagnostics has recently been approved by FDA in the United States to rule out AD based on the absence of Aβ in the brain, and other countries are expected to follow shortly. Despite recent emergence of various fluorine-18 labeled amyloid tracers, such as florbetapir,[11] florbetaben,[12] flutemetamol,[13] and NAV4694,[14] [^{11}C]PiB remains the most studied tracer for Aβ PET imaging due to high affinity for Aβ plaques (K_d = 1.4nM),[6] fast uptake and low non specific binding.

The original radiosynthetic procedure of [^{11}C]PiB ([^{11}C]6-OH-BTA-1) involved *N*-methylation of the *O*-methoxymethyl (MOM) protected compound 6-OMOM-BTA-0 using ^{11}C-methyl iodide ([^{11}C]CH_3I) followed by the deprotection of the MOM group with hydrochloric acid (Figure 1A).[6] Subsequently, a one-step synthesis from the unprotected compound 6-OH-BTA-0 (0.4 mg) was developed by Wilson[15] using ^{11}C-methyl triflate ([^{11}C]CH_3OTf) either in methylethylketone solution or by elegant captive solvent "loop" method.[16,17] Consequent purification by means of high performance liquid chromatography (HPLC), reformulation, and sterile filtration affords [^{11}C]PiB for clinical imaging within 30 minutes after end of bombardment. Currently, most PET centers use between 0.8 and 1 mg of precursor methods using "loop", solution, or on-column[18] approach followed by semipreparative HPLC purification and reformulation.

A recent trend in PET radiochemistry is the development of cassette-based kits that allow for production of various fluorine-18 labeled tracers with reduced technical effort from the laboratory personnel and minimal maintenance of the equipment between syntheses. The first kit-based synthesis was introduced for the radiolabeling of the most widely used PET tracer [^{18}F]FDG; lately, similar kits have been developed for other tracers including [^{18}F]MISO and [^{18}F]FMC. These kits are commercially available from ABX advanced biochemical compounds,[19] Huayi Isotopes,[20] and other vendors for most of the existing automated modules. Outside of the physical half-life limitations ($T_{1/2}$ = 20.3 min), one of the major reasons carbon-11 remains a less popular isotope for PET radiochemistry than fluorine-18 is a lack of similar GMP-grade production kits that would allow for fast and reliable radiolabeling. Subsequently, while many ^{18}F-tracers have found application in clinical trials and have been successfully commercialized, ^{11}C-tracers are mostly used in highly specialized research PET centers worldwide. Development of similar kits for ^{11}C-labeled tracers would significantly simplify their production and eliminate the need for cleaning and drying of the module between consecutive batches. Finally, fully disposable kits would prolong the intervals between preventive maintenance of the production modules, improve synthesis reliability, and allow avoiding sterilization of the reusable equipment.

Of special interest for the kit development are the reactions that can proceed at room temperature on a disposable cartridge, for example, [^{18}F]fluoromethylation of dimethylaminoethanol in production of [^{18}F]fluoromethylcholine or hydrolysis of [^{18}F]fluorodeoxyglucose tetraacetate in the [^{18}F]FDG synthesis. Although sorbent-supported radiolabeling of several ^{11}C-tracers have been reported, including pioneering work by the University of Michigan PET center,[21,22] most of the radiosyntheses rely on time- and labor-consuming HPLC purification and reformulation of the tracers. As part of our latest endeavors in simplifying the labeling with carbon-11[23] and fluorine-18 PET isotopes,[24] we wish to report a new highly efficient solid phase supported radiosynthesis of [^{11}C]PiB by [^{11}C]methylation of the 6-OH-BTA-0 on a disposable cartridge used as "3-in-1" entity for reaction, purification, and formulation. Briefly, gaseous [^{11}C]CH_3OTf is passed through a disposable cartridge preloaded with 6-OH-BTA-0 precursor and nearly quantitative separation of synthesized [^{11}C]PiB from starting material and radioactive impurities is achieved using a biocompatible aqueous ethanol as an eluent. Based on this very reliable technique, we developed a method for [^{11}C]PiB production using automated module and disposable cassette kits. The resulting tracer meets all specifications to be compliant with requirements of multicenter Dominantly Inherited Alzheimer Network Trials Unit (DIAN-TU)[25] clinical trials: radiochemical and radionuclidic identity; radiochemical purity (RCP >95%); chemical purity—amount of residual precursor or other UV impurities <1.3 μg; pH 4-8; ethanol content <10%, sterile and endotoxin free.

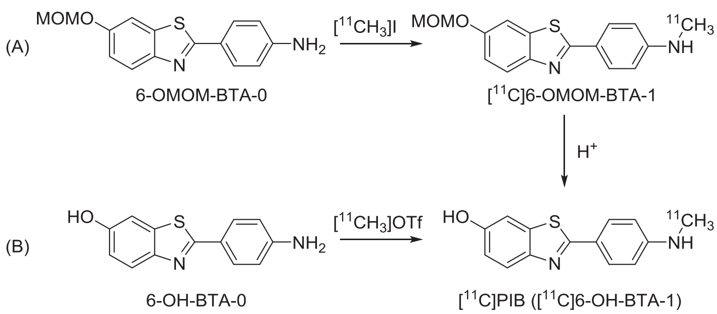


FIGURE 1 A, The original radiosynthetic procedure of [^{11}C]PiB ([^{11}C]6-OH-BTA-1) involved *N*-methylation of the 6-OMOM-BTA-0 using [^{11}C]CH_3I and B, the one-step radiosynthesis of [^{11}C]PiB from the unprotected 6-OH-BTA-0 using [^{11}C] CH_3OTf

2 | EXPERIMENTAL

2.1 | Materials and general procedures

All radiochemistry procedures were performed at the PET radiochemistry facility of the Montreal Neurological Institute (MNI) as described before.[26] Briefly, the isotope was obtained in the form of [^{11}C]CO_2 via $^{14}N(p,\alpha)^{11}C$ nuclear reaction by irradiation of N_2/O_2 (99.5:0.5) with 18 MeV protons in the gas target of the cyclotron (Cyclone 18/9 IBA, Louvain-La-Neuve, Belgium). The resulting [^{11}C]CO_2 was converted to [^{11}C]CH_3OTf using a commercially available Synthra module. The [^{11}C]CH_3OTf output line was directly attached to the manifold secured on the Scintomics GRP automated module for ^{11}C-methylation.

Compounds 6-OH-BTA-0 (precursor) and 6-OH-BTA-1 (cold standard) were purchased from ABX advanced biochemical compounds (Cat No 5101 and 5140, respectively). Disposable cartridges Oasis HLB (Cat No. 186000132), Sep-Pak tC18 Plus (Cat No. WAT036810), and Sep-Pak C18 Plus (Cat No. WAT020515) were provided by Waters. Disposable polycarbonate and solvent-resistant manifolds were purchased from Scintomics (Cat. No. ACC-101 and ACC-201, respectively). HPLC solvents were purchased from Fisher and inorganic salts for buffer preparation from Sigma-Aldrich. Buffer solutions were prepared according to Sigma-Aldrich buffer reference center[27] and their pH verified with pH strips. Quality control procedures were performed according to the validated standard operating procedures used at the PET radiochemistry facility of the MNI for routine production of radiotracers intended for use in humans. Specifically, Agilent 1200 HPLC instrument equipped with a reversed phase column (MZ Analytical PerfectSil 120 C8 5 μm, 100 × 4.0 mm; 40/60 acetonitrile/water at 0.7 mL/min), UV (350 nm), and radioactivity detector (Raytest Gaby) was used to confirm radiochemical identity and purity as well as chemical purity and molar activity. Perkin Elmer Clarus 480 gas chromatograph equipped with Restek MTX-Wax column (30 m, 0.53 mm) was used for detection and quantification of the residual solvents.

2.2 | Separation of 6-OH-BTA-0 and 6-OH-BTA-1

Our first goal was to find the optimal conditions regarding solid phase extraction sorbent, pH of the aqueous solution, and ethanol content for efficient separation of nonradioactive 6-OH-BTA-0 and 6-OH-BTA-1 on a commercially available disposable cartridge. In a typical experiment, premixed aqueous ethanol (ca. 10%) solution containing both compounds was passed through the preconditioned cartridge followed by sequential elution with aqueous solutions of increasing ethanol concentration and all eluate fractions were analyzed by HPLC.

Among the three tested cartridges commercially available by Waters, trifunctional tC18 sorbent provided the best results for separation of 6-OH-BTA-0 and 6-OH-BTA-1 in cold simulation experiment and were later translated to radiolabeling procedure. Other cartridges (Oasis HLB and Sep-Pak C18) performed poorly and were not tested in radiolabeling experiments (data not shown). Excellent separation of the compounds in both "cold" simulations and later in radiosynthesis of [^{11}C]PiB was achieved using 0.2M acetate buffer at pH 3.7, prepared by mixing 0.2M sodium acetate solution (50 mL) with 0.2M acetic acid (450 mL). We rationalized that these aromatic amines have sharper elution profiles and therefore better separation in moderately acidic conditions where they exist predominantly in protonated forms. Thus, a 20% aqueous ethanol solution in 0.2M acetic buffer at pH 3.7 (80 mL) allowed for almost quantitative washout of the 6-OH-BTA-0 from tC18 cartridge, while the 6-OH-BTA-1 remained trapped. The latter was eluted by increasing the concentration of ethanol to 40% in 20-mL total volume. These conditions were later slightly modified for production of radiochemically and chemically pure [^{11}C]PiB as described below.

2.3 | General radiolabeling procedure

In a typical radiolabeling experiment, preconditioned (10-mL water followed by 5-mL acetone) and dried by the stream of nitrogen (50 mL/min, 1 min) tC18 cartridge was slowly loaded with a 2-mg/mL solution of 6-OH-BTA-0 in acetone (50, 100, or 150 μL). ^{11}C-methylation was performed by passing gaseous [^{11}C]CH_3OTf directly through the loaded cartridge secured on a manifold (Figure 2A). Once all the [^{11}C]CH_3OTf was trapped on the cartridge as monitored by the radioactivity detector mounted behind the cartridge holder, it was allowed to react with the precursor for 2 to 3 minutes at room temperature and then successively eluted with aqueous (pH 3.7) ethanol solutions of increasing concentrations: first, 12.5% EtOH (92 mL), then 15% EtOH (55 mL) into the waste bottle (Figure 2B and 2C), and finally with 50% EtOH (2.5 mL) followed by sterile phosphate buffer (10 mL) into the final vial (Figure 2D).

3 | RESULTS AND DISCUSSION

The solid-state radiochemical ^{11}C-alkylations in general require lower precursor amount than the comparable reactions in solution as previously reported by Wilson[15-17]

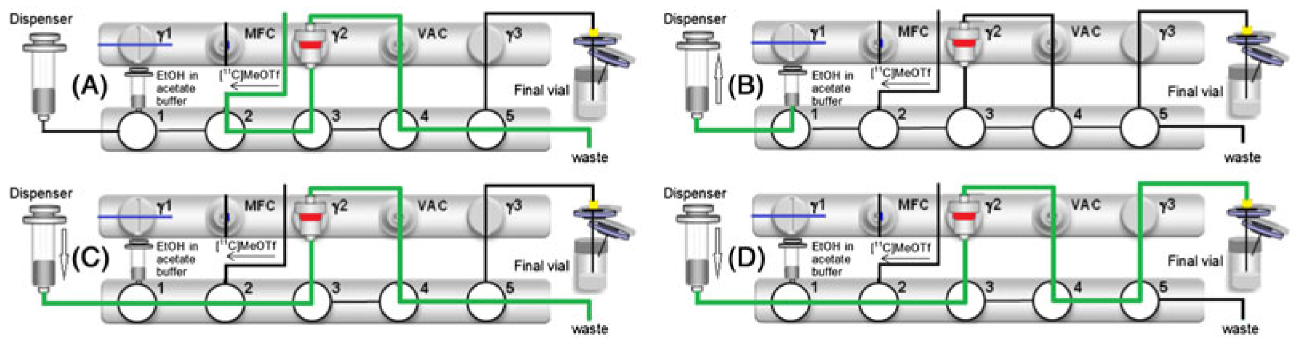


FIGURE 2 Step-by-step synthesis and purification of [^{11}C]PiB on tC18 cartridge: A, gaseous [^{11}C]CH_3OTf is passed through the cartridge loaded with 6-OH-BTA-0; B, aqueous ethanol (18.5 mL) is withdrawn into the 20-mL dispenser syringe (100 mL/min); C, the impurities are washed out into a waste bottle (50 mL/min); D, [^{11}C]PiB is eluted into the final vial through a sterile filter

and more recently, Scott.[28] Our first goal was to investigate if even lower amounts of precursor (0.1, 0.2, and 0.3 mg) would provide high radiochemical yield of the product using on-cartridge technique. The results of the radiochemical yield optimization experiments are summarized in Table 1.

To our delight, as little as 0.2 mg of precursor per synthesis provides excellent radiochemical yields of [^{11}C]PiB in SP-supported procedure (Table 1, entry 2). Notably, reducing the amount even further to 0.1 mg (entry 1) still provides a reasonable quantity of the tracer, although the final amount of [^{11}C]PiB is lower and the yield is less reliable. Increasing the amount to 0.3 mg (entry 3) further improves the yield, while still providing a reasonable chemical purity of the final product despite a higher amount of the precursor in the final product. However, we observed that the acetone used to solubilize the precursor can affect the stability of the polycarbonate manifolds used in the synthesis, which are particularly vulnerable to this solvent. Thus, in 2 experiments using 150 μL of the precursor solution (0.3 mg), the manifold was destroyed, prompting us to manually intervene in the synthesis to recover the labeled product. This problem can be alleviated by using higher quality solvent-resistant manifolds (see Supporting Information). An optimal amount of precursor will depend on particular needs of the PET center in terms of yield of radiotracer and other considerations. Our attempt to repeat the tC18-suported synthesis using ethanol (Table 1, entry 4) only yielded 3% [^{11}C]PiB (from [^{11}C]CH_3OTf) with less than 70% RCP, deeming this solvent unsuitable for the proposed alkylation technique. Further investigation of ethanol compatibility with solid phase supported ^{11}C-methylation might be required.

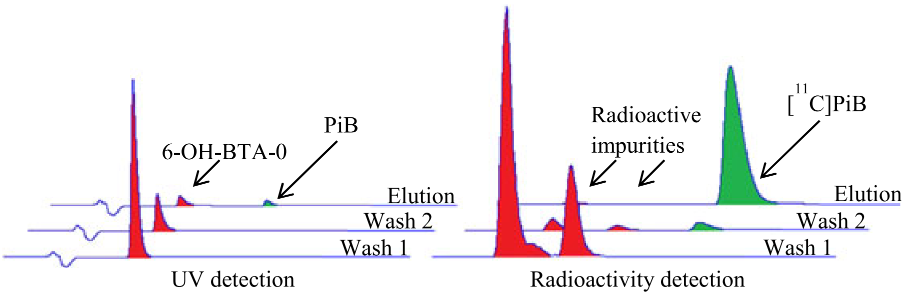
The most challenging part of the described technique was to find conditions for quantitative separation of the reaction mixture on a relatively short solid phase extraction cartridge. After thorough optimization of the ethanol content and volumes of washing solutions, we found the optimal conditions. First, 12.5% EtOH (92 mL) is used to elute the radioactive impurities and majority of the 6-OH-BTA-0, then 15% EtOH (55 mL) washes out the residual precursor and a negligible amount of the product (~5%). Finally, the elution of desired [^{11}C]PiB, pure both radiochemically (>95% RCP) and chemically (<1.3 μg of 6-OH-BTA-0), is achieved at the 50% ethanol concentration. Results of purification optimization can be found in Supporting Information. Typical chromatograms and radioactivity distribution between fractions are represented in Figure 3.

After the procedure optimizations described above, [^{11}C]PiB is synthesized and prepared for direct injection from a starting activity of [^{11}C]CO_2 ranging from 13 to 37.5 GBq as follows. [^{11}C]CH_3OTf is passed through the preconditioned, dried, and loaded with 0.2 mg of 6-OH-BTA-0 tC18 Plus cartridge, allowed to react with precursor for 2 to 3 minutes, and the reaction mixture is efficiently separated using successive elution with

TABLE 1 Optimization of precursor amount, ^{11}C-methylating agent, and solvent

Entry	Precursor amount, mg	[^{11}C]CH_3X	n	Solvent	RCY[a]
1	0.1	[^{11}C]CH_3OTf	3	Acetone	18.1 ± 3.8%
2	0.2	[^{11}C]CH_3OTf	11	Acetone	22.0 ± 3.1%
3	0.3	[^{11}C]CH_3OTf	3	Acetone	32.1 ± 3.7%
4	0.2	[^{11}C]CH_3OTf	1	Ethanol	<3%

[a]Not corrected for decay yield starting from [^{11}C]CH_3OTf.



Solution	V, mL	$[^{11}C]CH_3X$*		[11C]PiB		6-OH-BTA-0	
		%**	MBq***	%**	MBq***	%****	μg
Wash 1	92.0	62.3	4070	<0.01	<4	~90	~180*****
Wash 2	55.0	0.2	15	2.4	163	~10	~20*****
Elution	12.5	0.3	18	34.8	2276	0.3	0.58

*$[^{11}C]CH_3I$, $[^{11}C]CH_3OTf$ and $[^{11}C]CH_3OH$; **Quantity expressed as a percentage of the total activity corrected for decay; ***Decay-corrected values; ****Percentage of the total mass of 6-OH-BTA-0 eluted from the cartridge; *****Absolute values outside of the calibration curve.

FIGURE 3 Elution profile with aqueous (pH 3.7) ethanol solution of increasing concentrations. Wash 1 (92 mL of 12.5% EtOH), wash 2 (55 mL of 15% EtOH), and elution (2.5 mL of 50% EtOH) were sequentially passed through the cartridge to elute the radioactive impurities, the residual 6-OH-BTA-0, and finally the [11C]PiB, respectively

aqueous ethanol solutions of increasing concentrations. From the end of bombardment to the end of the synthesis, the whole procedure is completed within 20 minutes. The final tracer synthesized under optimized conditions meets all the criteria specified in the certificate of analysis for use in humans under DIAN-TU clinical trial protocol. Radiochemical purity is consistently above 95%, the 6-OH-BTA-0 content is below 1.3 μg per 10 mL dose, and the ethanol content is below 10%. [11C]PiB is stable within 1 hour in the final solution, sterile and free from pyrogens and bacterial endotoxins. The results of full batch successful validation runs from $[^{11}C]CH_3OTf$ generated by dry chemistry method are summarized in Table 2.

In an attempt to develop a fully disposable all-in-one kit for production of [11C]PiB from $[^{11}C]CO_2$ released from the cyclotron target, we combined this technique with our previously reported "[11C]kits" for cassette-based conversion of $[^{11}C]CO_2$ into $[^{11}C]CH_3I/[^{11}C]CH_3OTf$ using wet method. Despite a higher radiochemical yield, relatively low molar activity leads to formation of the unidentified radiochemical impurity co-eluting with

TABLE 2 Summary of the [11C]PiB production validation batches under optimized conditions

Batch	PiB161025	PiB161027	PiB161110	PiB161118
[11C]MeOTf, GBq	9.21	11.25	7.84	6.44
[11C]PiB radioactivity, GBq	2.26	2.37	2.11	1.41
RCY, %[a]	24.5	21.1	26.9	21.8
RCP, %	98.0	97.2	97.8	99.2
Molar activity, GBq/μmol	154.6	322.6	121.1	162.1
Residual precursor, μg	0.32	0.55	0.58	0.87
pH	5	5	5	5
EtOH content, %	9.4	8.8	7.7	8.1
Acetone content, ppm	33	38	46	33
BET test	N/A	<10 EU/mL	<10 EU/mL	<10 EU/mL
Sterility test	N/A	No growth	No growth	No growth

[a]From [11C]MeOTf, not corrected for decay.

[^{11}C]PiB, which we attributed to a double methylation product. Although selective elution of radiochemically pure [^{11}C]PiB was achieved (27 mL of 30% aqueous ethanol), low molar activity and high ethanol content would make tracer batches produced by all-in-one kits unsuitable for clinical applications. We are currently working on improving the molar activity of [^{11}C]CH_3OTf produced with "[^{11}C]kits" by wet method.

4 | CONCLUSION

We have developed a solid phase supported technique to produce a clinically relevant [^{11}C]PiB tracer from [^{11}C]CH_3OTf in an automated mode and avoiding HPLC purification. Our method takes advantage of the disposable tC18 cartridges as "3-in-1" entity for production, purification, and formulation of this tracer. In our work, we optimized the RCY regarding precursor amount and reaction solvent; and purification regarding cartridge type, pH of the buffer, ethanol content, and volume of the eluent. This synthesis from [^{11}C]CH_3OTf is completed within 10 minutes and affords [^{11}C]PiB in high yield and molar activity as well as excellent radiochemical and chemical purity as an injectable solution for clinical or preclinical imaging. The described methodology allows for reduction of chemicals (including precursor and HPLC solvents) used in the synthesis, shortens the synthesis time, and reduces the technical involvement of the personnel. Most importantly, high reliability is achieved by avoiding HPLC-related failures, while use of biocompatible ethanol instead of most commonly used acetonitrile for tracer purification simplifies GMP-compliant quality control procedures. Furthermore, it opens new avenues to develop a fully automated disposable kits for [^{11}C]PiB production. Development of similar highly efficient solid phase supported syntheses of other clinically relevant tracers produced by ^{11}C-methylation is currently underway in our lab.

ACKNOWLEDGEMENTS

We thank McGill University, Montreal Neurological Institute, and McConnell Brain Imaging Centre for support of this work. We also thank Dr Gassan Massarweh for access to radioisotopes and radiochemistry facility, Mrs Monica Lacatus-Samoila for help with quality control, and Dr Vadim Bernard-Gauthier for proofreading the manuscript and valuable suggestions.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

How to cite this article: Boudjemeline M, Hopewell R, Rochon P-L, et al. Highly efficient solid phase supported radiosynthesis of [^{11}C]PiB using tC18 cartridge as a "3-in-1" production entity. *J Label Compd Radiopharm*. 2017;60:632–638. https://doi.org/10.1002/jlcr.3569