P023 SYNTHESIS OF CARBON-11 LABELED *N*-METHYL-LAUDANOSINE AND ITS DERIVATIVES AS NOVEL PET AGENTS FOR SK CHANNELS IN THE HEART

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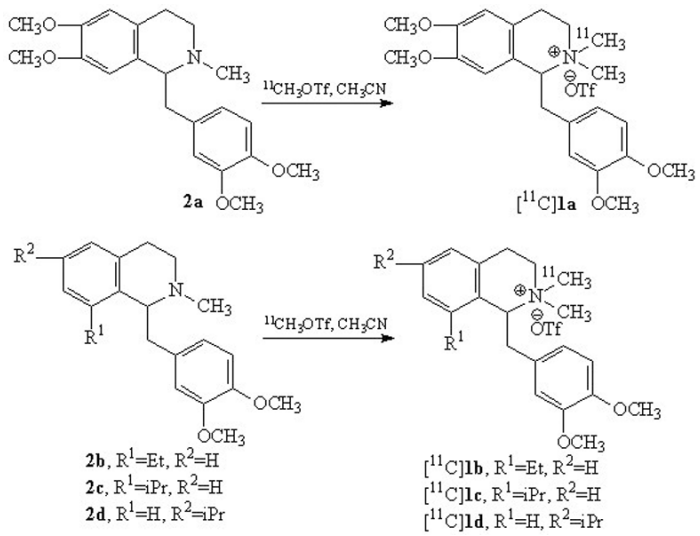
Introduction: Three types of calcium-activated potassium channels, including large (BK), intermediate (IK) and small (SK) conductance, have been identified. SK channels are widely expressed in different tissues such as the brain, peripheral nervous system, skeletal muscle, smooth muscle and heart, and regulate cognitive dysfunction, neuronal hyperexcitability, dopamine-related disorders, depression, hormone secretion from endocrine cells, and repolarization of cardiac action potentials. We are interested in the development of PET heart imaging agents. *N*-methyl-laudanosine (NML) is a potent SK channel blocker. Carbon-11 labeled NML and structurally close to NML derivatives, substituted 1-(3,4-dimethoxybenzyl)-2,2-dimethyl-1,2,3,4-tetrahydroisoquinoliniums may serve as novel radiotracers for PET to image SK channels in the heart. Here we present the synthesis of carbon-11 labeled NML and its derivatives.

Experimental: Precursor (**2a**) is commercially available, and precursors (**2b-d**) and their corresponding standards (**1a-d**) were synthesized in multiple steps starting from the substituted benzaldehydes and aminoacetaldehyde dimethyl acetal in moderate to excellent chemical yields using a modification of the literature procedure (Graulich A, et al. *J Med Chem*, **2005**, *48*, 4972-82).

Results and Discussion: Carbon-11 labeled quaternary ammonium target tracers, 6,7-dimethoxy-1-(3,4-dimethoxybenzyl)-2-[^{11}C]methyl-2-methyl-1,2,3,4-tetrahydroisoquinolium triflate ([^{11}C]NML, [^{11}C]**1a**) and its derivatives, 1-(3,4-dimethoxybenzyl)-8-ethyl-2-[^{11}C]methyl-2-methyl-1,2,3,4-tetrahydroisoquinolium triflate ([^{11}C]**1b**), 1-(3,4-dimethoxybenzyl)-8-isopropyl-2-[^{11}C]methyl-2-methyl-1,2,3,4-tetrahydroisoquinolium triflate ([^{11}C]**1c**) and 1-(3,4-dimethoxybenzyl)-6-isopropyl-2-[^{11}C]methyl-2-methyl-1,2,3,4-tetrahydroisoquinolium triflate ([^{11}C]**1d**), were prepared by the *N*-[^{11}C]methylation of their corresponding precursors **2a-d** using [^{11}C]CH_3OTf and purified by a simplified SPE method using a cation-exchange CM Sep-Pak cartridge in 40-65% radiochemical yield based on [^{11}C]CO_2, 15 min overall synthesis time from EOB, >95% radiochemical purity and 1.0-2.0 Ci/μmol specific activity at EOS (Scheme 1).



Scheme 1. Synthesis of carbon-11 labeled *N*-methyl-laudanosine and its derivatives.

Conclusion: An efficient and convenient synthesis of the tetrahydroisoquinoline precursors, tetrahydroisoquinolium standards and carbon-11 labeled substituted 1-(3,4-dimethoxybenzyl)-2,2-dimethyl-1,2,3,4-tetrahydroisoquinoliniums has been well developed.

Acknowledgement: Supported in part by INGEN of Indiana University.

Keywords: Carbon-11 Labeled N-Methyl-Laudanosine, SK Channels, PET, Heart Imaging

P024 SYNTHESIS AND *IN VITRO* EVALUATION OF CARBON-11 LABELED SULFONANILIDE ANALOGUES AS NEW POTENTIAL PET AGENTS FOR IMAGING OF AROMATASE IN BREAST CANCER

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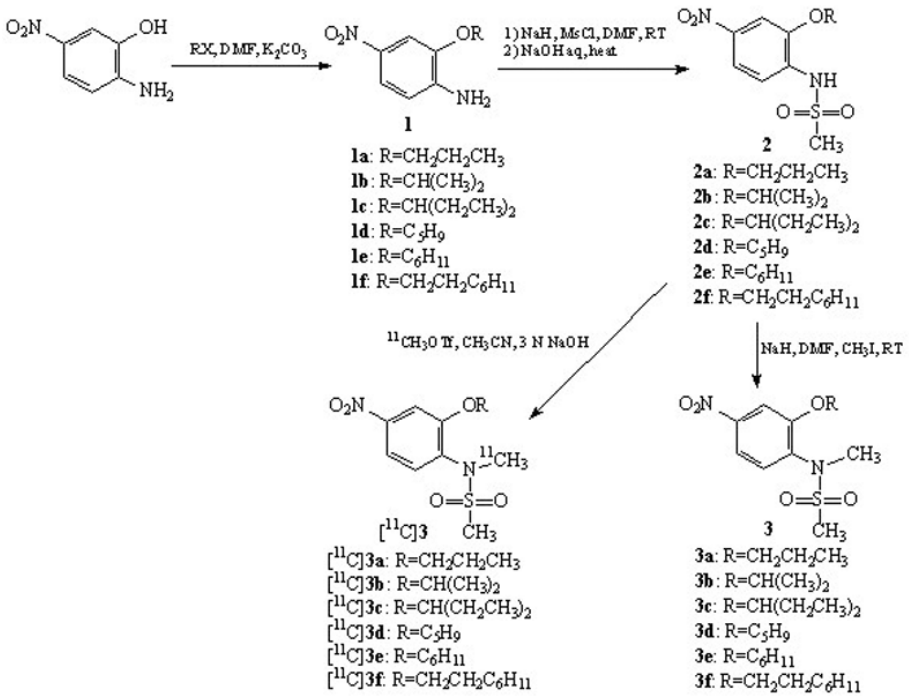
Introduction: Aromatase is a particularly good target in the treatment of estrogen receptor (ER) positive breast cancer. The aromatase inhibitors (AIs) have been extensively studied as effective hormonal therapeutic drugs for ER^+ breast cancer. Recently, a novel series of sulfonanilide analogues derived from the COX-2 selective inhibitor NS-398 have been developed as AIs (Su B, et al. *J Med Chem*, **2006**, *49*, 1413-9). Sulfonanilide analogues labeled with a positron emitting radionuclide may enable non-invasive monitoring aromatase expression in breast cancer and breast cancer response to AIs therapy using PET. Here we report the design, synthesis and in vitro biological evaluation of carbon-11 labeled sulfonanilide analogues.

Experimental: Synthesis of precursors (**2a-f**) and standards (**3a-f**) was achieved using a modification of the literature procedure aforementioned. 2-amino-5-nitrophenol was reacted with alkyl halides to provide compounds (**1a-f**) in 5-90% yield. Treatment of **1a-f** with excess of MsCl formed sulfonimide intermediates, which were hydrolyzed to give **2a-f** in 54-85% yield. Methylation of **2a-f** with iodomethane produced target compounds **3a-f** in 85-91% yield.

Results and Discussion: Precursors (**2a-f**) were labeled with $[^{11}C]CH_3OTf$ through *N*-[^{11}C]methylation and isolated by revised-phase HPLC purification to give target tracers, *N*-[^{11}C]methyl-*N*-(2-alkyloxy-4-nitrophenyl)-methanesulfonamides ([^{11}C]**3a-f**, alkyl = propyl, isopropyl, 1-ethyl-propyl, cyclopentyl, cyclohexyl, and cyclohexylethyl), in 30-35% radiochemical yields based on $[^{11}C]CO_2$, 20-25 min overall synthesis time from EOB, >98% radiochemical purity and 1.0-2.0 Ci/μmol specific activity at EOS (Scheme 1).

Cytotoxicity of the compounds **3a-f** in comparison with the parent compound NS-398 (**2e**) was assessed by a dose-response MTT assay in SK-BR-3 breast cancer cells. The results show that the compound **3e** (IC_{50} 0.66 μM) exhibits the strongest cytotoxicity activity greater than NS-398 (IC_{50} 0.72 μM), and the new compound **3f** (IC_{50} 2.54 μM) is a potent aromatase inhibitor too albeit not as effective as NS-398.



Scheme 1. Synthesis of carbon-11 labeled sulfonanilide analogues.

Conclusion: Chemistry results with *in vitro* biological data of the unlabeled compounds **3a-f** encourage further *in vivo* evaluation of the radiolabeled compounds [^{11}C]**3a-f**.

Acknowledgement: Supported in part by the Komen Foundation and INGEN of Indiana University.

Keywords: Sulfonanilide Analogues, Carbon-11, PET, Aromatase, Breast Cancer

P025 RADIOFLUORINATION OF BOMBESIN PEPTIDE ANALOGS: A POTENTIAL RADIOPHARMACEUTICALS FOR CANCER DETECTION BY PET IMAGING

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Introduction: Peptide-based agents have attracted enormous attention as biological vehicles to deliver radioactivity to tumor cells for external imaging and targeted radiotherapy. One of these peptides is Bombesin's analogue (BN) is a 14-amino acid peptide that has a high affinity for the gastrinreleasing peptide receptor[1]. A wide variety of human tumors, including small cell lung, prostate, breast, gastric, colon and pancreatic cancers are known to express receptors specific for BN-peptide analogs. It has been shown that the C-terminal amino acid sequence, Trp^{8}-Ala^{9}-Val^{10}-Gly^{11}-His^{12}-Leu^{13}-Met^{14}-NH_2, is necessary for retaining receptor binding affinity and preserving the biological activity of BN-peptide analogs[2]. A number of potent BN-peptide analogs bearing chelating groups at the N-terminus, for labeling with various radionuclides have been synthesized and investigated for possible tumor imaging applications[3,4].

Experimental: Several BN-peptide analogues were synthesized using solid-phase synthesis following standard Fmoc (9-fluorenylmethoxycarbonyl) chemistry. The crude peptides obtain was purified by reversed-phase HPLC. These BN-peptide analogs were radiofluorinated through the primary amine of the lysine residue utilizing the conjugate approach N-succinimidyl activated ester of the ^{18}F-benzoic and ^{18}F-nicotinic acids. Work up of these products by C-18 Sep-Pak column gave radiochemically and chemically pure ^{18}F-BN-peptide analogs as assessed by HPLC.

Results and Discussion: In this study, we report the design and synthesis of several BN-peptide analogs by introducing hydrophilic amino acids such as aspartic acid in the original sequence. The structure and purity of these peptides were confirmed by mass spectrometry and HPLC analysis. As a continuation of our on-going research effort to develop potent radiofluorinated BN-peptide[5], we have radiolabeled several BN-peptide analogs with fluorine-18 using the lipophilic ^{18}F-benzoic and hydrophilic ^{18}F-nicotinic acids. The chelation process occurred at the non-receptor binding N-terminal through the primary amine of the lysine residue. Radiochemical yields for both chelations appear to be consistently higher than 50%. In vitro and in vivo characterization of these radiofluorinated BN-peptide analogues are currently in progress.

Acknowledgement: The authors acknowledge KACST and KFSHRC for the financial support (grant #AT-25-6)

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P026 TRIFLUOROMETHANESULPHONIC ACID: AN ALTERNATIVE SUPERACID FOR THE DIRECT RADIOFLUORINATION OF D- AND L-ENANTIOMERS OF DOPA

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Introduction: Positron Emission Tomography (PET) is an important method for tumor imaging. Because malignant tumors represent a hypermetabolic state, glucose or an amino acid analog, labeled with a positron emitting radionuclide, can be used to detect viable cancer cells using PET. Recently, it has been shown that imaging brain tumors, particularly recurrent low grade tumors, with [^{18}F]6-Fluoro-L-DOPA is superior to imaging with FDG. However, [^{18}F]6-fluoro-L-DOPA-PET is complicated because of the presence of radioactive metabolites present in the blood and brain, which contribute significantly to the background and reduce the signal-to-noise ratio. Because the enzyme COMT is specific to L-DOPA, the use of [^{18}F]6-fluoro-D-DOPA might reduce the formation of radioactive metabolites resulting in higher signal-to-noise ratios.

To date, anhydrous hydrogen fluoride (aHF) is the only solvent suitable for the radiosynthesis of [^{18}F]6-FDOPA by the direct fluorination of commercially available DOPA. In this study, we have shown that the reactivities and selectivities of [^{18}F]F_2 towards DOPA in trifluoromethanesulphonic acid (Hammet acidity, H_0 = 13.8) and aHF (H_0 = 15.1) are comparable. We have also shown that the former is a versatile solvent for the synthesis of D- and L- enantiomers of ^{18}F-labelled 6-FDOPA by the direct fluorination of commercially available D- and L-DOPA, respectively.

Experimental: Fluorine-18 labelled F_2 is produced by the ^{18}O(p,n)^{18}F nuclear reaction in a Siemens 11 MeV (RDS 112) cyclotron using the double-shoot method. ^{18}F- Labelled D- and L-FDOPA were produced by the direct fluorination of D- and L-DOPA in CF_3SO_3H at –40°C or in aHF at –65°C. After removal of the solvent, ^{18}F- labelled products were separated from the reaction mixture using reverse phase HPLC (Thermo-Hypersil Keystone, Fluophase PFP 5 μ, 250 x 10 mm) with 0.1% acetic acid in sterile water containing 0.04 ± 0.01 mg/mL ascorbic acid as the mobile phase and and a flow rate of 3.5 mL/min.

Results and Discussion: Direct fluorination of DOPA enantiomers in aHF or CF_3SO_3H produces mainly the 2- and 6-fluoro isomers of FDOPA. The radiochemical yield of [^{18}F]6-FDOPA was 5 ± 1% (CF_3SO_3H) and 7 ± 2% (aHF) at the end of 60 min synthesis. Removal of CF_3SO_3H (v.p. 8 Torr at 25°C, b.p. 162°C) proved to be a challenging step in the synthesis.

Conclusion: Trifluoromethanesulphonic acid is resistant to oxidation by fluorine and can be used for the low-temperature fluorination of aromatic aminoacids. It is a suitable solvent for the synthesis of clinically useful quantities of ^{18}F-labelled 6-fluoro-D-DOPA and 6-fluoro-L-DOPA by the direct radiofluorination of commercially available D- and L-DOPA.

Keywords: [^{18}F]6-Fluoro-D-DOPA, Electrophilic Fluorination, Tumor Imaging

P027 MICROWAVE ASSISTED SYNTHESIS *VS* CONVENTIONAL SYNTHESIS OF *CIS*-^{18}F-4-FLUORO-L-PROLINE: A PET TRACER FOR IMAGING PULMONARY FIBROSIS

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Introduction: Proline and hydroxyproline are important constituents of the protein collagen. Because fluoroproline is also taken up by collagen, *cis*-^{18}F-4-fluoroproline has been suggested as a PET tracer for studying abnormal collagen synthesis occurring in pulmonary fibrosis (PF), tumors and liver cirrhosis. We report an improved synthesis of *cis*-^{18}F-4-fluoroproline using a commercial microwave and a conventional heating block. We also present preliminary results from small animal PET imaging study using *cis*-^{18}F-4-fluoroproline as a marker of collagen biosynthesis in a PF animal model.

Experimental: The stereospecific nucleophilic fluorination was carried out by heating 8±3 mg N-Boc-trans-4-tosyloxy-L-proline methyl ester (ABX) and 8 mg Krypt in 1 mL ACN in a commercial 700 W microwave oven for 4x1 minute at 50% power or using a conventional heating block at 110°C for 10 min. The ^{18}F-labelled intermediate, separated using a Silica Sep-Pak, was hydrolysed using 2 M CF_3SO_3H at 140°C for 10 min. The final product was purified using anion exchange column.

Adenovirus vectors expressing IL-1β (AdIL-1β) were administered intratracheally inducing an initial inflammatory response followed by fibrosis. Sixty minute dynamic PET scans were acquired weekly on sedated animals using the Philips Mosaic PET after the injection of 18 MBq of *cis*-^{18}F-4-fluoroproline or ^{18}F-FDG.

Results and Discussion: The radiochemical yield of the reaction intermediate was 71±7% (Microwave) and 88±3% (Thermal). The radiochemical yield of *cis*-^{18}F-4-fluororproline was 37±5% at the end of 80 min synthesis. The radiochemical purity was 98±1%.

Animal studies showed an increase in ^{18}F-FDG uptake in the lung of exposed rats at day 7, correlating with an influx of inflammatory cells seen by histology. An increase in lung *cis*-^{18}F-4-fluoroproline uptake was observed 14 days after AdIL-1β exposure compared to no lung uptake in controls.

Conclusion: Radiochemical yield of cis-^{18}F-4-fluoroproline (37±5%) is significantly higher than that is previously reported. Uptake of *cis*-^{18}F-4-fluoroproline during active collagen synthesis and fibroproliferation in the lung suggests that this radiotracer could be used to study the progression of fibrotic disease and efficacy of anti-fibrotic therapies in animal models with PF.

Keywords: 18F-Cis-4-Fluoroproline, Pulmonary Fibrosis, Biomarker for Collagen, Animal Imaging

P028 IMPROVED RADIOSYNTHESES OF (^{18}F)FET UNDER MICROWAVE-ASSISTED CONDITIONS

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Introduction: O-(2-[^{18}F]Fluoroethyl)-L-tyrosine ([^{18}F]FET) is an almost established metabolic imaging for brain tumor diagnosis by positron emission tomography (PET). Herein, microwave-enhanced radiosyntheses of [^{18}F]FET were investigated to attempt to be applied into its two existed radiochemical synthetic routes, improve the radiochemical yields (RCYs) and shorten the time of synthesis.

Experimental: Microwave irradiation was introduced into the step of ^{18}F-fluorination and/or ^{18}F-fluoroalkylation during the synthesis of [^{18}F]FET using the two following radiochemical routes. One consists of nucleophilic ^{18}F-fluorination of 1,2-bis(tosyloxy)ethane and ^{18}F-fluoroethylation of unprotected L-tyrosine reported by Wester[1] (Route I), another is direct nucleophilic ^{18}F-fluorination of protected L-tyrosine reported by Hammaker[2] and Wang[3] (Route II), both of which were made some modifications in this report, such as using new precursor *N*-BOC-(*O*-(2-tosyloxyethyl))-L-tyrosine methyl ester in Route II. Radio-TLC was used to measure the RCYs of each step at various time points post-reaction under microwave irradiation conditions.

Results and Discussion: The experiment results were listed in Table 1. For Route I, the RCYs in step one was up to 86% at 3mins post reaction under microwave irradiation, and in step two was as high as 96%. Consequently, the synthesis of [^{18}F]FET via Route I could be completed within 20mins with good total RCYs. For Route II, however, the RCYs in the fluorination step were not high enough under the same reactions conditions as that in Route I.

Table 1 Radiochemical yields of each step at various time points post-reaction under microwave irradiation conditions

Time (min)	RCY(%)		
	Route I		Route II
	First step	Second Step	
1	50	85	28
2	80	90	32
3	86	96	37

Note: Microwave oven as microwave source.

Conclusion: Microwave irradiation as efficient heating model for PET radiopharmaceuticals would be implanted into the synthesis of [^{18}F]FET via Route I to shorten its synthesis time with good RCYs.

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Keywords: [^{18}F]FET, L-Tyrosine, 18F-Fluorination, Microwave Irradiation

P029 (^{18}F)FBAM AND (^{18}F)FBOM: NOVEL PROSTHETIC GROUPS FOR THE MILD LABELING OF THIOL GROUP-CONTAINING BIOMACROMOLECULES

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Introduction: The incorporation of 18F into peptides and proteins usually takes advantage of prosthetic groups, also referred to as bifunctional labeling agents. This approach comprises 18F incorporation into a small organic molecule capable of being linked to peptides and proteins under mild conditions. This work deals with a comparative discussion on the synthesis and application of N-[6-(4-[^{18}F]fluorobenzylidene)aminooxyhexyl]-maleimide ([^{18}F]FBAM) and 4-[^{18}F]fluorobenzaldehyde-O-(2-{2-[2-(pyrol-2,5-dion-1-yl)ethoxy]ethoxy}ethyl)oxim ([^{18}F]FBOM) as novel prosthetic groups for the mild and selective conjugation to thiol group-containing biomacromolecules (Fig. 1).

Experimental: The aminooxy-functionalized labeling precursor for radiosynthesis of [^{18}F]FBAM was prepared in a convenient three-step synthesis sequence in a total yield of 59%. The corresponding labeling precursor for the radiosynthesis of [^{18}F]FBOM succeeded in a four-step reaction sequence in 14% total yield. Formation of the prosthetic groups [^{18}F]FBAM and [^{18}F]FBOM was achieved through condensation reaction with [^{18}F]fluorobenzaldehyde to form the desired oximes in radiochemical yields of 20-30% ([^{18}F]FBAM) and of 14-19% ([^{18}F]FBOM), respectively.

Results and Discussion: The syntheses were carried out in a remotely-controlled radiofluorination module allowing the convenient and reliable performance of the radiolabeling reactions. The radiochemical purity exceeded 95% and the specific activity ranged from 50 to 80 GBq/μmol. The total synthesis time was 70 to 80 min. The lipophilicity was determined to be logP=2.71 for [^{18}F]FBAM and logP=0.84 for [^{18}F]FBOM. The usefulness of [^{18}F]FBAM and [^{18}F]FBOM as thiol-reactive group prosthetic group was demonstrated by the reaction with glutathion, low density lipoproteins (LDL) and modified neurotensin derivatives. Reaction of [^{18}F]FBAM and [^{18}F]FBOM with glutathione showed that the use of as little as 1 μg/ml glutathione after 30 min provides excellent radiochemical yields of 95% of the desired coupled products. Labeling of LDL showed superior results with [^{18}F]FBAM, whereas comparable results for both prosthetic groups were obtained for the labeling of modified neurotensin derivatives.

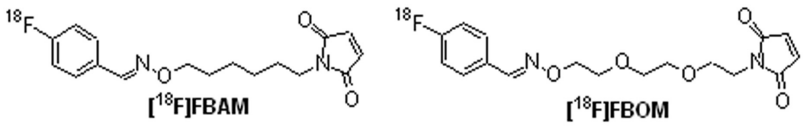

Fig. 1. Thiol group selective prosthetic groups [^{18}F]FBAM and [^{18}F]FBOM.

Conclusion: The ease of production and the excellent performance in radiolabeling reactions make compounds [^{18}F]FBAM and [^{18}F]FBOM very promising prosthetic groups for the mild and selective conjugation to thiol group-containing biomacromolecules.

Keywords: Prosthetic Group, 18F-Labeling, Maleimide

P030 RADIOLABELING OF MULTIMERIC NEUROTENSIN(8-13) ANALOGUES WITH THE SHORT-LIVED POSITRON EMITTER FLUORINE-18

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Introduction: Neurotensin receptors are expressed with high incidence in several human tumour entities. Thus, radiolabeled neurotensin derivatives might be used for tumour targeting. However, its application is limited by insufficient metabolic stability. Metabolic stability might be improved by the synthesis of multimeric peptides.

Experimental: Three methods for 18F-labeling of dimeric and tetrameric neurotensin(8-13) derivatives were evaluated with respect to the labeling yield and the required peptide amounts.

Results and Discussion: Labeling using N-succinimidyl-4-[^{18}F]fluorobenzoate ([^{18}F]SFB) gave low radiochemical yield for the dimeric peptides. Coupling of the tetramer with [^{18}F]SFB was not successful. Furthermore, labeling of aminooxy-functionalized neurotensin(8-13) derivatives using 4-[^{18}F]fluorobenzaldehyde ([^{18}F]FBA) was investigated. High yields of up to 96% were obtained for the dimer whilst coupling of the tetramer only gave low yields of up to 10%.

In contrast to these findings, labelling of sulfhydryl-functionalized neurotensin(8-13) derivatives using the maleinimide 4-[^{18}F]fluorobenzaldehyde O-[6-(2,5-dioxo-2,5-dihydro-pyrrol-1-yl)-hexyl]-oxime ([^{18}F]FBAM) resulted in high radiochemical yields for both, the dimer and the tetramer, being 94% and 40%, respectively. Therefore, [^{18}F]FBAM seems to be the most suitable 18F-labeling agent for multimeric neurotensin(8-13) derivatives. The synthesized 18F-labeled multimeric neurotensin derivatives are depicted in Fig. 1.

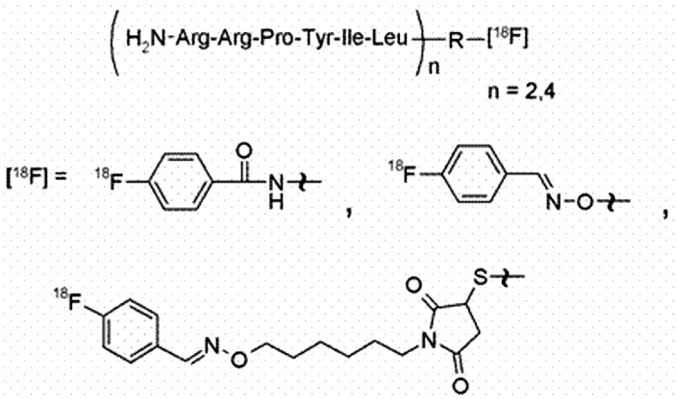

Fig. 1. ^{18}F-labeled multimeric neurotensin derivatives.

Conclusion: In summary, 18F-radiolabeling of dimeric and tetrameric NT(8-13) derivates was investigated. Suitable results were obtained by labeling of the sulfhydryl-functionalized peptides using [^{18}F]FBAM. Using [^{18}F]SFB or [^{18}F]FBA as the labeling agent gave only low radiochemical yields. Furthermore, labeling of the dimer gave better radiochemical yields than labeling of the tetramer – independent from the labeling method which was used. Therefore, the nature of the peptide exhibits a strong influence on the coupling reaction.

Keywords: Neurotensin, Fluorine-18, Tumor Targeting, Multimer

P031 EFFICIENT RADIOSYNTHESIS OF CARBON-11 LABELLED THIOFLAVIN T DERIVATIVES USING (^{11}C)CH_3I FOR A-BETA-AMYLOID IMAGING

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Introduction: The Thioflavin T derivative [^{11}C]-BTA-1 was evaluated in vitro and vivo assays and showed a great potential in diagnosis of Alzheimer's Disease with PET. However, the radiosynthesis yield(RY) of [^{11}C]-BTA-1 was low as 10-12% by [^{11}C]-CH_3I. It is reported that the use of [^{11}C]methyl triflate can improve the RY of [^{11}C]-BTA-1 significantly. Here we report that another way of radiosynthesis method can get 58% RY with [^{11}C]-CH_3I for [^{11}C]-BTA-1 also.

Experimental: The 2-(4-aminophenyl)benzothiazole (APBT) was synthesized according to the reported. The carbon-11 labeled APBT was performed by improved-methods with [^{11}C]-CH_3I, which mixed precursor solution with [^{11}C]-CH_3I stock solution. A stock of [^{11}C]-CH_3I was prepared by bubbling the produced [^{11}C]-CH_3I into a flask filled with 0.2ml of DMSO. The 2-3mg APBT dissolved in 0.2ml DMSO was mixed with [^{11}C]-CH_3I stock solution at room temperature after the 12uL 5N NaOH was added to APBT solution within 2min. Reaction was quenched by added 10ml water. The mixture was delivered to Sep-Pak C-18 to separate the products. The RCP was done by HPLC.

Results and Discussion: The improved-methods led to [^{11}C]-BTA-1 RY of 58%(n=10). Contrastively, the bubbled method was 10-30%(n=6), the [^{11}C]methyl triflate method was 51%(n=3).It suggested that the time, after 12uL 5N NaOH added to APBT solution to mixed with stock, has affected the RY. The optimized time was 2min. If the time is over 5min, the RC was declined to 25%. The NaOH may be taken the precursor low activity if it mixed with precursor longer time.

Conclusion: The improved-methods for [^{11}C]-BTA-1 was a highly efficient synthesis routed was developed for application in clinical studies.

Keywords: Alzheimer's Diseases, Carbon-11, Beta-Amyloid, Thioflavin T

P032 SYNTHESIS OF (*N*-METHYL-^{11}C)-, (*O*-METHYL-^{11}C)- AND (*C*-METHYL-^{11}C)RTI-32 FOR THE STUDY OF PHENYLTROPANE METABOLISM

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Introduction: A multitude of labelled phenyltropanes exist for the study of the dopamine transporter (DAT) with PET or SPECT. Dependent on the labelling position, radiometabolites that obstruct the quantification of DAT may be formed *in vivo*. The phenyltropane derivative, RTI-32 (**1**), contains a *N*-methyl, the *O*-methyl- and *p*-methyl group. Labelling of RTI-32 in one of each of these methyl groups will give differently labelled compounds that can be used for the elucidation of phenyl tropane metabolism *in vivo*.

Experimental: ^{11}C-labelling at the *N*- and *O*-groups were achieved by trapping [^{11}C]MeOTf at 4°C in a solution of the desmethyl precursor (**2** or **3** respectively, 0.40 mg in 100 μl of acetone). ^{11}C-Methylation of the phenyl moiety was approached via two reactions (**A** or **B**); **A**: [^{11}C]MeI was trapped in Lappert's stannylene-THF. After complete evaporation of THF the generated [^{11}C]mono-organotin was activated *in situ* by 3 eq. of TBAF and then reacted with *p*-iodophenyl precursor **4** (0.55 mg) and Pd_2dba_3 in 1,4-dioxane. **B**: [^{11}C]MeI was trapped in a solution of Pd_2dba_3 and P(o-tolyl)$_3$ in NMP or DMF (0.4 mg/0.5 mg/200 μl) and then reacted with *p*-tri-butylstannylphenyl **5** precursor and CuCl in NMP or DMF (0.5 mg/0.4 mg/150 μl). Product was purified by HPLC (silica gel column and CH_2Cl_2/CH_3OH/TEA/HOAc at entry #2, C18 column and MeCN in 10mM H_3PO_4 at all other entries). After evaporation of mobile phase, the purified product was dissolved in sterile 0.1M phosphate buffer and sterile filtered.

Results and Discussion: *N*- and *O*-methylations proceed well even without heating (Table 1, #1-4). For *C*-methylation reaction **B** was preferable to **A** (#5-10). Propylene glycol-ethanol (PG-E) was an effective radiolysis scavenger (#5-6).

Table 1

#	Prec.	Rgnts	Solvent[d)]	Heat [°C]/[min]	EOS [min]	RCY [%][e)]	RCP [%]][f)]
1	**2**		acetone	60/1	43	>90	99.9
2	**2**		–"–	–	30	>90	99.9
3	**3**	a	–"–	60/1	45	>80	99.9
4	**3**	a	–"–	–	30	>90	99.9
3	**3**	a	–"–	120/5	58	~10	3.5
7	**5**	c	NMP	90/5	58	~50	98.7
8	**5**	c	–"–	–	30	>90	99.9
3	**3**	a	–"–	90/4	65	~30	99.7

a) 0.4M QOH (1.1 eq.) b) Lappert's stannylene, 1.0M TBAF in THF (3 eq.), Pd_2dba_3, *) without PG-E. c) Pd_2dba_3, P(*o*-tolyl)$_3$, CuCl. d) # 7-10: reagent solutions were purged by Ar or N_2 for ~15min. e) Radiochemical yield from [^{11}C]MeI or [^{11}C]MeOTf. f) Radiochemical purity

Conclusion: Phenyltropane derivative RTI-32 (**1**) was labelled with [^{11}C]MeI or [^{11}C]MeOTf in three different positions in moderate to high yield and high purity.

Keywords: Carbon-11, Tropane, Dopamine, Labelling Position

P033 RAPID SYNTHESIS OF (^{18}F)FLUORO-L-THYMIDINE WITH SIMPLIFIED PURIFICATION USING A COMBINATION-COLUMN

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Introduction: 18F-Fluoro-L-Thymidine (18F-FLT) is an established PET-Radiopharmaceutical to study cell-proliferation rate in tumours. However, its production is more complex, compared to 18F-FDG, since in-line HPLC-purification is required. This makes 18F-FLT equipment costly, increases synthesis-time with often inefficient elution of the product. We have done experiments and standardised a process for making 18F-FLT avoiding HPLC-purification, making it as simple as that of 18F-FDG. By this, automated equipment for 18F-FDG can be used for making 18F-FLT, by just changing the purification column. The synthesis time is considerably shortened and validation for 'parametric release' (essential for PET-radiopharmaceuticals) is much easier.

Experimental: 18F-FLT was prepared by nucleophilic 18F-fluorination, in presence of phase transfer catalyst of 3-N-BOC-1-[5-O-(4,4'-dimethoxy-trityl)-3-O-nitrophenylsulphonyl-2-deoxy-β-D-lyxofuranosyl]-L-thymidine, at 130°C for 6 min and hydrolysis effected with 1M HCl (1ml, 105°C, 5 min). The reaction-mixture was passed through ion-exchange resins and adsorbents, arranged in a specific sequence and proportion in a column, the purified 18F-FLT collected in a vial and sterile-filtered before dispensing.

Results and Discussion: The total synthesis time is 40±1 min and yield was 25±3% (n=6). The radiochemical purity of >95% was seen both by TLC and radio-HPLC.In all 6 batches of 18F-FLT that were prepared, and the product was satisfactory in all respects: clear and colorless; free-18F- <5%; pH (4.5-7.5); residual solvents below permissible levels; and the product complied with sterility and BET tests. There was no detectable labeled precursor and other by-products. Bio-distribution of 18F-FLT in mice with fibrosarcoma tumour as well as PET-CT imaging of rabbit showed distinct localization of 18F-FLT in organs having rapid cell division. No significant uptake was seen in brain and bones.

18F-FLT synthesis data

Batch No.	Synthesis Details				
	18F-starting (MBq)	18F-FLT produced (MBq)	Yield % (no decay correction)	Radioactivity Concentration	Total Volume (ml)
1	5920	1813	30.6	3.1	10
2	5735	1702	29.7	2.8	10
3	3700	1036	28	2.8	10
4	4070	999	24.5	2.4	10
5	2960	518	17.5*	1.75	10
6	11100	2775	25	7.5	10

*18F-activity too low for accurate estimate of yield

Conclusion: The simplified synthesis procedure for 18F-FLT can be readily carried out in existing automated synthesis modules for FDG making this PET-Radiopharmaceutical easily available.

Acknowledgement: The suuport from Dr. V Rangarajan and Dr. Aban M Samuel of the Bio-Imaging unit of Tata Memorial Hospital is gratefully acknowledged.

Keywords: 18F-FLT, Biodistribution, PET-Radiopharmaceutical, Cell-Proliferation, PET-CT Imaging

P034 A NOVEL AND FLEXIBLE ROBOTIC PLATFORM FOR THE PRODUCTION OF HIGH PURITY ^{18}F-RADIOPHARMACEUTICALS

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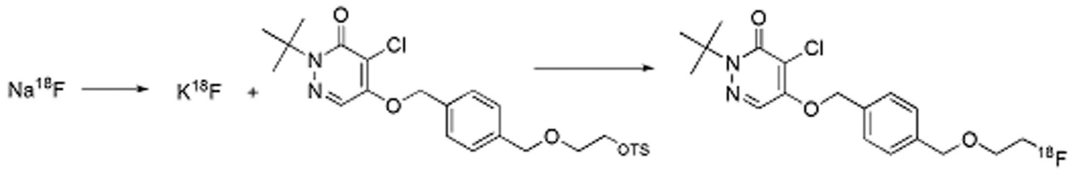
Introduction: A majority of the research incorporating ^{18}F into potential radiopharmaceuticals uses modified automated radiosynthetic units designed for production of [^{18}F]-FDG. The relative simplicity of [^{18}F]-FDG production may not reflect the complexity required for many radiosyntheses. More complex radiosynthetic procedures typically are performed using well shielded laboratory glassware, requiring minimization of radioactivity used in experiments limiting the quantity and variety of experiments in research projects. Currently units are being designed to enable more elaborate radiosynthetic procedures. Most of these units use compressed gases and vacuum lines to move materials from one unit operation to the next.

Experimental: We have designed and constructed an Automated Liquid Handling System for Applications in Radiation Chemistry (ALSARC) to conduct sophisticated radiopharmaceutical syntheses. The ALSARC is housed within a lead-lined hot cell. The system has been designed to conduct research experiments at the 3 Ci level. The central component of the system is a Gilson 215 liquid handler with multiple modular stations located within the transit area of the robotic arm. Available unit operations include evaporation, extraction, reactors, variable temperature controllers, microwave irradiation and collection vessels. Incorporation of syringe pumps enables the transfer of materials to and from points outside robotic transit area. Purifications by disposable column in combination with or independent of HPLC are facile, as well as concurrent radiochemical/chemical purity analyses by both radiation and UV/VIS detectors. Three quantitative radiation detectors built into the system measure the radioactive content of samples in various matrices. A system of solenoid valves controlled externally allows for fluid paths to be directed to desired locations with precision. S_N2 reactions are conducted easily and routinely using the ALSARC in conjunction with an ion trap, Sep Pak™, and MP1 resin purifications followed by HPLC purification and analysis.

Results and Discussion: The following scheme illustrates the S_N2 reaction for production of BMS747158-02, a novel PET myocardial perfusion agent.



Conclusion: We have demonstrated the versatility of the system by executing multi-step organic reactions including SNAr substitutions, acid and base deprotections, Pd/C catalyzed reactions. A description of the system, capabilities and its operation will be presented.

Keywords: Positron Emitters, Automated, Radiosynthesis, Radiopharmaceuticals, High Levels Radioactivity

P035 EFFECT OF PENTAFLUOROPROPANOL ON DIRECT FLUORINATION OF AROMATIC AMINO ACIDS IN FORMIC ACID: A HIGH YIELD SYNTHESIS OF (^{18}F)3-FLUORO-L-α-METHYLTYROSINE

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Introduction: Recent studies have shown that fluorine solubility can be increased by using solvents or additives having an –OH group, the acidic hydrogen of which can react with F_2 to form HF and, consequently, the hypofluorite group –OF can be formed. It is suggested that through hypofluorite formation, fluorine can react like an F^+ species. This increase in the electrophilicity of fluorine minimizes unselective radical reactions on the aromatic ring and, thus, increases the yield of monofluorinated isomers. In this study, the effect of pentafluoropropanol (PFP) on direct fluorination of L-α-methyltyrosine (L-α-MT) in formic acid (FA) using [^{18}F]F_2 was investigated. The final product, [^{18}F]3-fluoro-L-α-methyltyrosine ([^{18}F]3-F-α-MT), has proved to be useful in the diagnosis of different tumours.

Experimental: The direct fluorination was carried out by passing [^{18}F]F_2 through a solution of substrate in FA containing different concentrations of PFP. The ^{18}F-labelled product was isolated from the reaction mixture and analyzed by HPLC. Multi-NMR spectroscopy as well as LC-MS were used to characterize 3-F-α-MT. *In vivo* studies were carried out using mice bearing glioma tumours. [^{18}F]3-F-α-MT was administered to each animal via tail vein. The animals were imaged for 60 min using a PET scanner, followed by the CT component of a SPECT/CT scanner for co-registration. The animals were then eutanized and tissue samples were collected for biodistribution studies.

Results and Discussion: The radichemical yields (RCY) of [^{18}F]3-F-α-MT, resulting from direct fluorinatin of L-α-MT in FA and in 5% PFP in FA, were 13 and 31% (relative to [^{18}F]F_2), respectively. The latter is the highest RCY of [^{18}F]3-F-α-MT resulting from direct fluorination of L-α-MT reported to date. This is in agreement with a recent study, which showed that highest yields of monofluorinated isomers of several aromatic systems were generally obtained using protic solvents having an acidic hydrogen capable of forming the hypofluorite group –OF. The *in vivo* studies showed very evident uptake of [^{18}F]3-F-α-MT in the areas of tumour growth. The target-to-background ratio within the brain was also high enough to allow for a good visualization of the tumour.

Conclusion: The present study has shown that the presence of PFP in FA during direct fluorination of L-α-MT increased the RCY of [^{18}F]3-F-α-MT up to two fold. The *in vivo* studies provided promising results towards the diagnosis of glioma. Additional *in vivo* studies are underway to further determine the potential application of [^{18}F]3-F-α-MT as a PET tracer and to evaluate its feasibility with early onset of tumour growth as well as late stage tumours.

Keywords: L-α-Methyltyrosine, [^{18}F]3-Fluoro-L-α-Methyltyrosine, Glioma

P036 NOVEL RADIOPHARMACEUTICALS FOR IN VIVO IMAGING OF TAU PATHOLOGY AND THEIR USE AS BIOMARKERS FOR ALZHEIMER'S DISEASE

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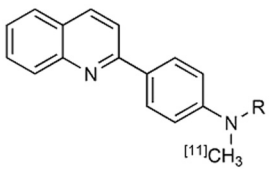
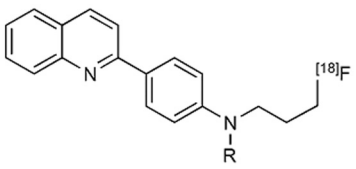
Introduction: Alzheimers disease (AD) is the most common form of dementia, afflicting 35% of people over the age of 85. AD is characterized by the deposition of β-amyloid plaques and neurofibrillary tangles resulting from abnormal aggregation of tau protein but dementia only presents itself when AD is well advanced and beyond treatment. The ability to analyze levels of plaques and tangles early enough to allow effective treatment represents a major goal in AD therapy and PET imaging is playing a key role in this analysis. Radiopharmaceuticals used to image β-amyloid plaques are becoming increasingly common whereas, in contrast, biomarkers allowing for the PET imaging of Tau tangles have received much less attention to date.[1] We herein report the labeling of a family of novel compounds based around a 2-substituted quinoline core using carbon-11 (1) and fluorine-18 (2) radionuclides. For in vivo evaluation of these new radiopharmaceuticals, a line of transgenic rats over-expressing Tau has been established. In vivo biodistribution and imaging studies will be presented.

Typical Experimental Procedures: *[11]C-Labeled Compounds.* Quinoline precursor (1.0 mg) was dissolved in methylethyl ketone (MEK, 1 ml) in a screw-cap vial. This precursor was methylated by bubbling [^{11}C]methyl triflate, carried on a N2 stream, through the MEK solution at room temperature until radioactivity accumulation in the reaction vial maximized. The vial was sealed and heated to 80°C. Purification by semi-preparative HPLC gave [11]C-labeled tracers which were used directly.

[18]F-Labeled Compounds. Quinoline precursor (1 mg) in DMSO (1 ml) was added to the reactor of a GE Tracerlab FXN containing K[18]F complexed with Kryptofix 2.2.2. The reaction was heated to 120°C and then purified by semi-preparative HPLC to give [18]F labeled tracers which were used directly.



1
R = H, Me



2
R = H, Me

In both cases, QC samples were analyzed by HPLC to ensure radiochemical purity (>95%) and specific activity (dose concentration <5 μg/mL).

Acknowledgement: Financial support of this work by the NIH (Grant NS15655) is gratefully acknowledged.

Reference: [1] N. Okamura et al., 2005. Quinoline and Benzimidazole Derivatives: Candidate Probes for In Vivo Imaging of Tau Pathology in Alzheimer's Disease. J. Neurosci., 25, 10857–10862.

Keywords: Alzheimers Disease, Positron Emission Tomography, Carbon-11, Fluorine-18, Tau Pathology, Neurofibrillary Tangles

P037 OPTIMIZED RADIOSYNTHESIS OF (^{18}F)-2-FLUOROMETHYL-L-PHENYLALANINE, A NEW TUMOUR SPECIFIC TRACER

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Introduction: A major requirement for the clinical future of new tumour specific tracer is a simple and fast radiosynthesis with a high yield comparable to the [^{18}F]-FDG production. A SAR study revealed that phenylalanine substituted on the 2 and 4 position with methyl or ethyl showed high affinity for LAT1 related uptake in tumour cells. We decided to replace the 1 H atom by a F atom. 2-Fluoromethyl-L-phenylalanine (2-F-MeLPhe) showed affinity for LAT1 uptake in R1M rat rhabdomyosarcoma cells (Ki: 0.050 mM) comparable to phenylalanine. This presentation deals with the radiosynthesis, purification and radiopharmaceutical formulation of [^{18}F]-2-Fluoromethyl-L-phenylalanine.

Experimental: [^{18}F] $^{-}$ exchange on 4 mg of the fully protected 2-Br-MeLPhe (N-Boc, tBut-ester) is performed within 3 minutes in 0.4 mL of acetonitrile (ACN)/K_{222}/K_2CO_3 at 120°C with a yield of at least 85%. The ACN phase was transferred through an Alumina cartridge and evaporated. Deprotection occurred at 50°C in trifluoro acetic acid (TFA)/CH_2Cl_2: 1/2 during 20 minutes followed by N_2 flow evaporation. 1.5 mL of isotonic saline containing 0.1 mg of 2-F-MeLPhe was added for HPLC injection. Pure C.A [^{18}F]-2-MeLPhe was recovered with a high radiochemical yield (> 60% not corrected for decay) by means of RP-HPLC (Varian PFP 250 x 10 mm column, isotonic saline, pH 7). Sterilisation occured by filtration through a sterile dry apatite containing filter coupled to 0.22 micron Millipore filter. Labelling yields, purity and shelf live were controlled by RP-HPLC and RP-TLC.

Results and Discussion: The highly activated benzyl carbon allows to use bromide as a leaving group with high yield radiofluorination. To remove both Boc and tBut in a single step acid deprotection is needed. In aqueous conditions (HCL, TFA) defluorination up to 50% occurred due to the formation of a Phe-C-F-H^{+} complex. Using TFA in CH_2Cl_2 in the appropriate ratio reduces it to 5% with complete deprotection.The N_2 flow allows quantitative evaporation of both dichloromethane and TFA (pH of water added is ~7.0). The formation of the complex also occurs in isotonic saline at room temperature yielding 30% free $^{18}F^{-}$ within an hour in case of NCA [^{18}F]-2-MeLPhe. As 2-MeLPhe shows no acute toxicity 0.1 mg was added before HPLC separation allowing to recover the tracer within a sharp peak. Addition of the non radioactive compound ([H^{+}]/compound ratio: $\sim 7.10^{-3}$) reduces free $^{18}F^{-}$ to maximum 2% which is eliminated by the apatite.

Conclusion: The use of fully protected 2-Br-MeLPhe and the described radiosynthesis pathways allow a high yield (> 60% injectable at the end of chemistry) production of C.A. [^{18}F]- 2-Fluoromethyl-L-phenylalanine for initial clinical trials and the method is suitable for automation.

Acknowledgement: The authors thank FWO-Vlaanderen and GOA-VUB.

Keywords: [^{18}F]-2-Fluoromethyl-Phenylalanine, 2-Bromo-Benzyl-Alanine, High Yield Radiosynthesis

P038 A NEW AUTOMATED SYNTHESIS OF (^{18}F)FLUOROETHYLCHOLINE

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Introduction: Since Hara T. et al. (*J Nucl Med.* 2002;43:187–199) first reported an automated preparation of [^{18}F]fluoroethylcholine (FECH), it has attracted attention as an alternative tracer to [^{18}F]fluoromethylcholine (FCH) for cancer detection using PET imaging. The aim of this study was to develop a more practical, automated process for production of [^{18}F]FECH.

Experimental: Using a prototype commercial synthesizer TS1 (Tracera, Zionsville, IN), [^{18}F]FECH was prepared in two steps in a 2-pot strategy. First, nucleophilic [^{18}F]fluorination of ethyleneglycol-1,2-3,4-dibromobenzenesulfonate (Musachio JL. et al., *J. Label. Compd. Radiopharm.* 2005; 48: 735-747; 2 mg) was performed in acetonitrile/K2.2.2/K_2CO_3 for 8 min at 80°C. The fluorinated product, [^{18}F]fluoroethyl-3,4-dibromobenzenesulfonate was purified by reversed-phase HPLC (Econosil C18, 250 x 10 mm, 10 μ), collected in water (10 ml) then trapped on a C-18 SPE cartridge. The product was eluted and transferred to a second reactor with acetone. The second step was N-alkylation of dimethylethanolamine (200 mg) at 80°C for 5 min. The product was held up on a cation-exchange SPE cartridge, washed with ethanol (10 mL), then water (5 mL), and finally eluted with sterile isotonic saline. All synthesis steps were monitored and controlled by a laptop computer.

Results and Discussion: [^{18}F]FECH was produced in good radiochemical yields (20-26% decay-corrected in 45 min from end of bombardment) and high radiochemical purity (99%).

Conclusion: A practical, fully automated procedure was developed to synthesize [^{18}F]FECH.

Acknowledgement: Supported in part by NIH grant (HL-63771, CA-108620) and SBIR grant, HHSN 261200522012C.

Keywords: Automated, PET, Fluoroethylcholine

P039 AUTOMATED RADIOSYNTHESIS OF (^{18}F)FAZA WITH SYNTHERA RADIOCHEMISTRY BOX

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Introduction: [^{18}F]FAZA, 1-(5-[^{18}F]fluoro-5-deoxy-α-D-arabinofuranosyl)-2-nitroimidazole, is an azomycin-based nucleoside for studying hypoxic tumors in patients and animals. There is a substantial interest in a simplified and automated radiosynthesis of this PET tracer [1–4]. Here we present a radiosynthesis of [^{18}F]FAZA using a new automated system called Synthera® (commercially available from Ion Beam Applications, Belgium).

Experimental: All reagents and solvents used were purchased from Aldrich. The tosyl-FAZA precursor was obtained from ABX. Production of [^{18}F]FAZA has been done via simplified method [1] using disposable integrated fluid processor (IFP™) followed by direct HPLC purification without removal of unreacted [^{18}F]fluoride by solid phase extraction (Fig 1).

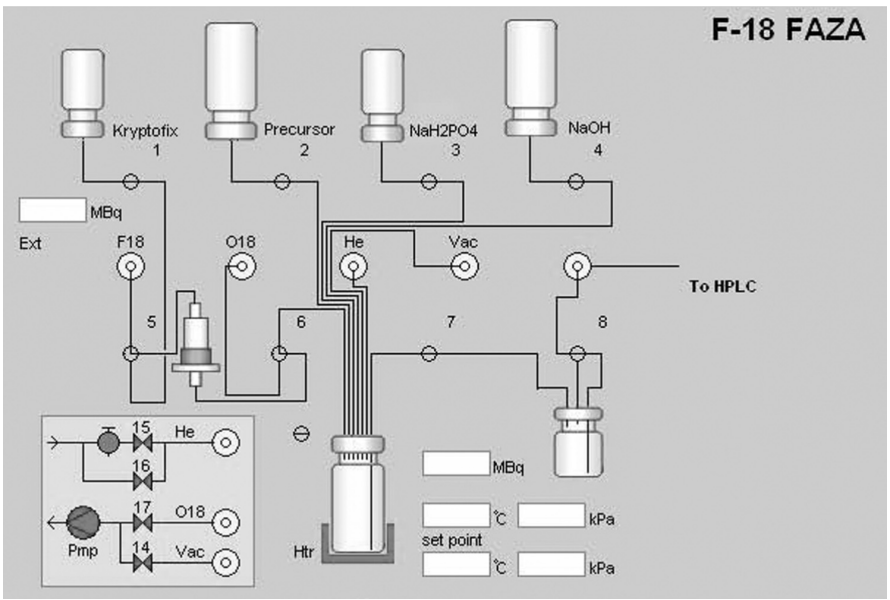

Fig. 1. Radiosynthesis of [^{18}F]FAZA with the Synthera radiochemistry box.

Results and Discussion: The radiochemical purity and radiochemical yield of the final product were >98% and 20±4%, respectively. The time of radiosynthesis is 26 min. If required, an automatic ejection of IFP™ will allow multiple production runs per day.

Conclusion: A simple, efficient and automated radiosynthesis of [^{18}FAZA has been achieved with the Synthera[reg] (IBA) radiochemistry box.

Acknowledgement: This research was supported by the Department of Radiology of Johns Hopkins University School of Medicine and IBA Molecular.

References: [1] Reischl, G.; Ehrlichmann, W.; Bieg, C.; Solbach, C.; Kumar, P.; Wiebe, L.I.; Machulla, H.J., Appl Radiat Isot 2005, 62, (6), 897-901. [2] Sorger, D.; Patt, M.; Kumar, P.; Wiebe, L.I.; Barthel, H.; Seese, A.; Dannenberg, C.; Tannapfel, A.; Kluge, R.; Sabri, O. Nucl Med Biol 2003, 30, (3), 317-26. [3] Kumar, P.; Patt, M.; Machulla, H.J.; McEwan, A.J.B.; Wiebe, L.I., [^{18}F]-FAZA: a putative PET radiotracer for hypoxia. Synthesis and Applications of Isotopically Labelled Compounds, Proceedings of the International Symposium, 7th, Dresden, Germany, June 18-22, 2000, 367-370. [4] Kumar, P.; Wiebe, L.I.; Asikoglu, M.; Tandon, M.; McEwan, A.J. Appl Radiat Isot 2002, 57, (5), 697-703.

Keywords: FAZA, Synthera

P040 RADIOLABELING AND LABELING MECHANISM OF ^{18}F-WC-II-89 FOR IMAGING CASPASE-3 ACTIVATION IN APOPTOSIS

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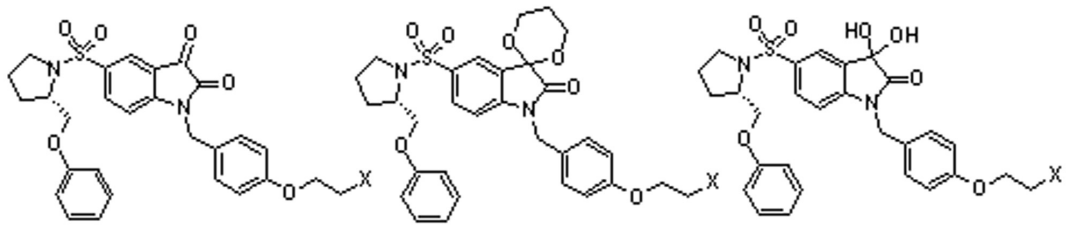
Introduction: Apoptosis, or programmed cell death, is critical for the normal development and function of multicellular organisms as a common and universal mechanism of cell death. It is a conserved process that is mediated by the activation of a series of cysteine aspartyl-specific proteases termed caspases. The abnormal regulation of cellular death via apoptosis is believed to play a key role in a variety of human diseases. In addition, the beneficial effect of antitumor drugs can be attributed to ability to activate the apoptotic process in tumor cells. Therefore, the development of a noninvasive imaging procedure that can measure caspase-mediated apoptosis with PET would be of tremendous value to imaging community.

Experimental: The isatin sulfonamide analogue, **WC-II-89**, has high potency for inhibiting caspase-3 and -7 and high selectivity against caspases-1, -6, -8 (IC_{50} (nM): Caspase-1: >50,000, Caspase-3: 9.7 ± 1.3, Caspase-6: 3,700 ± 390, Caspase-7: 23.5 ± 3.5, Caspase-8: >50,000). Therefore, **WC-II-89** is a good candidate for labeling with ^{18}F as a tracer for imaging caspase-3/7 activation in apoptosis.

Results and Discussion: Attempts to prepare **[^{18}F]WC-II-89** from the mesylate precursor **1** were not successful presumably because the nucleophilic [^{18}F]fluoride attacks the C-3 carbonyl group of the isatin ring instead of displacing the mesylate group. When the C-3 carbonyl group of isatin was protected as the ethylenedioxo ketal, **2**, labeling with [^{18}F]KF, Kryptofix[2,2,2] in DMSO proceeded rapidly to afford the intermediate **3**, which was hydrolyzed with 1N HCl to afford **[^{18}F]WC-II-89** in a radiochemical yield of 70-80%. Similarly, treatment of the mesylate precursor **1** with base (Bu_4NOH) formed the corresponding hydrate, **4**, which underwent nucleophilic displacement with [^{18}F]fluoride to give the intermediate, **5.** Hydrolysis of **5** with 1 N HCl afforded **[^{18}F]WC-II-89** in a radiochemical yield ranging from 50-90%; the total synthesis time was about 90 minutes and the specific activity of **[^{18}F]WC-II-89** ranged from 1000-4000 Ci/mmol.



Conclusion: [^{18}F]WC-II-89 can be efficiently prepared provided that the C-3 carbonyl group is protected as either the corresponding hydrate or ethylenedioxo ketal. Imaging studies in animal models of apoptosis indicate that **[^{18}F]WC-II-89** is a useful radiotracer for imaging caspase-3 activation in apoptosis.

Acknowledgement: This work was supported by HL13851 and CA121952.

Keywords: Fluorine-18, Apoptosis, PET

P041 AUTOMATED SYNTHESIS OF 16-(^{18}F)FLUORO-4-THIA-PALMITATE (FTP) AND (^{18}F)FLT USING A NEW GENERAL RADIOCHEMISTRY MODULE

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Introduction: The aim of this study was to develop a fully automated general radiochemistry module for the routine production of PET tracers, including [^{18}F]FTP (16-[^{18}F]fluoro-4-thia-palmitate) and [^{18}F]FLT.

Experimental: A two-reactor prototype commercial general fluorine-18 synthesis module (TS1, Tracera, Zionsville, IN) was developed to accomplish our goals for this study. The [^{18}F]fluorination reaction for [^{18}F]FTP was performed in acetonitrile at 110°C for 10 min using precursor methyl 16-bromo-4-thia-hexadecanote with K^{18}F/Kryptofix 2.2.2. For [^{18}F]FLT, [^{18}F]fluorination was carried out at 120°C for 20 min using precursor 3-*N*-Boc-1-[5-*O*-(4,4[apos]-dimethoxytrityl)-3-*O*-nitrophenylsulfonyl-2-deoxy-β-D-lyxofuranosyl)thymidine with K^{18}F/Kryptofix 2.2.2. Deprotection reaction was performed with 2 N KOH at 95°C for 10 min for [^{18}F]FTP and with 2 N HCl at 100°C for 10 min for [^{18}F]FLT, respectively. After neutralization, the desired product was isolated using RP-semi-preparative HPLC. Since the mobile phase for [^{18}F]FLT was composed of 5% EtOH in water, the product peak was collected directly in the product vial fitted with a 0.22μm filter. For the [^{18}F]FTP, the product peak was diluted with water, trapped on a C-18 SPE (solid-phase extraction) cartridge, and then eluted with ethanol through a 0.22mm filter to yield concentrated [^{18}F]FTP. Isotonic saline was added to reconstitute the product (ethanol contents <5%). All synthesis steps were monitored and controlled by a laptop computer. An automated self-clean cycle allows the cleaning of the system.

Results and Discussion: [^{18}F]FTP and [^{18}F]FLT were produced in good radiochemical yields (26-32% and 16-20%, respectively) and high radiochemical purities (>98%). Synthesis times were 76 min and 80 min, respectively. Back-to-back runs of same tracer or different tracers validated the effectiveness of the self-clean cycle. No cross-contamination or loss of reactivity was observed during our experiments.

Conclusion: The design of the new TS1 module allows for high configurability for the production of radiotracers with minimal effort done to physically reconfigure the module. Automated radiosynthesis produced routine tracers in quantities and quality suitable for the preclinical application in animal studies and the clinical application in human studies using PET. Applications will be expanded to include synthesis of [^{18}F]FDG, ^{18}F-labeled peptides and misonidazoles, [^{18}F]fluoroestradiol and compounds utilizing intermediates p-[^{18}F]fluorobenzylamine, p-[^{18}F]fluorobenzyliodide, p-[^{18}F]fluorobenzoic acid and [^{18}F]fluoroalkylsulfonate esters.

Acknowledgement: Supported in part by a NCI SBIR grant, HHSN 261200522012C.

Keywords: FLT, Fatty Acids, Automated Synthesis

P042 COMPARISON OF DIARYLIODONIUM SALTS AND TRIAZENES AS PRECURSORS FOR RADIOFLUORINATION

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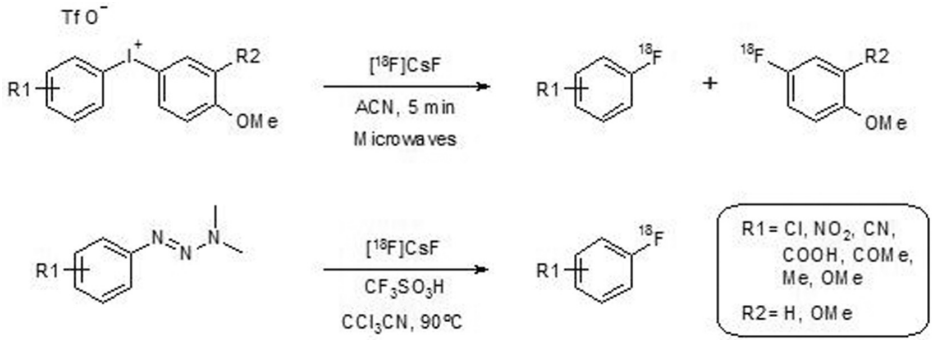
Introduction: Aromatic rings with electron-donating groups are notoriously difficult to label with [^{18}F]fluoride and successful methods for labelling typically require the use of [^{18}F]fluorine and an appropriate precursor. Unfortunately this leads to tracers that are not suitable for early phase clinical biodistribution studies and/or for the delineation of proteins *in vivo*. Diaryliodonium salts have proven to be useful for the introduction of [^{18}F]fluoride onto electron rich aromatic rings (1-2). Unfortunately, the preparation of these salts requires oxidative conditions that are not suitable for all substrates. The reaction of [^{18}F]fluoride with a diazonium salt, formed by the acidic decomposition of a triazene precursor, has been reported as an alternative (3-4), but this method requires further characterisation. The aim of this work was to compare these two methodologies to determine if the use of triazenes is a feasible alternative to the use of iodonium salts.

Experimental: [^{18}F]KF or [^{18}F]CsF was either added to a solution of a diaryliodonium triflate salt in acetonitrile or to a solution of a 1-aryl-3,3-dimethyltriazene in trichloroacetonitrile under acidic conditions (Figure). Reactions were studied using both traditional heating and microwave conditions. The reaction solutions were analysed for radiochemical products and yields by reverse phase HPLC.

Results and Discussion: Under optimized conditions ([^{18}F]CsF, 5 mg of precursor, microwaves, 100 W, 5 min), high radiochemical yields are obtained for iodonium salts bearing electron-withdrawing groups in *ortho* or *meta* position [76-97%]. The use of salts bearing electron-donating groups provides lower but potentially suitable radiochemical yields [26-52%]. In contrast, the use of triazenes resulted in poor radiochemical yields [0-8%], currently unsuitable for clinical studies.



Conclusion: Under the conditions studied to date, triazenes do not appear to offer a viable alternative to the use of iodonium salts in aromatic nucleophilic substitution reactions with [^{18}F]fluoride. Further work is ongoing to improve reaction conditions and radiochemical yields.

Acknowledgement: The authors would like to thank colleagues from GSK and the LIMBP, University of Metz, for their support.

References: [1] V.W. Pike *et al*, *JCS Chem Comm*, **1995**, 2215. [2] A. Shah *et al*, *JCS Perkin Trans 1*, **1998**, 2043. [3] T.J. Tewson *et al*, *JCS Chem Comm*, **1979**, 1149. [4] T. Pages *et al*, *J Fluor Chem*, **2001**, 329.

Keywords: Radiofluorination, Iodonium Salts, Triazenes, Microwaves

P043 NOVEL TRAPPING AND RELEASE OF (^{11}C)CO VIA COPPER(I) COMPLEXES FOR THE SYNTHESIS OF RADIOLABELLED AMIDES

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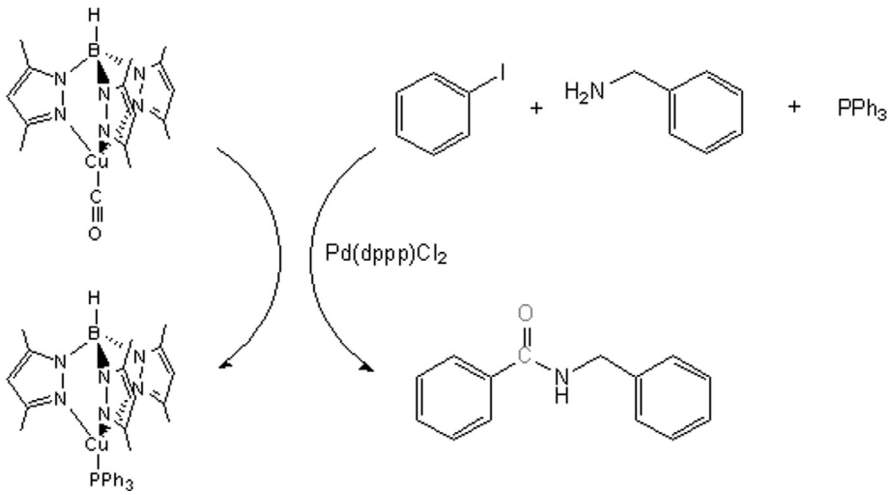
Introduction: The ubiquitous nature of carbon in biological compounds makes incorporation of [^{11}C] into tracer molecules an extremely desirable radiolabelling route. As such, [^{11}C]carbon monoxide is an important synthon in the radiolabelling of molecules for PET studies. Despite its potential, the use of [^{11}C]carbon monoxide had been limited, to date, due to difficulties of the poor solubility of CO in most organic solvents and its poor reactivity. In an attempt to address the solubilty issue, we have made use of a copper(I)tris(pyrazolyl)borate (CuTp*) solution to 'trap' the CO in solution. This CO can then be released, in a concerted fashion, by addition of a competing ligand such as triphenyl phosphine and subsequently used in palladium-catalysed cross-coupling reactions to form amides.

Experimental: A molecular seive loop was used to preconcentrate the ^{11}CO which was then swept from the loop under a stream of nitrogen. The gases were then bubbled through a suspension of potassium tris(3,5-dimethylpyrazolyl)borate and copper(I) chloride in tetrahydrofuran in a sealed glass vial with a septum cap. Subsequent cross-coupling reactions between benzylamine and aryl halides were performed in the presence of palladium catalysts and triphenyl phosphine by injection of these cross-coupling reagents into the sealed vial and heating at 90°C for 10 minutes. The products were analysed by radio HPLC.

Results and Discussion: The ^{11}CO trapping system proved to be very efficient at trapping the ^{11}CO with a 95% trapping efficiency (measured as a fraction of radioactivity in the vial versus total radioactivity in the waste gases + vial). Cross coupling reactions were performed with three different aryl halides in separate experiments (iodobenzene, 4-iodoanisole and 4-trifluoromethyl iodobenzene) and the radiolabelled amides were detected in moderate radiochemical yields.



Conclusion: We have developed a straighforward, rapid and inexpensive method of solubilising carbon monoxide for subsequent release for use in palladium-catalysed carbonylative cross-coupling reactions. This method allows the synthesis of simple [^{11}C]-labelled amides under relatively mild reaction conditions.

Acknowledgement: GlaxoSmithKline and the Department of Chemistry, Imperial College, London are thanked for their joint funding of this project.

Keywords: Carbon-11, Carbonylation, Palladium, Cross-Coupling, Positron Emission Tomography

P044 RAPID (^{11}C)CO RADIOLABELLING USING A SUPPORTED PALLADIUM CATALYST MICRO-TUBE REACTOR

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Introduction: In recent years [^{11}C]carbon monoxide has become a recognised precursor for ^{11}C-labelling because of the wide range of compounds it can be incorporated into. ^{11}CO labelling can, however, be problematic due, in part, to the poor reactivity of carbon monoxide and the difficulties with trapping ^{11}CO. To enhance ^{11}CO carbonylative cross-coupling reactions (fig. 1) we have used a continuous flow micro-tube reactor made from a silica supported palladium catalyst packed into PTFE tubing (fig .2). A series of ^{11}C-radiolabelled amides were synthesised, using this micro-tube reactor system, in reaction times of $<$10 min.

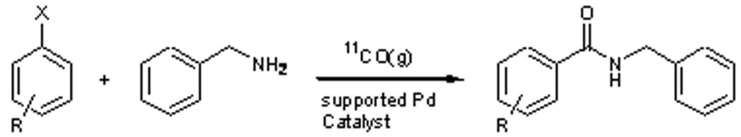

Fig. 1

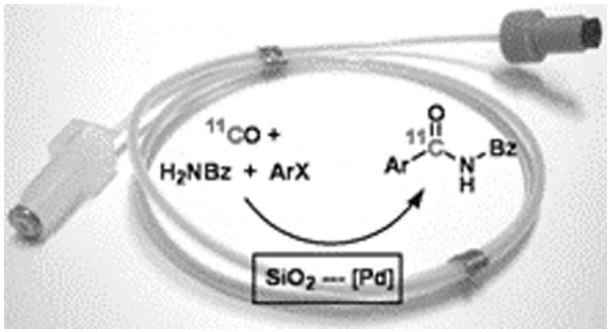

Fig. 2

Experimental: In a typical reaction, reagents (arylhalide and benzylamine) were preloaded into the micro-tube reactor and heated to 80°C. After a ^{11}CO trapping step, the ^{11}CO was released and forced through the micro-tube reactor initiating the reaction. After a 6 min reaction time, solvent was pumped through the reactor flushing off the crude labelled amide which was analyzed by analytical radio HPLC.

Results and Discussion: Four different arylhalides (iodobenzene, 4-bromobenzonitrile, 4-bromobenzotrifluoride and 4-iodoanisole) were investigated to test the micro-tube reactor system for ^{11}CO labelling. Separate micro-tube reactors were used for each different substrate and two consecutive runs carried out for each substrate. Moderate to good radiochemical yields ranging from 33-64% and purities of 70-93% for the crude products were obtained, depending on the substrate used, within *ca.* 10 min of ^{11}CO release. Consistent results were obtained between conceutive runs.

Conclusion: We have provided a simple and effective method for the synthesis of [^{11}C]amide molecules, via [^{11}C]CO carbonylation, using a continuous flow a micro-tube reactor packed with a palladium supported catalyst. We have successfully labelled a series of secondary amides, obtaining modest to good radiochemical yields and purities in short reaction times.

Keywords: Carbonylation, Positron Emission Tomography, Carbon-11, Palladium, Microfluidics

P045 NEW SYNTHESIS MODULE UTILIZING A CLOSED LOOP INSTEAD OF A FLOWTHROUGH SYSTEM

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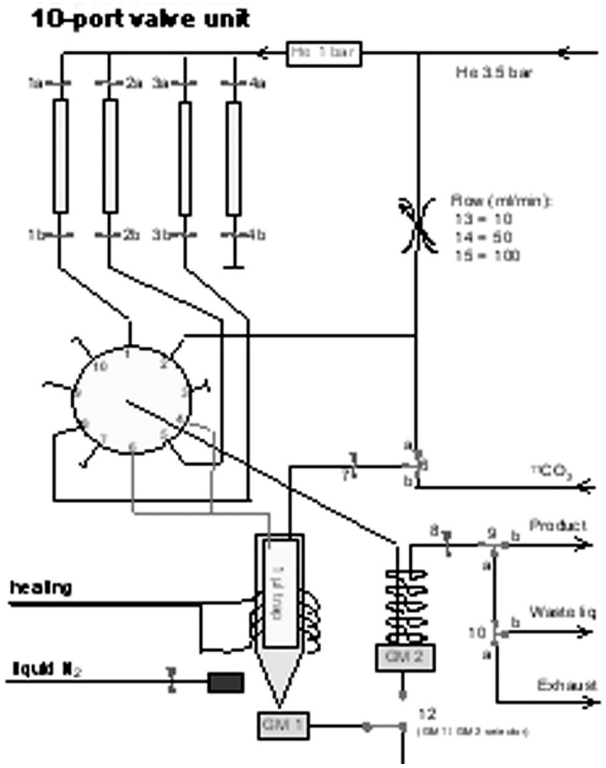
Introduction: For radiosynthesis loops are often used as a system to perform reactions. For instance coating a polypropylene loop with a grignard reagent for the subsequent reaction with $^{11}CO_2$ [1], or filling a loop with a reaction mixture after which a methylation reagent is passed through for a methylation reaction [2]. Disadvantage of these flow through systems is that the reaction time is very difficult to control.

An new automated synthesis module was developed in order to trap volatile radioactive intermediates in a closed loop, thus enabling more control over the reaction time.

Aim: The synthesis of *carbonyl*-[^{11}C]-cyclohexanecarbonyl chloride for the synthesis of *carbonyl*-[^{11}C]WAY100635, via a technically improved method.

Experimental: The 10-port valve starts in position 1. Via valve 1 dry THF is purged through the loop into the liquid waste to wash the tubing. The 10 port valve is then switched to position 2 (10p-2) to dry the reaction loop with helium and subsequently closed (10p-3). The [^{11}C]CO_2 is then transported to the unit and trapped on the 1μl silica trap [3] (Alltech Silica Gel grade 12 100/120) at -120°C (10p-4). When activity is maximal, the 10-port valve is switched to 5. Then cyclohexylmagnesium chloride is transferred from vial 2 through the reaction loop, to the waste liquid, thus coating the reaction loop with the grignard. All valves are then closed, 10p-6 and the silica trap is heated to 100°C. The [^{11}C]CO_2 is now expanding to the loop. When GM2 is at its maximum 10p-7, the loop is closed and the [^{11}C]CO_2 is allowed to react for 2 minutes. Then the valve is switched to position 8 and via valve 3 a solution of thionylchloride in THF is purged through the loop to a vial to collect the product. The collected *carbonyl*-[^{11}C]-cyclohexanecarbonyl chloride was reacted with morpholine to yield the corresponding amide.

Results and Discussion: Initial experiments showed that the desired product, *carbonyl*-[^{11}C]-cyclohexanecarbonyl chloride, was obtained in yields up to 45%, as shown by the control reaction with morpholine.



Conclusion: It was shown that this module can be used for the synthesis of *carbonyl*-[^{11}C]-cyclohexanecarbonyl chloride from [^{11}C]CO_2. Although there is room for improvement, the principle works and might be utilized for several types of volatile radiochemical intermediates, as long as they can be trapped on the 1μl silica trap.

Keywords: C11, Loop Synthesis, Automation

P046 SYNTHESIS AND EVALUATION OF ([18F)F-PECMO AS A PET LIGAND FOR IMAGING THE METABOTROPIC GLUTAMATE RECEPTORS SUBTYPE 5 (mGluR5)

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Introduction: Metabotropic glutamate receptor subtype 5 (mGluR5), which belongs to class 1 of mGluRs, is recognized as involved in numerous brain disorders such as pain, epilepsy, focal and global ischemia and neurodegenerative diseases. To date, no [^{18}F] labeled useful PET ligands as been reported for the *in vivo* imaging of these glutamate receptors in humans. As part of our program to develop a [^{18}F] labeled PET tracer, we synthesized fluor-18 labeled (*E*)-3-((6-fluoropyridin-2-yl)ethynyl)cyclohex-2-enone *O*-methyl oxime ([^{18}F]FPECMO) and evaluated it potential for PET imaging.

Experimental: The radiosynthesis of ([^{18}F]F-PECMO) was accomplished by an aromatic nucleophilic substitution on a bromo precursor as depicted in Scheme 1. The appropriate starting material in DMSO was added to dry K_{222}-K^{18}F and heated at 120°C for 30min. After adding water to the reaction mixture, the crude was purified by reversed-phase HPLC using a Waters C18-μBondapak column with a mobile phase consisting of H_2O/MeCN (65/35) with 1% (v/v) H_3PO_4, at a flow of 3.7ml/min. The pure compound was collected from HPLC over a C18 SepPak cartridge which was then washed with water to remove MeCN. The labeled tracer was removed from the cartridge with 2ml of EtOH. After evaporation of the solvent, the tracer was formulated in 4ml of 5% EtOH in water. The total synthesis time was 80min and the radiochemical purity was over 98%.

Results and Discussion: Radiochemical yield was on average 25% and specific radioactivity was greater than 500GBq/μmol. Using the shake-flask method with octanol and phosphate buffer (0.15M, pH 7.4), a logD value of 2.1 was obtained for [^{18}F]FPECMO.

Scheme 1. Radiosynthesis of [^{18}F]-FPECMO

Conclusion: Scatchard analysis of [^{18}F]FPECMO binding to rat brain homogenates revealed a high affinity binding site with a K_D of 3.7 ± 0.3 nM. Further characterization of this new tracer including autoradiography and PET imaging is in progress.

Keywords: mGluR5, PET, [^{18}F]-FPECMO

P047 ATTEMPTED SYNTHESIS OF (^{18}F)FLT FROM 3'-SULFONYLESTERS OF 2,5'-ANHYDRO-1-(2-DEOXY-β-d-*THREO*-PENTOFURANOSYL)THYMINE

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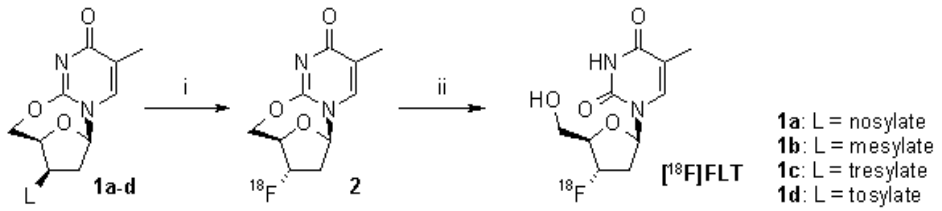
Introduction: Since the first introduction in human subjects in 1998 [1], ^{18}F labelled 3'-deoxy-3'-fluorothymidine, [^{18}F]FLT, has drawn a lot of attention in oncology as a marker for cell proliferation, both in clinical as in preclinical research. Despite considerable improvements achieved by Grierson [2], Machulla [3] and Martin [4] the synthesis of [^{18}F]FLT remains tedious. Yields are relatively low (5-20%, decay corrected) and are not very reproducible.

Aim: The aim was to develop a fast synthesis method to produce [^{18}F]FLT without the need of HPLC purification using commercially available FDG synthesis modules.

Experimental: The 3'-sulphonyl esters (**1a-d**) were synthesized [5] and subsequently subjected to a radiofluorination according to scheme 1.



Scheme 1. Synthesis of [^{18}F]FLT. (i): (Kryptofix[2.2.2], $KHCO_3$, DMSO or CH_3CN) or (Kryptofix[2.2.2], K_2CO_3, DMSO or CH_3CN) or ((*n*-Bu)$_4NH_4CO_3$, DMSO or CH_3CN), 5-15 min, 100-120°C, 50-70%; (ii): 0.1-1M NaOH, 2 min, 100°C, 100% or 0.1-1M NaOH on solid phase, 10 min RT, 100%.

Results and Discussion: Starting from 3'-(4-nitrobenzenesulfonyl)-2,5'-anhydro-3',5'-dideoxythymidines **1a** [5] and [^{18}F]fluoride yielded a labelled compound up to 76%. Subsequent quantitative basic hydrolysis, either in solution or on solid phase, yielded a compound with the same Rf-value as [^{18}F]FLT on TLC. Careful analysis with 2 different HPLC analysis systems revealed that this product did not co-elute with [^{18}F]FLT.

Surprisingly starting with other 3' substituted 2,5'-anhydro-3',5'-dideoxythymidines **1b-d**, the yields were less then 5%. After subsequent basic hydrolysis also these compounds did not co-elute with [^{18}F]FLT.

Conclusion: Unfortunately it had to be concluded that the in high yield obtained product was not [^{18}F]FLT and 3'-sulphonyl esters **1a-d** are not suited as starting materials for the synthesis of [^{18}F]FLT. Investigations regarding the indentification of the 76% yielding intermediate product are ongoing.

References: [1] A.F.Shields *et al*, Nature Medicine, **1998**, 4, 1334-6. [2] J.R. Grierson *et al*, Nucl. Med. & Biol., **2000**, 27, 143-56. [3] H.J. Machulla *et al*, J. Radioanal. & Nucl. Chem., **2000**, 243,843-6. [4] S.J. Martin *et al*, Nucl. Med. Biol., **2002**, 29, 263-73. [5] J. Eisenbarth *et al*, PCT WO 03/018599A1, **2003**.

Keywords: 18F, FLT, Radiosynthesis, Positron Emission Tomography

P048 SYNTHESIS OF ([18]F)FLT USING THE SYNTHERA SYNTHESIS MODULE

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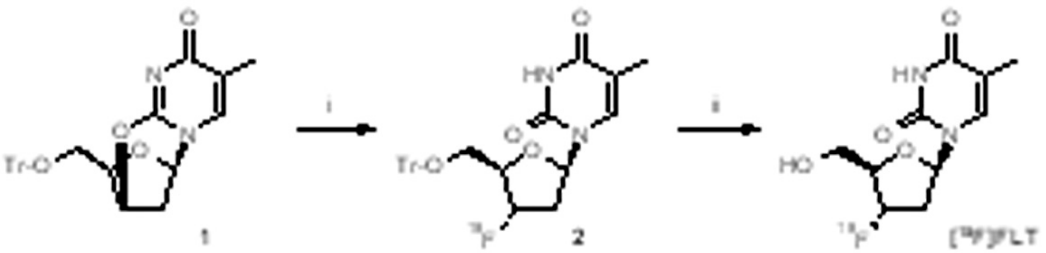
[1]Nuclear Medicine & PET Research, VU University Medical Center, Amsterdam, Netherlands; [2]IBA Molecular, Sterling, VA, USA; [3]BV Cyclotron VU, Amsterdam, Netherlands

Introduction: Especially in a GMP routine production situation a highly reliable synthesis method with reasonable yields is very important. The Synthera® synthesis module, recently presented by IBA Molecular provides an IFP™ (Integrated Fluidic Processor) based synthesis system for FDG. Major advantages of this synthesis module are its compact size, ease of use and its versatile multi run capabilities. Given the increased need for [18]F]FLT this synthesis module could provide a good platform for the routine synthesis of [18]F]FLT upon modification of the applied IFP™.

The aim of this research is to develop a reliable synthesis method of [18]F]FLT on the Synthera® synthesis module, applying a custom IFP™ based on an adapted method from Machulla *et al* [1].



Scheme 1. Synthesis of [18]F]FLT. (i): (Kryptofix[2.2.2], KHCO, DMSO, 15 min, 160°C; (ii) 1 N HCl, 5 min, 100°C.

Experimental: Synthera® FDG synthesis module from IBA was used for the production of [18]F]FLT. The standard disposable [18]F]FDG IFP™ was adapted for the [18]F]FLT synthesis as follows: Valve 1 was connected to needle 1, valve 3 was connected to needle 3 and the [18]F]FDG purification cartridges were replaced by a Waters SAX and a Silica plus cartridge (figure 1).

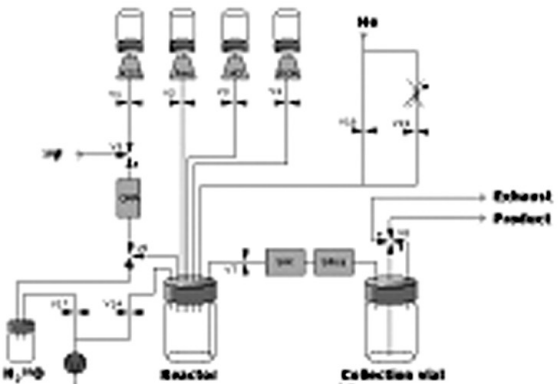


Fig. 1. Scheme of the [18]F]FLT IFP.

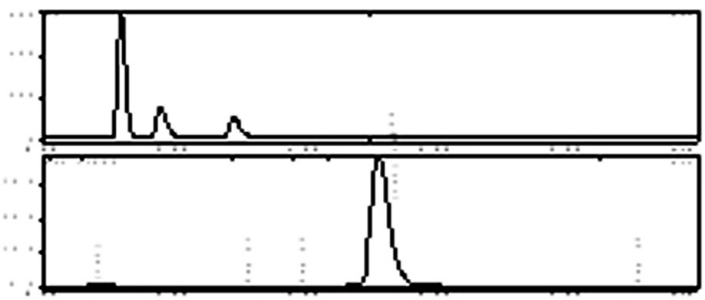


Fig. 2. Analytical HPCL of cartridge purified reaction mixture. Chromolith Performance RP-18e 100*4.6 mm; 7.5% MeOH in water; 3 ml/min; 254 nm. Ri. of [18]F]FLT: 53 minutes.

Results and Discussion: [18]F]FLT was synthesized according to the reaction and conditions as depicted in scheme 1. After addition of ethanol to the reaction mixture, it was pre-purified by the SAX and Silica plus cartridge. The decay corrected yield was 16±7%. (n=4) and radiochemical purity > 98% (figure 2, n=3). Purification was achieved by already described methods using semiprep HPLC on a Luna C18(2), 10 μm, with 10% of ethanol in saline (data not shown).

Conclusion: A method was developed for the IFP™ based preparation of [18]F]FLT on a Synthera synthesis module. Although the yields are not high, and average as compared to literature, the method provides means for a fast repetitive synthesis of [18]F]FLT.

References [1] H.J.Machulla *et al*, Radioanal. & Nucl. Chem., **2000**, 843-846.

Keywords: [18]F]FLT, Automation, Synthera, Radiosynthesis

P049 AUTOMATED SYNTHESIS OF 4-(^{18}F)-ADAM AND ITS APPLICATION IN HUMAN STUDIES

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Introduction: Abnormalities in serotonin transporters (**SERTs**) have been implicated in several neuropsychiatric disorders and are the target for antidepressants. For the last decade, [^{11}C]-(+) McN5652 has been the most promising PET agent for studying SERTs in humans. However, this agent has high nonspecific binding and has only moderate signal contrast in human PET studies. Additionally, its pharmacokinetics are not optimal because of its slow brain uptake and the short half-life of ^{11}C. We recently reported that N,N-dimethyl-2-(2-amino-4-[^{18}F]fluorophenylthio)-benzylamine (4-[^{18}F]-ADAM) is a potent SERTs imaging agent. In order to fulfill the demand of clinical studies, we have developed an automated synthesis module to synthesize and to test the feasibility of using this agent as a SERT imaging agent in human studies.

Experimental: The automated synthesis module of 4-[^{18}F]-ADAM is a home-modified nuclear interface commercial apparatus which comprised both nucleophilic and electrophilic substitution reactions apparatus. The reaction sequences involved in the synthesis are similar to that of the reported manual synthesis, i.e. nucleophilic substitution of the nitro-precursor with K[^{18}F]/K2.2.2 followed by reduction with $NaBH_4$/$Cu(OAc)_2$, and purifications with HPLC and Sep-Pak extration. The PET scanner used for this study was ECAT EXACT HR+ (Siemens Medical Solutions USA, Inc). The radiotracer was injected i.v. as a bolus to a subject and dynamic scan for 90 min. Binding parameters were determined with Logan plots using cerebellum as reference.

Results and Discussion: The radiochemical yield of 4-[^{18}F]-ADAM synthesized by this module is not optimized and is relatively low (2-5% EOB). The specific activity is 1.3-2.2 Ci/μmol and the synthesis time is 120 min from EOB. The radiochemical and chemical purities are $>$ 95 and 98%, respectively. The solvent residues in the final formulation are CH_3CN $<$ 0.04%; C_2H_5OH $<$ 2%; DMSO, n.d. The final product is stable for more than 4 hr at rt and is sterile and pyrogen free. PET studies in humans showed that 4-[^{18}F]-ADAM had high uptake in raphe nucleus (RN), thalamus (Th), striatum (Str), intermediate uptake in frontal cortex (FC), occipital cortex (OC) and low uptake in cerebellum (CB). The DVR for RN, Th, Str, FC and OC was 3.53, 2.73, 2.39, 1.57 and 1.59, respectively.

Conclusion: The automated synthesis module has been used routinely to synthesize 4-[^{18}F]-ADAM in useful quantities for clinical studies. The same module also can be used to synthesize other F-18 labeled SERTs imaging agents, such as AFM and AFE. Preliminary studies in humans showed that 4-[^{18}F]-ADAM is a potent SERTs imaging agent for human studies.

Acknowledgement: This research was supported by the National Science Council of Taiwan, Grants NSC 95-2811-B-016-002 and NSC95-2321-B-016-001-MY2.

Keywords: 4-[^{18}F]-ADAM, Serotonin Transporters, PET Radiopharmaceuticals, Automated Synthesis Module

P050 NUCLEOPHILIC ^{18}F-RADIOFLUORINATION BY A MODIFIED MICROWAVE REACTOR SYSTEM

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Introduction: One of the most critical aspects of the sequence of events in a PET research is labeling the compound of interest. The short half-lives of the positron emitting radioisotopes led researchers to employ the use of microwave in the radiosynthesis process. In this study, a microwave reactor setup has been modified to suit the requirements for radiolabeling process, also taking into consideration the ease of operation and minimal operator exposure.

Experimental: A microwave reactor system has been modified to perform open or closed system reactions. The system was also designed for stop and flow operation with the use of a 6-way valve which then provides for easy transfer of the end-product for purification. The system is able to run in a completely sealed condition, hence it is suited for pressurized reactions as it can accommodate upto 20 atm of inside pressure. Preliminary studies conducted in this system includes the preparation of dry [K/K222]$^{+}$ $^{18}F^{-}$ complex and [^{18}F]-radiofluorination of nitro-aromatic compounds.

Results and Discussion: Progress was made in the preparation of dry [K/K222]$^{+}$ $^{18}F^{-}$ complex in only 1 min time. Traditional azeotropic drying was eliminated, in accordance with the previous study done by Gomzina, et al, using K222/K_2CO_3 solution in 96% Acetonitrile[1]. Furthermore, microwave assisted radiofluorination of nitro-aromatic compounds were investigated and the yields were compared with previous reports. One of the nitro compound studied is the nitro-analog of flumazenil. The integration of microwave in the radiofluorination step is a modification made to the radiosynthesis of [^{18}F]Flumazenil developed by Ryzhikov et al[2]. At present, an incorporation yield ranging from 38 -57% could be obtained at a 10 min reaction time in DMF at a temp of 140-160°C with an average microwave power of 25-65 W (peak at 300 W). Acetonitrile and DMSO, as solvent, were also studied but gave lower yield as compared to the DMF reaction.

Conclusion: The modified setup for microwave assisted radiofluorination offers fast reaction time and simplicity in operation. The system is robust, flexible and can easily be manipulated to produce other desired radiopharmaceuticals. Hence, future work is also geared towards nucleophilic substitution of other leaving groups in aromatic compounds with [^{18}F]Fluoride ion.

References: [1] Gomzina NA, Zaitsev VV, Krasikova RN. *J Label Compd Radiopharm.* 2001; 44: S895-97. [2] Ryzhikov NN, Seneca N, Krasikova RN, et al. *Nuc Med Biol.* 2005; 32: 109-16.

Keywords: [^{18}F]Flumazenil, Microwave, [^{18}F]-Radiofluorination, Fluorine-18, Nucleophilic

P051 USE OF LYSINE AS TRIFUNCTIONAL SYNTHON ALLOWING COUPLING OF TWO PHARMACOPHORES AND A RADIOLABEL

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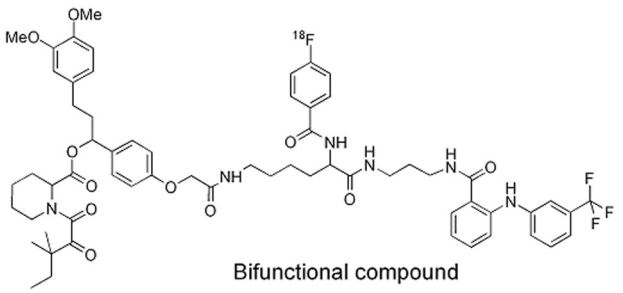
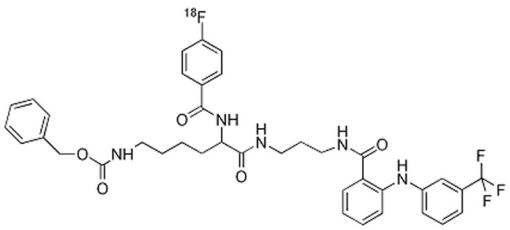
Introduction: We have been synthesizing bifunctional ligands for a number of potential imaging applications including β-amyloid and chaperone proteins. We have searched for a general method for preparing analogues of these bifunctional ligands that were amenable to radiolabeling with positron emitting radionuclides. In this work, we utilized lysine as a linking agent between two different ligands. The carboxylate and ε-amine were used for linking of two different ligands and the α-amine was available for attaching a radiolabel. We also exploited the versatility of the diethyl cyanophosphonate reagent for coupling [^{18}F]fluorobenzoic acid to a variety of amines.

Experimental: Standard chemical synthetic methods were employed to make the requisite ligands. Ligands were designed to have a single reactive amine. Radiofluorination was accomplished by initial radiosynthesis of [^{18}F]fluorobenzoic acid from pentamethylbenzyl 4-trimethylammoniumbenzoate triflate. Subsequent hydrolysis of the ester was accomplished with trifluoroacetic acid. The acid is coupled to the unprotected primary amine using diethylcyanophosphonate as a coupling reagent. The desired product with every amine coupling was isolated by preparative HPLC with good radiochemical yields and high radiochemical purity. This radiochemical synthetic method proved versatile and could be completed in 45 min.

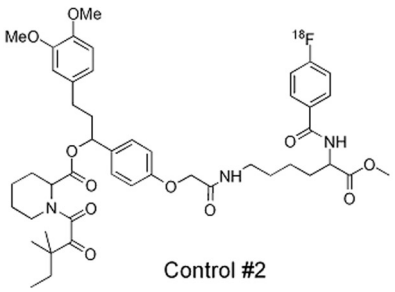
Results and Discussion: We prepared bifunctional ligands, in which the two pharmacophores were coupled employing an appropriately protected lysine to allow eventual exposure of the α-amine. The coupling of the primary amine with [^{18}F]fluorobenzoic acid, using the method previously used for [^{18}F]fluoropaclitaxel, provided the radiochemical product. Realized radiochemical yields for the desired coupled products ranged between 8% and 42%.



Bifunctional compound



Control #1



Control #2

Conclusion: The use of a lysine, a trifunctional linker, allowed coupling of two ligands possessing pharmacophores to bind to two different targets and provided a primary amine for incorporation of a radiolabel. The incorporation of [^{18}F]fluorobenzoic aicd onto this primary amine was accomplished using diethylcyanophosphonate as the coupling reagent.

Acknowledgement: Funding provided by the Intramural Research Program of the NIH.

Keywords: Fluorine-18, Chaperone, Beta-Amyloid

P052 ^{18}F)FLUOROPROPYLSULFONYL CHLORIDE: A NEW REAGENT FOR RADIOLABELING PRIMARY AND SECONDARY AMINES FOR PET IMAGING

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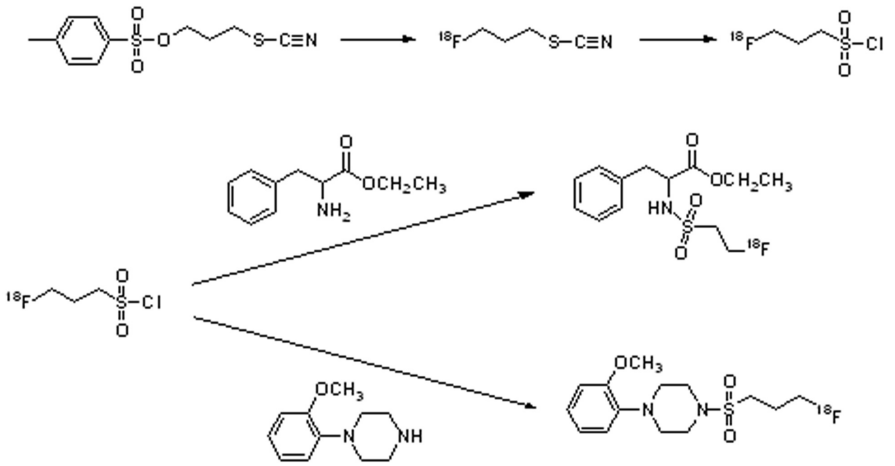
Introduction: Noninvasive molecular imaging using positron emission tomography (PET) is playing an increasing role in monitoring biochemical changes *in vivo* in various diseases. Despite the increasing reliance of the biomedical science on imaging, the development of new radiopharmaceuticals for PET remains a slow process. One bottleneck is the limited methods available for introduction of radionuclide into biologically interesting molecules. In this work, we developed F-18 labeled fluoropropylsulfonyl chloride that can be used for the efficient radiolabeling of molecules containing a primary or secondary amine.

Experimental: [^{18}F]]Fluoropropylsulfonamides were synthesized in a three-step reaction beginning with treatment of 3-toluenesulfonyloxypropyl thiocyanate with [^{18}F]fluoride and Kryptofix[2.2.2.]. The product, [^{18}F]fluoropropyl thiocyanate was trapped on a C-18 column. Chlorine gas, which was passed through the column for two minutes, converted the thiocyanate into a sulfonyl chloride. Purging with argon followed by elution of [^{18}F]fluoropropylsulfonyl chloride with methylene chloride into a solution of an appropriate amine provide the [^{18}F]fluoropropylsulfonamide products. The primary amine, 1-phenylalanine ethyl ester hydrochloride and the secondary amine, 1-(2-methoxyphenyl)-piperazine were radiolabeled using this reaction. The final products were purified by HPLC.

Results and Discussion: Optimal reaction conditions were determined for each step and all the reactions had very good reproducibility. The optimized three-step procedure required 90 min from delivery of aqueous [^{18}F]fluoride until isolation of product. The overall yield for the radiolabeling of 1-phenylalanine ethyl ester hydrochloride was 16.4 ± 8.1% (n=6, EOB) and the radiolabeling of 1-(2-methoxyphenyl)-piperazine was 22.8 ± 9.2 (n=6, EOB).



Conclusion: A new method was developed to radiolabel primary and secondary amines with F-18 by using [^{18}F]fluoropropylsulfonyl chloride. This method provides a useful and easy way to make new F-18 labeled radiopharmaceuticals for PET imaging.

Acknowledgement: The funding was provided by intramural program of National Institutes of Health.

Keywords: F-18, Amine, PET

P053 R AND S (^{18}F)FPMPA: NUCLEOTIDE ANALOGUE REVERSE TRANSCRIPTASE INHIBITOR FOR BIODISTRIBUTION STUDIES

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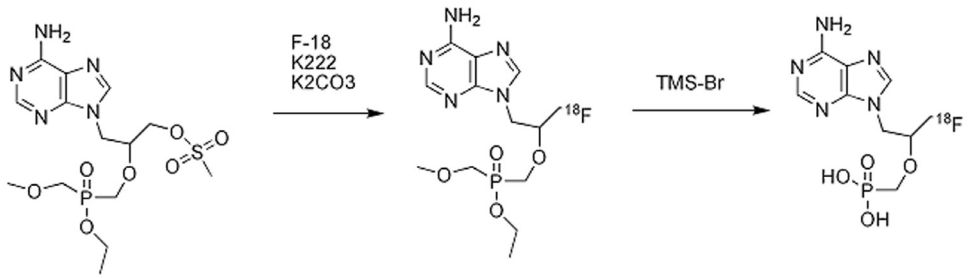
Introduction: PMPA **(9-(*R*)-2-(phosphonomethoxypropyl)adenine (Tenofovir)),** a nucleotide analogue reverse transcriptase inhibitor, is often included in the antiretroviral regimens of HIV infected patients. We wished to prepare a radiolabeled analogue for use in determining the in vivo biodistribution of the drug under conditions of chronic treatment. The fluorine-containing analogue has previously been synthesized and found to exhibit similar biological activity [Balzarini, 1993]. We have developed radiochemical syntheses of both R and S enantiomers of this fluorinated analogue for use as PET imaging agents.

Experimental: The synthetic sequence followed literature precedent. The chirality was introduced in the first step by reaction of adenine with R or S glycidyl butyrate. Following the hydrolysis of the ester, the terminal hydroxyl group and the primary amine were protected with trityl groups [Webb, 1987]. The methyl phosphonate was then introduced using anion chemistry as the diethyl ester. The trityl groups were removed and the resulting primary alcohol activated as a methanesulfonate. Radiofluorination was achieved using standard conditions with Kryptofix/K_2CO_3. The diethylphosphonate was deprotected by treatment with bromotrimethylsilane. The final product was purified by HPLC.

Results and Discussion: Both enantiomers of **9-[2-(phosphonomethoxy-3-[^{18}F]fluoropropyl)adenine] (FPMPA),** were prepared in similar radiochemical yields; 42 and 37% (corrected for decay) for S and R, respectively (n = 3); and in a synthesis time of approximately 60 min. The products had high radiochemical and enantiomeric purity as demonstrated by HPLC analysis of isolated product. The preparative HPLC method allowed use of the product for biological studies without isolation from the eluate.



Conclusion: We prepared both enantiomers of the chiral methanesulfonate analogue of PMPA and converted into the corresponding enantiomers of [^{18}F]FPMPA in an efficient incorporation reaction. Following deprotection, the products were obtained in high radiochemical and enantiomeric purity.

Acknowledgement: Funding provided by the Intramural Research Program of the NIH.

References: [1] Balzarini J et al. Antimicrobial Agents and Chemotherapy, 1993, 37: 332-338. [2] Webb RR and Martin JC, Tetrahedron Lett., 1987, 42: 4963-4964.

Keywords: Fluorine-18, Tenofovir, HIV

P054 SYNTHESIS AND REACTIVITY OF N-(^{18}F)FLUOROBENZENESULFONIMIDE

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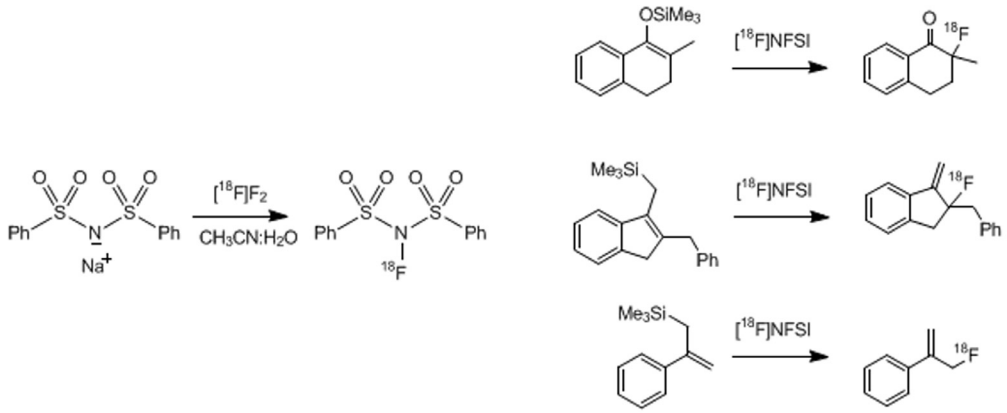
Introduction: The increasing use of Positron Emission Tomography (PET) for clinical diagnosis, drug development and biological research has prompted many chemists to develop new labelling and purification methods [1]. ^{18}F stands out as being a particularly useful positron emitting isotope because of its advantageous half-life of 110 minutes, enabling relatively complex synthetic sequences to be carried out after fluorination. Specifically, electrophilic fluorination offers exciting opportunities to access ^{18}F-labelled compounds unattainable via nucleophilic fluorination [2]. Much attention has been devoted to the synthesis and reactivity of electrophilic fluoronitrogen reagents [3], however few ^{18}F-labelled NF reagents are known to date [4]. The aim of this research was to prepare additional labelled N-F reagents and study their reactivity with the aim of expanding the repertoire of available labelling processes. We focused our attention on N-fluorobenzenesulfonimide (NFSi), a reagent commonly used to access various fluorinated compounds including drug-like targets [5].



Results and Discussion: [^{18}F]N-Fluorobenzenesulfonimide (^{18}F-NFSI) was efficiently prepared in good yield by passing [^{18}F]F_2 through an CH_3CN/H_2O [9/1] solution of sodium dibenzenesulfonimide. Three model substrates, that are known to react with electrophilic sources of fluorine, were selected to test the reactivity of ^{18}F-NFSI and the results of these studies will be presented.

References: [1] For a reference book on the subject, see: Handbook of Radiopharmaceuticals, Radiochemistry and Applications; Editors Michael J. Welch and Carol S. Redvanly **2003** John Wiley & Sons Ltd England. [2] Singh, R.P.; Shreeve, J.M.; *Acc. Chem. Res.*, **2004**, *37*, 31; Nyffeler, P.T.; Duron, S.G.; Burkart, M.D.; Vincent, S.P.; Wong, C.-H.; *Angew. Chem. Int. Ed.*, **2005**, *44*, 2708. [3] Lal, G.S.; Pez, G.P.; Syvret, R.G.; *Chem. Rev.*, **1996**, *96*, 1737. [4] Oberdorfer, F.; Hofman, E.; Maier-Borst, W.; *J. Label. Compd. Radiopharm.*, **1988**, *25*, 999; Oberdorfer, F.; Hofman, E.; Maier-Borst, W.; *Appl. Radiat. Isot.*, **1988**, *39*, 685. [5] Boger, D.L.; Brunette, S.R.; Garbaccio, J.; *J. Org. Chem.*, **2001**, *66*, 5163.

Acknowledgement: The BBSRC (Industrial Studentship HT BBS/S/M/2005/12407), and the Hammersmith Imanet are gratefully acknowledged for generous financial support.

Keywords: Electrophilic Fluorination, [^{18}F]N-F Reagent, Fluoroketone, Allylic Fluoride

P055 SYNTHESIS AND MICROWAVE ^{18}F LABELING REACTIVITY OF AROMATIC DERIVATIVES: 3-SUBSTITUTED-5-METHYLBENZONITRILE

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Introduction: Microwave methods for PET radiolabeling chemistry can be used to achieve rapid and efficient ^{18}F incorporation into tracer molecules. Nucleophilic aromatic [^{18}F]fluorination normally requires a leaving group activated at the *ortho* or *para* position for reaction to occur. To achieve efficient [^{18}F] labeling of non-activated aromatic ring, a single-mode dedicated chemistry microwave was incorporated into a commercial fluorination module (GE Medical TRACERlab® FX-$_{FN}$). Representative *meta*-substituted-benzonitrile derivatives analogous to the mGluR5 ligand F-MTEB (-NMe_3, -NO_2, -F, -Cl, -Br and -I) were synthesized to test the effect of the leaving group on microwave-accelerated nucleophilic fluorination.

Experimental: [^{18}F]-fluoride (30–100 mCi) produced on a Siemens 11 MeV RDS 112 cyclotron was transferred to the TRACERlab® module for ^{18}F trapping on an ion exchange cartridge (QMA). The QMA cartridge was eluted with a 1/1 (v/v) CH_3CN/H_2O solution containing Kryptofix-222 and K_2CO_3 directed to a 5-mL V-vial contained in the cavity of the microwave accelerator (Resonance Instruments Model 521A). After evaporation under $N_2(g)$ flow and microwave irradiation and additional CH_3CN addition (3x), precursor (0.037 mmol) was added in DMF or DMSO (0.3 mL). The reaction was induced by a sequence of 20 s, 150 W microwave pulses.

Results and Discussion: Initial experiments showed that the reaction proceeded more readily in DMSO than in DMF. Highest ^{18}F incorporation was observed with NO_2 (70%) and F (64%), with lower reactivity for Br and Cl. No ^{18}F labeling was obtained with the iodo compound under any conditions (Table 1).

Table 1. Effect of leaving group and microwave pulse on ^{18}F labeling in DMSO

	^{18}F Incorporation (%) (mean ± SD of 3 independent runs)		
Substituent	1st pulse	2nd pulse	3rd pulse
–NO_2	41± 29	58 ± 12	70 ± 4
–F	48 ± 16	58 ± 15	64 ± 11
–Cl	4 ± 3	7 ± 1	9 ± 3
–Br	3 ± 2	13 ± 3	13 ± 1
–I	0 ± 0	0 ± 0	0 ± 0

Conclusion: The results indicate that the order of reactivity of leaving group toward non-activated aromatic nucleophilic substitution is NO_2>F>>Br>Cl>>I. High radiochemical labeling yields were obtained with the nitro- and fluoro-substituted derivatives in a semi-automated module well suited for further purification and isolation as radiotracers.

Acknowledgement: National Institute of Health (NCI R25T-CA092043) and Vanderbilt University, Department of Radiology & Radiological Sciences.

Keywords: Fluorine-18, Radiolabelling, Microwave, PET Tracer, Substituent Effect

P056 PALLADIUM(0) CATALYSED CARBONYLATION REACTIONS WITH (^{11}CO): UPDATE ON THE BH_3.^{11}CO METHOD AND APPLICATION

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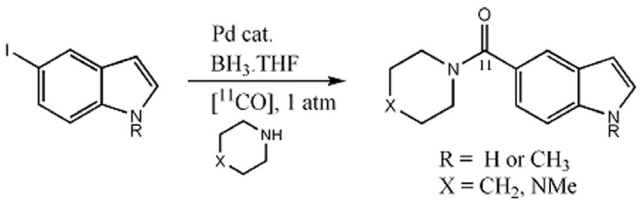
Introduction: In PET-chemistry, the use of [^{11}C]carbon monoxide represents an interesting avenue to a whole range of PET probes like amides, esters, lactams and lactones. Because of the poor trapping of carbon monoxide in solution, these target molecules are not easy to synthesize, especially when micromolar scale reactions are used. In a previous work, we found that the complexation of carbon monoxide to BH_3 could be applied to the radiochemistry field as a way to trap and deliver [^{11}C]CO and make it react in palladium catalysed reactions in order to make amides, without the need of specialized equipment like autoclaves [1].

Experimental: BH_3.^{11}CO is made online by reacting [^{11}C]CO with a BH_3.THF solution and trapped at -78°C in a vial containing the reactants for a palladium catalyzed aminocarbonylation. The amides are then synthesized after heating the vial for 10 to 15 minutes.

Results and Discussion: The aminocarbonylation of various iodo-aryl using BH_3.^{11}CO as a source of [^{11}C]CO and methylamine or benzylamine as nucleophiles, in the presence of a palladium(0) catalyst, a base and in solution in THF (containing 1% water) has been studied. The expected amides were obtained in moderate to good radiochemical yields and with good radiochemical purities. The method appears suitable for the general synthesis of other amides of biological interests for PET imaging. As an example, we will present as well the results obtained when using haloindoles as starting material which could give rise to the synthesis of CNS active amphetamine derivatives (Scheme 1) [2].



Scheme 1

Conclusion: The method described here allows the [^{11}C]carbonylation of a large range of halo-aryls at atmospheric pressure. Improving of the set-up is under way with the use of microreactors, or loop systems made of Teflon tubings.

References: [1] H. Audrain, L. Martarello, A. Gee, D. Bender, *Chem. Commun.*, 2004, 558-559. [2] K. Kumar, A. Zapf, D. Michalik, A. Tillack, T. Heinrich, H. Böttcher, M. Arlt, M. Beller, *Organic Letters*, 2004, 7-10.

Keywords: PET, [^{11}C]Carbon Monoxide, Carbonylation

P057 AN AUTOMATED RADIOSYNTHESIS OF THE β-AMYLOID IMAGING RADIOTRACER N-METHYL-(^{11}C)2-(4′-METHYLAMINOPHENYL)-6-HYDROXYBENZOTHIAZOLE ((^{11}C)PIB)

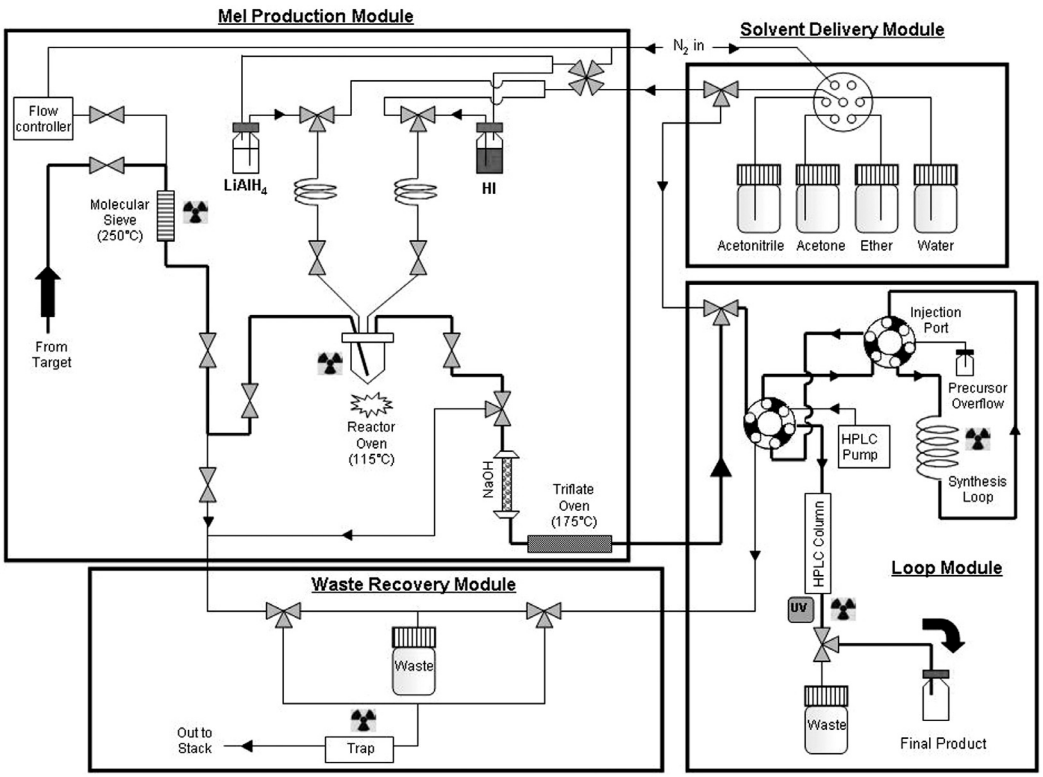
M. VERDURAND [1,2,3], G. BORT [1], V. TADINO [4], C. TOURVIEILLE [1], F. BONNEFOI [1], D. LE BARS [1] and L. ZIMMER [1,2]

[1]PET Department, CERMEP – Imagerie du Vivant, Lyon, France; [2]Laboratoire de Neuropharmacologie, Universite Lyon 1, Lyon, France; [3]Research Department, Advanced Accelerator Applications, Saint Genis Pouilly, France; [4]Bioscan, Washington, DC, USA

Introduction: The Pittsburg Compound B ([^{11}C]PIB) is a radiotracer for imaging amyloid plaques in Alzheimer's disease by PET. A simple, rapid and fully automated preparation of [^{11}C]PIB was achieved with the coupling of two commercial synthesizers designated for automated 11C methylations in an HPLC loop.

Experimental: Carbon-11 is initially produced at the cyclotron in the form of [^{11}C]CO2 by the 14N(p,α)11C nuclear reaction. [^{11}C]CH3I is then obtained from [^{11}C]CO2 by an automatic synthesis module using LiAlH4 in THF and HI. [^{11}C]MeOTf is automatically generated by reaction of [^{11}C]CH3I with silver trifluoromethanesulfonate and Graphpac mixed together in a quartz glass column and heated at 175°C. The automated methylation labelling system is based on the "loop method". The [^{11}C]MeOTf is swept into the HPLC loop coated with precursor solution. When activity peaks in the loop, the flow is stopped and the reaction allowed to proceed. The products of the reaction are transferred by passing mobile phase to a semi-preparative HPLC system. Total [^{11}C]PIB synthesis time is less than 20 min.

Results and Discussion: After optimization of the reaction parameters (modules drying, solvents, precursor amount and reaction time), the method produced [^{11}C]PIB in less than 20 min after end of bombardment, with a 6% radiochemical yield, a 40-60 GBq/μmol specific activity and a high radiochemical purity (>99%). These final [^{11}C]PIB activities are sufficient for a human PETscan or for several microPETscans. Moreover, our approach allows replicating several [^{11}C]PIB productions during a day with a one hour drying step between each synthesis process.



Conclusion: In this study, we demonstrated that the amyloid tracer [^{11}C]PIB can be prepared with a completely automated operation. We report the optimization of the precursor solvent for the "on-loop" method reaction of [^{11}C]PIB radiolabelling, granting a fast reaction rate, a high yield and eliminating the need for heating. Finally, the automatic cleaning and drying requires no operator intervention, so the next synthesis can be run in a matter of minutes. With this automated synthesizer, it is effectively possible to run several [^{11}C]PIB syntheses on a routine basis.

Keywords: [^{11}C]PIB, PET, [^{11}C]Methyl Triflate, Automated Synthesis, Commercial Synthesizer

P058 SYNTHESIS AND EVALUATION OF *D*- AND *L*-FORM 5-METHYL-2'-DEOXY-2'-(^{18}F)FLUOROARABINO-FURANOSYLURACIL FOR PET IMAGING OF HSV1-TK GENE EXPRESSION

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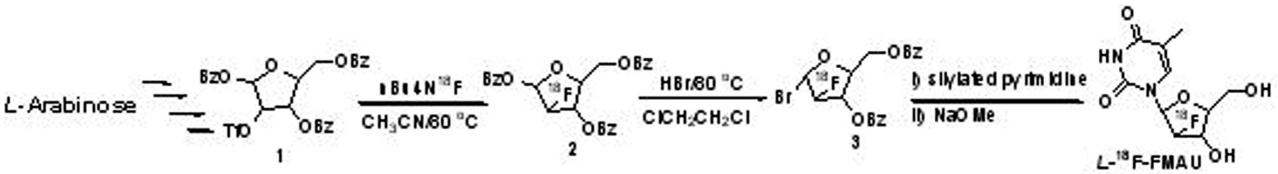
[1]Medicinal Chemistry Research Center, Korea Institute of Science and Technology, Seoul, Korea; [2]Radiopharmaceuticals Laboratory, Korea Institute of Radiological and Medical Sciences, Seoul, Korea; [3]Laboratory of Nuclearmedicine, Korea Institute of Radiological and Medical Sciences, Seoul, Korea

Introduction: Recently, a number of nucleosides with the unnatural *L*-configuration have been reported as potent chemotherapeutic agents. Among of them, *L*-FMAU show good antiviral activity, in contrast to the *D*-FMAU, did not exhibit any toxicities. We reported the synthesis and comparative evaluation of *D* (**A**) and *L*-[^{18}F]FMAU (**B**) for PET imaging of HSV1-TK gene expression.

Experimental: To synthesis of authentic compounds, *D*-FMAU and L-FMAU, was prepared in 5 and 13 steps from a commercially available benzoyl protected a-*D*-ribofuranose and *L*-arabinose,[1] respectively. F-18 labeled *D*-[^{18}F]FMAU (**A**) and *L*-[^{18}F]FMAU (**B**) were synthesized by coupling the radiolabeled fluorosugar with the corresponding silylated pyrimidine following a procedure reported by Alauddin and co-workers[2] with minor modification as shown in scheme 1. The products, including the α and β anomers, were purified using reverse-phase HPLC using a C-18 column (Waters, Xterra, 300 × 7.9) with an appropriate solvent (5% CH_3CN/H_2O)at a flow rate of 3 mL/min. The radiochemical purity of the product was >98% with decay-corrected yields of 25-35%. The total elapsed time of synthesis was about 220 min. All purified radioactive samples were confirmed using co-injection with pure nonradioactive analogues in every step. *In vitro* uptake studies were performed in HSV1-TK expressing MCF-TK+ cells and MCF cells to compare the accumulation of **A** and **B**.



Scheme 1. Synthesis of *L*-[^{18}F]FMAU (**B**).

Results and Discussion: The results of these uptake studies are showed the similar uptake pattern between **A** and **B** and both compounds are taken up a little selectively (about 6-7 folds) in MCF-TK+ cells with negligible uptake in MCF cells. In microPET study, the results indicate that *D*-FMAU (**A**) and *L*-FMAU (**B**) showed the similar results with cell uptake study in MCF-TK+ cells and MCF cells bearing mouse.

Keywords: L-[^{18}F]FMAU, D-[^{18}F]FMAU, HSV1-TK Gene Expression, PET Imaging, MCF-TK+

P059 IMPROVED AND GMP COMPLIANT SYNTHESIS OF 2-(1,1-DICYANOPROPEN-2-YL)-6-(2-(^{18}F)-FLUOROETHYL)-METHYLAMINO-NAPHTALENE ((^{18}F)FDDNP)

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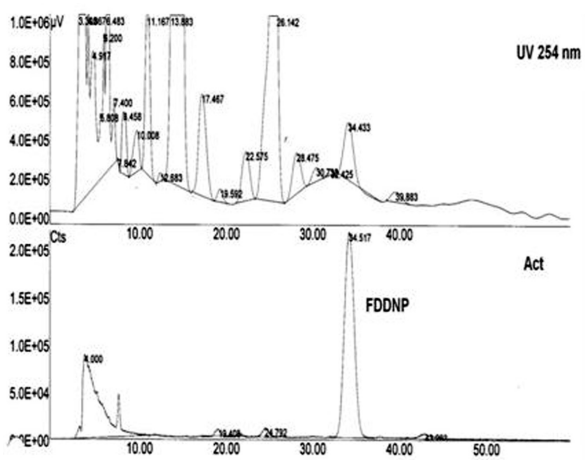
Introduction: [^{11}C]PIB and by [^{18}F]FDDNP are PET ligand the most frequently used for the *in vivo* visualization of senile plaques in the brains of patients with Alzheimer's disease The synthesis of [^{18}F]FDDNP has been described by Barrio *et al* [1]. However, this method requires the use of normal phase preparative HPLC purification, which is more difficult to apply than a reverse phase approach.

Aim: The purpose of the present study was to improve the method of synthesis of [^{18}F]FDDNP by introducing a more convenient reverse phase preparative HPLC purification method.

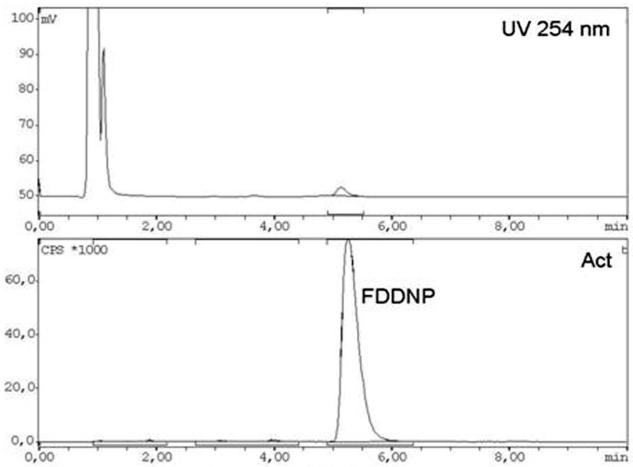
Experimental: After standard work-up, the ^{18}F solution was added to 5 mg of 2-(1,1-dicyanopropen-2-yl)-6-(2-tosyloxyoethyl)-methylamino-naphtalene in 500 μl of acetonitrile. This mixture was heated for 10 minutes at 100°C. After fluorination, the reaction mixture was quenched with HPLC solvent and subjected to preparative HPLC purification (Merck Lichrospher RP-Select B 10x250 mm; acetonitrile/water 1/1; 4 ml/min). Reformulation over a C18 Sep-Pak yielded a sterile and pyrogen free solution of [^{18}F]FDDNP in 2 mg/ml ascorbic acid in a citrate/acetate buffer (pH 5.3) containing 2.5% polysorbate-80.

Results and Discussion: The optimal reaction time was 10 minutes at 100°C in acetonitrile. Other solvents like DMSO, increased reaction temperature or reaction time, did not improve the yield of the desired product. The [^{18}F]FDDNP eluted from the preparative HPLC column at 35 minutes. The product appeared to be very susceptible to radiolysis. Therefore ascorbic acid was added to the formulation solutions. In addition, there was a high degree of sticking of [^{18}F]FDDNP to filters and glassware. This was overcome by the addition of polysorbate-80 to the formulation solutions.

The (radio)chemical purity of [^{18}F]FDDNP was > 97%, and free from organic impurities. Specific activity was 92 ± 32 GBq/μMol at time of injection. Synthesis time was 90 minutes and yield (corrected for decay) was 40 ± 10%.



Semi preparative HPLC chromatogram



Quality control HPLC chromatogram

Conclusion: [^{18}F]FDDNP could be synthesized reproducibly at moderate yields. [^{18}F]FDDNP was only stable in a formulation with ascorbic acid in a citrate/acetate buffered solution and polysorbate-80 as solubilizer.

References: [1] Barrio JR *et al.* J. Label. Cpd. Radiopharm. 42 (1999), S194-S195 and PCT US 6274119 B1 (2001).

Acknowledgement: The BV Cyclotron VU is acknowledged for providing fluorine-18.

Keywords: F-18, FDDNP, Beta-Amyloid, Alzheimer Disease, Positron Emission Tomography

P060 (^{18}F)-5-FLUOROINDOLE: A NOVEL PRECURSOR TOWARDS THE ENZYMATIC SYNTHESIS OF FLUORINE-18 LABELLED TRYPTOPHAN

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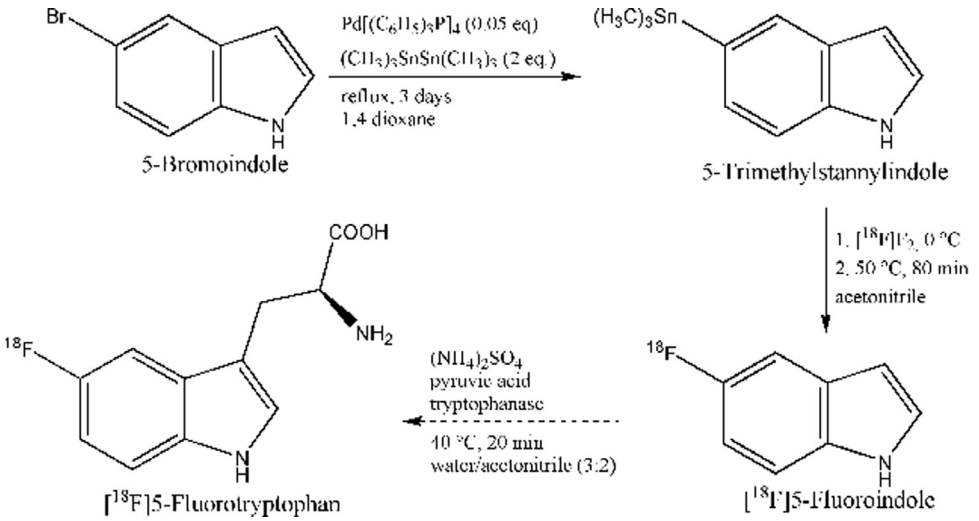
Introduction: [^{18}F]FDOPA and [^{11}C]-5-HTP are highly rated PET-tracers for staging neuroendocrine tumours. With increasing demand of a Fluorine-18 labelled tryptophan analogon we investigated the synthesis of a novel precursor towards an enzymatic synthesis of different [^{18}F]tryptophan isomers.

Experimental: 5-Trimethylstannylindole was obtained by reaction of the corresponding bromoindole isomer in 1,4-dioxane with 0.05 eq. *tetrakis* triphenylphosphine palladium and 2 eq. hexamethylditin under reflux for 3 days. After purification on silica gel, 30 mg of the obtained precursor was dissolved in 2 ml anhydrous acetonitrile. Carrier-added [^{18}F]F_2 was produced by the ^{20}Ne(d,α)^{18}F reaction in a 100 ml nickel target on a Scanditronix MC-17 cyclotron and trapped in the precursor solution at 0°C. After heating at 50°C for 80 minutes the liquid was filtered by an Alumina N solid phase extraction column. The obtained mixture was purified on an Econosphere C18 HPLC column (water:acetonitrile/3:2) to obtain [^{18}F]-5-fluoroindole. 10 μmol 5-Fluoroindole in a mixture of 10 ml water/acetonitrile (3:2) was treated with 100 μl $(NH_4)_2SO_4$ 1.5 M, 16 units tryptophanase and 150 μmol pyruvic acid and warmed up to 40°C for 20 minutes. A sample of the obtained mixture was purified on HPLC to give 5-fluorotryptophan.

Results and Discussion: Trimethylstannylindole is obtained in yields of 12% as 3 different isomers. [^{18}F]-5-Fluoroindole was obtained in yields of 18%. Reaction towards 5-fluorotryptophan starting with non-labelled 5-fluoroindole gives good results. Work is in progress to prepare [^{18}F]-5-fluorotryptophan in a similar manner in a total synthesis time of 120 minutes and to investigate this tracer in *in vitro* and *in vivo* studies.



Conclusion: A precursor towards a promising enzymatic synthesis of [^{18}F]-5-fluorotryptophan with future perspectives in imaging neuroendocrine tumours was developed.

Keywords: [^{18}F]-5-Fluorotryptophan, [^{18}F]-5-Fluoroindole, Neuroendocrine Tumours

P061 DEVELOPMENT OF A SIMPLE AUTOMATIC PREPARATION SYSTEM USING SOLID PHASE EXTRACTION METHOD FOR 16α-(^{18}F)FLUORO-17β-ESTRADIOL ((^{18}F)FES)

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Introduction: 16α-[^{18}F]fluoro-17β-estradiol ([^{18}F]FES) has been developed as a tracer for imaging estrogen receptors by positron emission tomography (PET). Several researcher reported the [^{18}F]FES synthesis methods for clinical use and they employed the HPLC system in the purification step. However, this procedure is cumbersome for routine because it requires the technical skill and the maintenance and so on. Solid phase extraction (SPE) using the disposable cartridge is widely used for the purification of the solution. Compared to the preparative HPLC purification, it offers several advantages such as reduced time, easy manipulation, easy automation. In this study, we performed the SPE method for [^{18}F]FES purification to establish a simple automatic preparation system.

Experimental: [^{18}F]FES was synthesized from 3-O-methoxymethyl-16,17-O-sulfuryl-16-epiestriol, by the method of reported using the cassette type [^{18}F]FDG synthesizer, TRACERlab MXFDG (GE, USA). This crude [^{18}F]FES solution was diluted with distilled water and passed through one of the SPE cartridges, tC18 Sep-Pak or Oasis HLB cartridge (Waters, USA) to trap the [^{18}F]FES. Based on the results of preparative HPLC chromatogram, we tested various concentrations of ethanol or acetonitrile to elute the [^{18}F]FES from the cartridges. The final solution was assessed the radiochemical purity by an analytical HPLC.

Results and Discussion: Trapping efficiency of [^{18}F]FES on the tC18 and the Oasis HLB cartridges were 75.5 ± 6.5% and 77.2 ± 4.6%, respectively (n=12, decay corrected). Trapped radioactivity was eluted by 2 mL of 100% ethanol or acetonitrile, whereas not eluted by 5 mL of less than 30% ethanol or acetonitrile. In the case of tC18, there was a clear correlation between the concentrations of ethanol and the eluted radioactivity. Under the optimized condition (three tC18 cartridges and 35% ethanol), the crude [^{18}F]FES was purified to the final product in 3 mL of 50% ethanol with a yield of 35% (n=3, decay corrected). The radiochemical purity was >97%. These results show that this method might be applicable for the [^{18}F]FES preparation at routine clinical use.

Conclusion: We developed the simple purification method using the commercially available disposable SPE cartridges for the [^{18}F]FES purification. This method realizes to reduce the cumbersome problem about preparative HPLC method for [^{18}F]FES preparation in clinical practice.

Acknowledgement: Part of this study was supported by the Research and Development Project Aimed at Economic Revitalization from Ministry of Education, Culture, Sports, Science and Technology (MEXT) Japan, the 21st Centry COE program “Biomedical Imaging Technology Integration Program” from Japan Society of the Promotion of Science (JSPS).

Keywords: FES, Simple Purification, Solid Phase Extraction (SPE), Automatic Preparation, Estrogen Receptors

P062 FULL AUTOMATIC SYNTHESIS OF (^{18}F)FLUOROMISONIDAZOLE IN PROTIC SOLVENT

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Introduction: [^{18}F]Fluoromisonidazole ([^{18}F]FMISO) is a promising candidate for hypoxia imaging radiopharmaceutical. In this study, we report the results of manual and automated preparation procedures for the synthesis of [^{18}F]FMISO using protic solvent.

Experimental: [^{18}F]Fluorination was performed with three reaction conditions. The first reaction condition was followed. After trapping of 185 MBq/0.5 mL [^{18}F]F^- on PS-HCO_3 cartridge, [^{18}F]F^- was eluted with a solution of 20 μL $TBAHCO_3$, 300 μL of H_2O and 300 μL of CH_3CN. We dried [^{18}F]F^- completely, and then added 5- 20 mg of precursor as 3-(2-nitroimidazol-1-yl)-2-*O*-tetrahydropyranyl-1-*O*-toluenesulfonyl propanediol, 100 μL of CH_3CN and 500 μL of t-BuOH. The reaction time and temperature for [^{18}F]fluorination was 5–30 min at 100–120°C. We checked [^{18}F]fluorination yield with radioTLC. After [^{18}F]fluorination, we removed the solvent and added 500 μL of 1N HCl for hydrolysis at 85°C for 5 min. For the second and third conditions, we performed the same [^{18}F]fluorination experiment using [^{18}F]F^- solution eluted with 5 mg of Cs_2CO_3 and 22 mg of K_{222} in 300 μL of H_2O and 300 μL of CH_3CN after trapping [^{18}F]F^- on a QMA cartridge (Condition II), or a mixture solution containing 185 MBq of [^{18}F]F^-/0.1 mL, 10 μL of TBAOH solution without trapping [^{18}F]F^- on an ion exchange cartridge (Condition III). After optimization with manual synthesis, we applied [^{18}F]fluorination conditions in t-BuOH to automatic synthesis using commercially available GE TracerLab MX chemistry module. We also had same automatic preparation with t-amyl alcohol to compare with the radiochemical yields from t-BuOH.

Results and Discussion: We achieved a high radiochemical yield of 82.6±13.7% by radioTLC with $TBAHCO_3$ as an elution solvent and 10 mg of precursor at 120°C. At the same temperature, we had 52.4±4.5, 80.7±5.5 and 81.5±8.5% of radiochemical yield after hydrolysis by radioTLC analysis from 5, 15 and 20 mg of precursor, respectively(n=3). With the same labeling conditions, use of Cs_2CO_3 and K_{222} in t-BuOH and TBAOH in t-BuOH generated low radiochemical yields than $TBAHCO_3$ elution system. Automated synthesis with 10 mg of precursor at 120°C for 15 min of [^{18}F]fluorination led to radiochemical yields of 67.8±6.2 and 60.4±5.2% after HPLC purification for t-amyl alcohol and t-BuOH, respectively (n=20 for each solvent). Total synthesis time was 70.2±12.8min. [^{18}F]FMISO obtained from automatic production showed high stability at 6 hours of 97.5±1.2% on HPLC.

Conclusion: New [^{18}F]fluorination method in a protic solvent system for simple and highly efficient radiochemical synthesis of [^{18}F]FMISO showed the possibility of facilitate routine clinical use of [^{18}F]FMISO in clinical positron emission tomography centers.

Keywords: [^{18}F]Fluoromisonidazole, Hypoxia, Protic Solvent, Nucleophilic Substitution, Tumor

P063 ONE-STEP HIGH RADIOCHEMICAL YIELD AUTOMATIC SYNTHESIS OF (^{18}F)FP-CIT IN PROTIC SOLVENT SYSTEM

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Introduction: [^{18}F]FP-CIT is a promising radiopharmaceutical for dopamine transporter imaging. But, it has not been used for clinical studies because of low radiochemical yield. The purpose of our study was to develop automatic preparation using a new radiolabeling method in the protic solvent system to obtain high radiochemical yield of [^{18}F]FP-CIT with single step.

Experimental: We added TBAOH 8 μL to 185 MBq/0.5 mL of [^{18}F]F^-/$H_2{}^{18}O$ solution in the reactor without use of cartridge, directly. After completely drying, [^{18}F]fluorination was performed with 2-6 mg of mesylate precursor (N-[3'-(mesyloxy)propyl]-2β-carbomethoxy-3β-(4'-iodophenyl)nortropane, 100 μL CH_3CN and 500 μL t-BuOH at 25-120°C for 5 to 30 min for each condition. After [^{18}F]fluorination, we have HPLC purification to obtain final product. HPLC purification condition was MeOH:H_2O:NEt_3 = 750:250:2 with 4 mL/min. We also developed an automatic synthesis method according to manual synthesis results with GE TracerLab MX and FX module. For automatic preparation, we used 37 GBq/mL of [^{18}F]F^- with 8 μL TBAOH condition without use of any solid phase extraction cartridge. Four reagent supply vials (blue, red, yellow, green) in the MX module were filled with 7 mL of CH_3CN for blue, 4 mg of the precursor in 2 mL of t-BuOH and 0.1 mL of CH_3CN, 2 mL of MeOH for yellow and 2 mL of green. For FX module, the different condition was the solvent amount for [^{18}F]fluorination. We only used 1 mL of t-BuOH and 0.2 mL of CH_3CN for this condition.

Results and Discussion: We obtained 52.2±4.5% of decay-corrected radiochemical yield in the manual synthesis. Optimal synthesis condition was 4 mg of mesylate precursor, 100°C and 20 min [^{18}F]fluorination (n=3). Radiochemical purity and preparation time were 98.5±1.2% and 80.0±12.5 min for all procedure. In the automatic production with FX module, we have 37.9±12.8% of decay-corrected radiochemical yield after HPLC purification and we did not have any synthesis failure (n=72). After HPLC purification in the automatic preparation, we removed HPLC solvent by C_{18} Sep-Pak cartridge. The specific activity after preparation was 64.4±4.5 GBq/mmol. With ascorbic acid addition, we obtained high radiochemical stability with 97.4±2.8% at 6 hours. With MX module, we only have 15.5±5.8% of radiochemical yield after HPLC purification and we considered the radiochemical yield of [^{18}F]FP-CIT depended on the precursor concentration.

Conclusion: We developed new method in protic solvent system for synthesis of [^{18}F]FP-CIT. Our method showed high radiochemical yield with high reproducibility and might enable [^{18}F]FP-CIT to be used clinically and commercially.

Keywords: [^{18}F]FP-CIT, Dopamine Transporter, [^{18}F]Fluoride, Protic Solvent, Automation

P064 PRACTICAL SYNTHESIS OF (^{18}F)FLUOROBENZENE STARTING FROM PHENYLTRIBUTYLSTANNE

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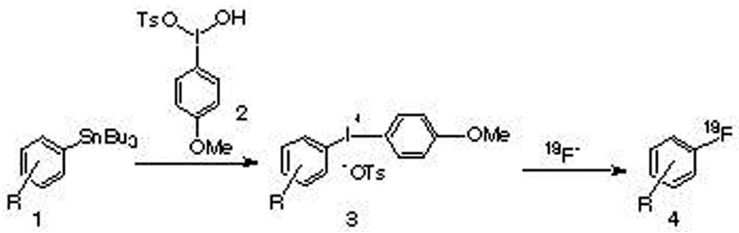
Introduction: Diphenyliodonium salt (tosylate, acetate and triflate etc.) was reported as a suitable precursor for single-step nucleophilic [^{18}F]fluorination of benzene ring. Due to excellent property of the phenyliodonium as a leaving group, reaction of diphenyliodonium salt with [^{18}F]F$^-$ could proceed well to give [^{18}F]fluorobenzene compound. In this study, using this reaction, we aimed to synthesize a practical [^{18}F]ligand (**4**) starting from phenyltributylstanne (**1**), a commonly used precursor for radiosynthesis.

The diphenyliodonium salt (**3**) has been prepared by the reaction of diacetoxyiodobenzene with benzene compound.[1,2] However, this route is lack of practical usefulness since a practical PET candidate is generally unstable for a strong oxidizing agent such as AcOOH. Here, we used **1** as the starting material which is easily prepared from the corresponding iodo- or bromo-benzene analogue. Since **1** could not react with diacetoxyiodobenzene, we used (hydroxy)tosyliodobenzene (**2**) in place of diacetoxyiodobenzene. In general, **2** offering electron-donating substitution group in the benzene ring is unstable. Thus, **2** obtained by treating diacetoxyiodobenzene with toluensulfonic acid was directly reacted with **1** without purification to form **3**. Starting from **1**, we prepared **3** with various substitution groups (OMe, Me, H, Br and Cl etc.) in high chemical yields. Radiochemistry was performed using cyclotron-produced [^{18}F]F$^-$, which was converted into the powerful nucleophilc radiofluorination reagent [^{18}F]n-Bu$_4$NF. This reagent was then treated with **3** (5-20 mg) in DMSO, CH_3CN, and DMSO at 80-120°C, respectively. These reactions gave substantial radiochemical yields (>50%) of **4**.



We used this method to prepare a practical PET ligand [^{18}F]DAA1106[3] for the imaging of peripheral-type benzodiazepine receptor in human brain. The labelling precursor DAA-I$^+$-anisole iodonium tosylate was prepared by the corresponding tributyl stanneous analogue with **2** under a mild condition with almost quantitative chemical yield. Then, the tosylate was heated with [^{18}F]F$^-$ in DMSO at 85°C to give [^{18}F]DAA1106 in 75% radiochemical yield, whereas [^{18}F]fluoroanisole as a by-product was formed in a low radiochemical yield (15%).

References: [1]. Pike V.W. et al. J Chem. Soc. Chem. Commun. 21, 2215-2216 (1995). [2] Shah A et al. J. Chem. Soc., Perkin Trans. 13, 2043-2046 (1997). [3] Zhang M.-R. et al. Nucl. Med. Biol. 30, 513-519 (2003).

Keywords: [^{18}F]Fluorobenzene, Diphenyliodonium Tosylate, Phenyltributylstanne, (Hydroxy)Tosyliodobenzene

P065 METHODOLOGY FOR THE ROUTINE SYNTHESIS OF (^{11}C)PK-11195 AT WUSM

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Introduction: Several syntheses of [^{11}C]PK-11195 including purification methods have been published. However, we have encountered difficulties trying to consistently reproduce them. For the past 12 months we have been producing [^{11}C]PK-11195 to image inflammation with PET in aging patients and in subjects with Alzheimer's type dementia.

Experimental: The synthesis uses the commercially available N-desmethylated precursor and [^{11}C] MeI (GE PETrace MeI Microlab). Our methylation system is a custom-made synthesizer, linked to a preparative HPLC system and a solid-phase purification stage for treatment of the final product. The substrate (1.0 mg) is dissolved in 250 μL of DMSO, transferred to a 3-mL conical vial and briefly vortexed. Two to 3 min prior to the delivery of [^{11}C] MeI, 3 μL of a 15% KOH solution is added and the vial connected to the synthesizer. After trapping the [^{11}C]MeI, the vial is moved via a platform to a heating block and heated at 90°C for 3 min. The vial is then nitrogen-purged of any unreacted [^{11}C]MeI. The contents are diluted with ~1.2 mL of HPLC solvent and remotely injected into an empty 2-mL injector loop. The HPLC uses a preparative C18 ODS-3 column 10 x 100 mm, eluted with a solvent mixture of ACN: 0.1 M ammonium formate buffer, pH 4.0 (49:51 V/V) at a flow rate of 3.7 mL/min. The product (monitored by UV and RA detectors) is obtained at ~ 12 min and is well-separated from the starting material, which elutes at ~ 21 min. The product fraction is collected into a flask containing 50-mL DI water and purified of any residual HPLC solvent via a C18 cartridge (Waters "classic SepPak"). The cartridge is back-flushed with 1.2 mL of absolute ethanol, filtered through a sterile 0.2 μ, 13 mm Nylon filter into a vial, diluted with 12 mL sterile USP 0.9% NaCl to a final ethanol concentration of ~10%.

Results and Discussion: We have consistently produced (ready to inject) clinical batches of 35 ± 15 mCi, sterile and pyrogen free. The chemical and radiochemical purity is >99%, and the SA ranges from 1,200-12,000 Ci/mmol at EOS (N = 30) in an overall synthesis time ~ 40 min (including 12 min for [^{11}C]MeI production). The total mass of the cold compound present in the batch (determined by analytical HPLC) is 2.5 ± 2.1 μg.

Conclusion: This reliable and reproducible synthetic method fulfills all the drug evaluation requirements of our Radioactive Drug Research Committee (RDRC). The detailed description of each phase and the acceptance criteria will be presented.

Acknowledgement: Work supported by NIH grant number NS048056.

Keywords: 11C-Radiopharmaceuticals, [^{11}C]PK-11195, 11C-Methyl Iodide, PET

P066 BIODISTRIBUTION AND Micro-PET EXPERIMENTS OF A NOVEL ^{18}F-LABELED ($R^{8,15,21}$, L^{17})-VIP PEPTIDE IN VIVO OF MICE BEARING COLORECTAL TUMOR

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Introduction: Previously, radiolabeled VIP and its analogs have shown their potential as various tumor imaging agents, however, fast proteolytic degradation in vivo has limited their clinical use. In order to develop a receptor specific VIP analog with longer half-life in vivo, we have designed a novel VIP analog named [$R^{8,15,21}$, L^{17}]-VIP.

Experimental: Through comparing the properties of ^{125}I labeled VIP and [$R^{8,15,21}$, L^{17}]-VIP peptide *in vitro* and *in vivo*, we found [$R^{8,15,21}$, L^{17}]-VIP showed higher stability and receptor binding affinity than native VIP. Therefore, we labeled this peptide with ^{18}F through N-succinimidyl-4-[^{18}F]fluorobenzoate ([^{18}F]SFB) for further characterization. For evaluating the potential of this tracer to diagnosing tumors overexpressed VIP receptors, biodistribution and Micro-PET experiments were done in mice with induced colorectal tumor.

Results and Discussion: [^{18}F]FB-[$R^{8,15,21}$, L^{17}]-VIP was obtained in greater than 99% radiochemical purity within 100 min in decay-for-corrected radiochemical yield of 33.6% $\pm$ 3% (n=5) and a specific radioactivity 255 GBq/μmol at the end of synthesis (EOS). Fast clearance of [^{18}F]FB-[$R^{8,15,21}$, L^{17}]-VIP from nontarget tissues and specific uptakes by tumors realized higher tumor-to-muscle ratio (3.55) and tumor-to-blood ratio (2.37) 60 min post injection (p.i.). Clear difference was observed between the unblocking and blocking experiments in Micro-PET imaging.

Conclusion: [^{18}F]FB-[$R^{8,15,21}$, L^{17}]-VIP has demonstrated its potential for diagnosing tumors over-expressed VIP receptors both *in vitro* and *in vivo*.

Acknowledgement: We thank Amersham Kexing Pharmaceuticals Co., Ltd for supplying No-carrier-added [^{18}F]F-solution. This work was supported by Knowledge Innovation Program of Chinese Academy of Sciences under Contract No. KJCX-SW-08 and Natural Science Foundation of China under Contract No.30371634.

Keywords: F-18, Radiolabeling, VIP, Biodistribution, Micro-PET

P067 ASPECTS OF ([11]C)FLB457 PREPARATION – DEVELOPMENT OF A NEW PREPARATIVE RP-HPLC METHOD: IMPORTANT ROLE OF INJECTION

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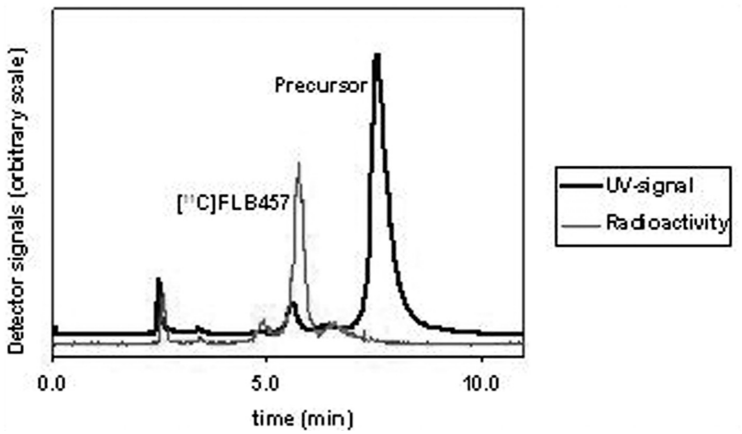
Introduction: FLB457 is an extremely potent D2 dopamine receptor agonist. Carbon-11 labelled FLB457 is useful for investigating extrastriatal dopamine receptors *in vivo* by positron emission tomography (PET)[1]. In order to visualise these receptors, the specific radioactivity of [^{11}C]FLB457 should be as high as possible. Shortening the total synthesis time can improve the specific activity. One possibility is to develop a preparative HPLC method that provides shorter retention time for FLB457 and avoids an evaporation or solid phase extraction step prior to formulation.

Experimental: 300ml methylation reaction mixture was diluted with 4.5 ml *eluent buffer* and was injected onto a Suplex pK_b100 5mm 10*250 mm preparative column Eluent: 0.025M acetate buffer pH=4.5/ethanol 96% = 85/15, flow rate 6.0 ml/min. The fraction containing the product was collected in 30 s (3.0 ml) and transferred through a sterile filter to a 30ml sterile glass containing 12.0 ml 2% phosphate buffer pH=7.

Results and Discussion: As can be seen in the chromatogram below, under the conditions applied, changing the retention order of product and precursor was achieved, thus reducing the retention time and avoiding contamination of the final product with precusor. In addition no toxic solvents were utilised, thus the collected fraction after diluting was of injectable quality. Development of the HPLC method and the pitfalls of the injection step which emerged during the development will be further discussed.



Conclusion: By using our new preparative RP-HPLC method, the overall synthesis time has been shortened and provides injectable [^{11}C]FLB457 without further purification or formulation steps. With this method the [^{11}C]FLB457 synthesis is completed within 20 minutes.

Keywords: D2 Receptor, FLB457, PET, Carbon-11

P068 SIMPLE AND HIGHLY EFFICIENT AUTOMATIC SYNTHESIS OF 3'-DEOXY-3'-([18]F)FLUOROTHYMIDINE USING NUCLEOPHILIC FLUORINATION CATALYZED BY PROTIC SOLVENT

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Introduction: 3'-deoxy-3'-[^{18}F]fluorothymidine ([^{18}F]FLT) is a promising candidate for tumor therapy evaluation and cell proliferation imaging. In this study, we report the results of manual and automated preparation procedures for the synthesis of [^{18}F]FLT using protic solvent.

Experimental: [^{18}F]F^- was eluted with a solution of 10 μL $TBAHCO_3$, 300 μL of H_2O and 300 μL of CH_3CN after collection of 185 MBq [^{18}F]F^- on a PS-HCO_3 cartridge. We dried [^{18}F]F^-, and then added 5- 40 mg of precursor as (5'-*O*-DMTr-2'-deoxy-3'-*O*-nosyl-β-D-threo-pentofuranosyl)-3-*N*-BOC-thymine, 100 μL of CH_3CN and 500 μL of t-BuOH. The reaction time and temperature for [^{18}F]fluorination was 5–30 min at 100- 140°C. We checked [^{18}F]fluorination yield with radioTLC. After [^{18}F]fluorination, we removed the solvent and added 500 μL of 1N HCl for hydrolysis at 85°C for 5 min. After neutralization, we checked the radiochemical yield by radioTLC. After optimization with manual synthesis, we applied them to automatic synthesis using GE TracerLab MX and FX module. TracerLab MX module has blue, red, yellow and green reagent vials. We added 7 mL of CH_3CN to the blue vial; 20 mg of precursor, 2 mL t-BuOH and 200 μL of CH_3CN to the red; 1.75 mL 2 N NaOH and 0.7 mL citrate buffer to the yellow; and 3 mL 1 N HCl and 0.25 mL CH_3CN to the green vial. We have 10 minutes of [^{18}F]fluorination at 120°C. For hydrolysis, we had 5 minutes at 85°C. The reaction mixture was moved to HPLC purification system automatically, and we purified [^{18}F]FLT with EtOH:H_2O=10:90 solution at 5 mL/min. For TracerLab FX module, we have same reagent condition but we only used 1 mL of t-BuOH and 0.1 mL of CH_3CN as [^{18}F]fluorination solvent.

Results and Discussion: We achieved a high radiochemical yield of 85.3±3.5% by radioTLC with $TBAHCO_3$ as an elution solvent and 20 mg of precursor at 100°C. At the same temperature, we had 18.3±9.0, 49.6±15.8 and 83.6±5.9% of radiochemical yield after hydrolysis by radioTLC analysis from 5, 10 and 40 mg of precursor, respectively(n=4). Automated synthesis with $TBAHCO_3$ and 20 mg of precursor at 120°C for 10 min of [^{18}F]fluorination led to radiochemical yields of 65.5±5.4% and 60.2±5.2% after HPLC purification with FX and MX modules, respectively (n=10 for each condition). Total synthesis time, including purification, was 70.5±10.5min. [^{18}F]FLT obtained from automatic production had a high stability at 6 hours of 98±1.2% and 98±0.8% on HPLC and radioTLC, respectively.

Conclusion: Our new [^{18}F]fluorination with a protic solvent system resulted in simple and highly efficient radiochemical synthesis of [^{18}F]FLT, which could facilitate routine clinical use of [^{18}F]FLT.

Keywords: [^{18}F]Fluorothymidine, [^{18}F]Fluoride, Protic Solvent, Nucleophilic Substitution, Automation

P069 REMOTE CONTROLLED AUTOMATED SYSTEM FOR THE SYNTHESIS OF 7α-(^{18}F)FLUORO-17α-METHYL-5α-DIHYDROTESTOSTERONE ((^{18}F)FMDHT)

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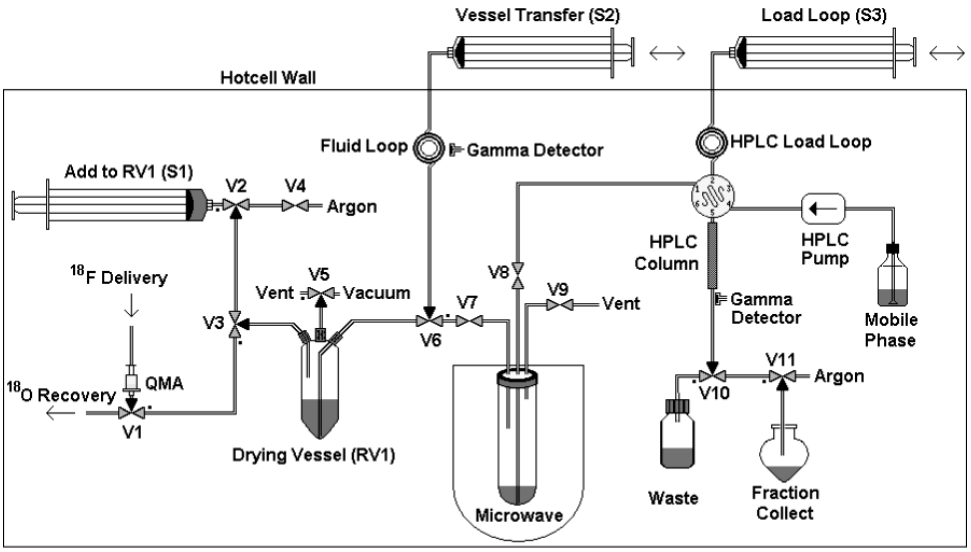
Introduction: [^{18}F]FMDHT is a promising ligand for prostate cancer imaging. The aim of this study was to develop a remote controlled automated synthesis system to reliably and efficiently synthesize [^{18}F]FMDHT using microwave. This automation would be immensely helpful in evaluating imaging characteristics of [^{18}F]FMDHT. We herein, report a completely automated remote control system for repeat production of [^{18}F]FMDHT.

Experimental: Using electrically controlled remote switches and valves, an automated system was constructed to synthesize [^{18}F]-FMDHT. The switch box to control electric valves is located outside the hot cell. First, F-18 fluoride received from the cyclotron was trapped on to a QMA cartridge and O-18 water recovered. The radioactivity was then eluted in RV1 using the K222/K_2CO_3 solution. The water was removed azeotropically. The residue was dissolved in acetonitrile, drawn into a loop using S2 (syringe) and V6 (switch valve) was triggered to deliver the radioactivity in to the reaction tube inside the the μ-wave containing precursor (7β-tosyloxy -17α-methyl-5α-dihydrotestosterone). After the μ-wave reaction, reaction contents were drawn into the HPLC loop and injected on to the HPLC for purification. The desired peak was collected, the solvent evaporated, and the product was reconstituted in 2% ethanol in saline solution.

Results and Discussion: The automated synthesis system produced [^{18}F]-FMDHT in 10-20% radiochemical yields (manual procedure, 5-15%). We performed six continuous productions using this system with no failure or complications, supporting the reliability, reproducibility, and the robustness of the system. The entire system is cleaned automatedly after the synthesis to render the equipment ready for next synthesis.



Schematic representation of automated [^{18}F]FMDHT production system.

Conclusion: A complete remote control automated synthesis module was developed for repeat production of [^{18}F]FMDHT. The system features 1) recovery of O-18 water using QMA cartridge, 2) conducting azeotropic removal of water, 3) transfer of radioactivity to the μ-wave unit for the reaction, and 4) isolation of desired product by purification on a semi-prep HPLC system. This system offers reliable and reproducible synthesis yields and significantly reduces radiation exposure to the production chemist. This cost effective and efficient production system can be adapted to synthesize other ligands with minor modifications.

Acknowledgement: This project was supported by a grant from NIH CA105382 (to PKG).

Keywords: Prostate Imaging, PET Imaging, Automation, F-18 FMDHT, Androgen Receptor

P070 2-BROMO-1-(^{18}F)FLUORETHANE – ALTERNATIVE PURIFICATION PROCEDURE FOR WIDER SOLVENT FLEXIBILITY IN SUBSEQUENT ALKYLATIONS

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Introduction: In reactions involving macromolecules, aqueous solutions are usually preferred to minimize denaturation and precipitation. Since the interest in performing PET studies with labeled proteins is growing, we sought a [^{18}F]fluoroalkylating agent that should be relatively stable in protic solvents and a way to produce it so that it can be isolated in water. Here we have used a disposable Oasis solid phase extraction column as a miniature gas chromatographic (GC) system for purifying 2-bromo-1-[^{18}F]fluoroethane ([^{18}F]FEtBr) so that it can be trapped in our solvent of choice.

Experimental: The dried Kryptofix-K_2CO_3-[^{18}F]fluoride mixture was reacted with 1,2-dibromoethane (BrEtBr) in acetonitrile. The reaction mixture, diluted with water, was then eluted through a preconditioned Oasis HLB (Waters) column. After washing with dilute methanol and briefly flushing with carrier nitrogen, the column was heated to 95° C and the released [^{18}F]FEtBr was carried by N_2 to the chilled (ice bath) solvent. Analyses of samples were performed by radio-HPLC: Hamilton PRP-1, AN:H_2O 55:45 with UV (l 222 nm) and radio-detector in series.

Results and Discussion: Good conversions of [^{18}F]F^- were obtained with radiochemical yields of [^{18}F]FEtBr of 80-90% in 2 minutes. The Oasis column efficiently retained the product as well as any unreacted dibromide: no traces of [^{18}F]FEtBr or BrEtBr were found in the flow-through or washing solutions. The recovery of [^{18}F]FEtBr in the heat-released Oasis purification strategy was >80% or 60% when trapped in acetonitrile or water, respectively, (based on the conversion in the fluorination reaction and decay-corrected). Residual BrEtBr was not detected in the trapped product solution. The radiochemical purity of [^{18}F]FEtBr was still 97% at 40 min after end-of-trapping in water, indicating good aqueous stability.

Conclusion: Similar to GC separations used for other fluoralkylating precursors (Bergman), the [^{18}F]FEtBr could be obtained in high chemical purity. The use of disposable SPE columns is inexpensive and amenable to automation (Iwata). The sequential trapping and heat-release from the Oasis HLB column provides a reliable, efficient method for generating [^{18}F]FEtBr for use in aqueous as well as organic media.

Acknowledgement: Financial support by the Karolinska Institutet, Swedish Cancer Society and EC FP6 (Contract LSHC-CT-2004-50585).

References: [1] Bergman J, Eskola O, Lehikoinen P, Solin O. *Appl Radiat Isot* 2001; **54**: 927–933. [2] Iwata R, Pascali C, Bogni A, Furumoto S, Terasaki K, Yanai K. *Appl Radiat Isot* 2002; **57**: 347–352.

Keywords: Fluoroalkylation, Fluorine-18, Fluoroethylbromide, Solid Phase Extraction, Positron Emission Tomography

P071 MICROWAVE-ASSISTED RADIOLABELLING OF 2-(4'-([18]F)FLUOROPHENYL)-1,3-BENZOTHIAZOLES

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Introduction: Conventional labelling of 2-phenylbenzothiazoles with a fluorine-18 atom directly attached to the 2-phenyl ring at the 4'-position was up to now realized by thermal heating (150°C) the 2-(4'-nitrophenyl)benzothiazole with [^{18}F]fluoride/Kryptofix® 222 in dimethylsulfoxide (DMSO). To enhance the yield and shorten the reaction time, we have now studied the labelling of such phenylbenzothiazoles using a microwave cavity.

Experimental: Classic aromatic nucleophilic substitutions in DMSO were done by heating a solution of 1-2 mg of the nitro-precursor in 0.5 ml of DMSO for 20 min at 150°C in the presence of 2.5 mg K_2CO_3 and 27.9 mg Kryptofix® 222.

For radiolabelling using a microwave cavity (Resonance Instruments model 521), [^{18}F]fluoride, produced by 18-MeV proton irradiation of 2 ml oxygen-18 water contained in a niobium target, was passed over a QMA cartridge (Waters) from which the fluoride was eluted using a solution of 2.5 mg K_2CO_3 and 27.9 mg Kryptofix® 222 dissolved in 750 μl H_2O/CH_3CN (5/95 V/V) in a 1 ml conical vial (Wheaton). The mixture was evaporated by heating with the microwave cavity to 80°C (35 W) during 6 min under a gentle flow of He (20 ml/min). CH_3CN (0.5 ml) was added to the residue and the solution was evaporated by heating (70°C, 35 W, 6 min) under a flow of He and this procedure was repeated once. A solution of 1 mg of the nitro-precursor in 0.3 ml of anhydrous DMSO was added to the vial which then was heated in the microwave cavity for 6 min (160°C, 100 W).

A sample of the reaction mixture was analyzed by RP-HPLC to assess the radiochemical yield.

Results and Discussion: The yields observed after thermal heating at 150°C during 20 min ranged from 10 to 30% (Figure 1). Using the microwave cavity the yield was 60% in a reaction time of only 6 min (Figure 2).

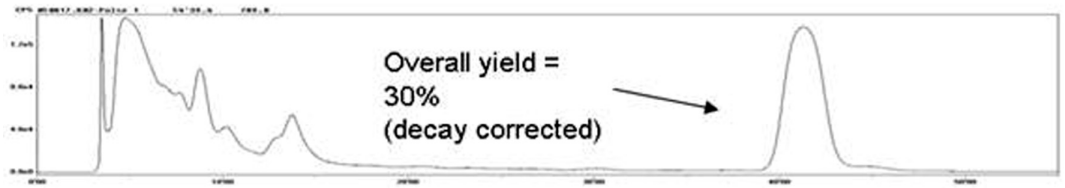

Fig. 1. Thermal heating: RP-HPCL analysis of the reaction mixture.

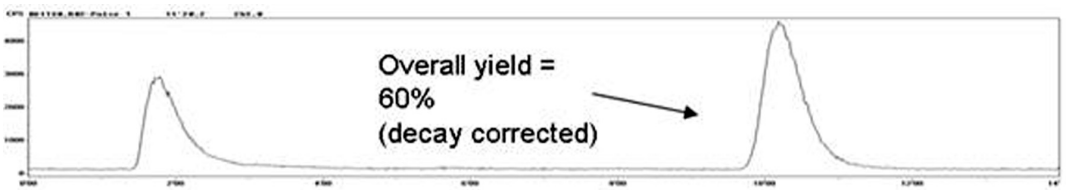

Fig. 2. Microwave cavity: RP-HPCL analysis of the reaction mixture.

Conclusion: The aromatic nucleophilic substitution using a microwave cavity shows great promise. The labelling yield is twice that after thermal heating and in a shorter reaction time. Other reaction conditions will be studied to further improve the labelling yield and the results will be presented.

Acknowledgement: This study was funded in part by the EC – FP6-project DiMi, LSHB-CT-2005-512146.

Keywords: Microwave-Assited Labelling, [^{18}F]Fluorophenylbenzothiazoles

P072 SYNTHESIS OF (*CARBONYL*-^{11}C)DAA1106 AND ANALOGUES USING (^{11}C)CARBON MONOXIDE AND PALLADIUM(0) COMPLEX

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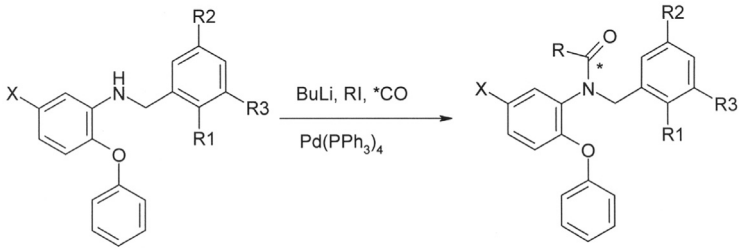
Introduction: Carbonylation using [^{11}C]carbon monoxide has been employed in ^{11}C-labelling of a wide range of carbonyl compounds.[1] This report describes ^{11}C-labelling of *N*-(2,5-dimethoxybenzyl)-*N*-(5-fluoro-2-phenoxyphenyl)acetamide (DAA1106) and some analogues using [^{11}C]carbon monoxide. The compound DAA1106 has been reported as a selective ligand for peripheral benzodiazepine receptors (PBR).[2]

Experimental: Tetrakis(triphenylphosphine)palladium (2.7 μmol) was dissolved in anhydrous THF (200 *m*L) and treated with methyl iodide (96.4 μmol). Amine (14.1 μmol) was taken in another vial, dissolved in anhydrous THF (200 μL)and treated with BuLi (16.0 μmol). The two reagent solutions were mixed together, filtered and injected into the loop of the equipments from where the mixture was transferred with pressure (35 Mpa) into the micro autoclave (200 ml), pre-charged with [^{11}C]carbon monoxide in helium. The micro-autoclave was heated for 5 min at 150°C. The crude product was purified by semi preparative HPLC using reverse phase C18 column.

Results and Discussion: The compound DAA1106 and eight structurally related analogues were labelled with ^{11}C using low concentration of [^{11}C]carbon monoxide and micro autoclave technique. Palladium mediated carbonylation using tetrakis(triphenylphosphine)palladium, methyl iodide or iodobenzene and different amines was employed in the synthesis. Butyllithium (BuLi) was used as base to activate the amines. The ^{11}C-labelled products were obtained with 15-45% decay-corrected radiochemical yields. This compound was previously labelled using [^{11}C]methyl iodid[3] but our method gives a possibility to make a series of ^{11}C-labelled analogues of the compound.



* = labelling position, X = F, Cl, H; R = Me, Ph; R1 = OMe, Cl, H; R2 = OMe, H; R3 = OMe, H

Conclusion: The presented approach is a novel method for the synthesis of [*carbonyl*-^{11}C]DAA1106 and analogues, and thereby making a library of ^{11}C-labelled analogues of this compound

References: [1] (a) Rahman O, Kihlberg T, Långström B. *Eur J Org Chem* 2004, 474-478. (b)Rahman O, Kihlberg T, Långström B. *J Org Chem* 2003, **68,** 3558-3562.(c)Itsenko O, Kihlberg T, Långström B. *Eur J Org Chem* 2005, 2830-3834. [2] Okuyama S, Chaki S, Yoshikawa R, Ogawa S-I, Suzuki Y, Okubo T, Nakazato A, Nagamine M, Tomisawa K. *Life Sci* 1999, **64,** 1455-1464 [3] Zhang M-R, Kida T, Noguchi J, Furutsuka K, Maeda J, Suhara T, Suzuki K. *Nucl Med Biol* 2003, **30,** 513-519.

Acknowledgement: Uppsala Imnet AB, GE Healthcare is acknowledged for the financial support of this work.

Keywords: [^{11}C]Carbon Monoxide, [^{11}C]DAA1106, Palladium(0), Micro Autoclave

P073 RADIOSYNTHESIS AND IN VITRO EVALUATION OF SEVERAL (^{18}F)FLUOROQUINOXALINEDIONE DERIVATIVES AS PUTATIVE AMPA RECEPTOR LIGANDS

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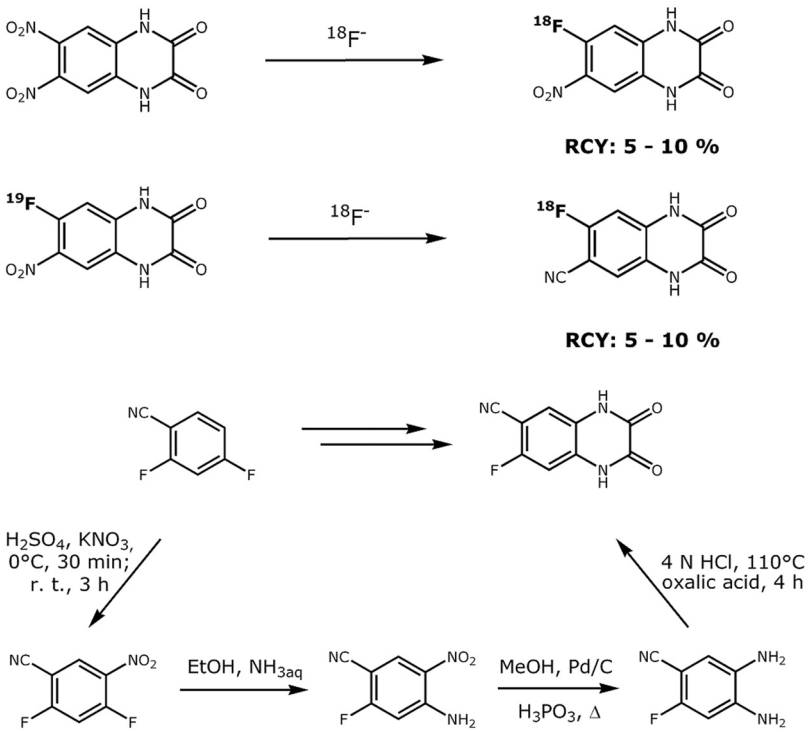
Introduction: The family of the quinoxalinediones (QX) offers a large variety of derivatives which are potential ligands for the AMPA receptor system. Until now there is no application known of any member of this family for PET. Just a related NMDA receptor antagonist has been radioionidated before [1]. Beside this the pharmaceutical properties of QX molecules are so far exclusively derived from in vitro tests with tritiated antagonists [2].

Experimental: While DNQX (dinitro-quinoxalinedione) is the simplest derivative it was first chosen for ^{18}F-labelling. It took place in DMSO at 180°C using the standard Kryptofix system. After 15 min of reaction the product n.c.a. [^{18}F]FNQX ([^{18}F]fluoro-nitro-quinoxalinedione) was obtained in radiochemical yields of up to 10%. Purification and formulation was performed via HPLC and cartridge procedures. The ^{19}F-standard is synthesized via a method described in literature [2]. FCQX (fluoro-cyano-quinoxaline) could be labelled in a fluorine-18 for fluorine-19 exchange reaction under similar condition as described above. As the in vitro tests with [^{19}F]FCQX had not been promising, no [^{18}F]FCQX experiments were performed. In vitro competition studies and autoradiographic tests with rat brain slices were performed with tritiated AMPA as standard for pharmaceutical evaluation.



Results and Discussion: Labelling of two members of the "QX family" with fluorine-18 was performed with radiochemical yields of up to 10%.

Autoradiographic competition tests of FNQX and FCQX against tritiated AMPA showed low binding affinity in μM range and high non-specific binding of the tracers.

Conclusion: These results indicate a loss of biological activity by substitution of a nitro group by a fluorine atom in DNQX or CNQX. The K_i-values correlate with values for unsubstituted mononitro- and cyano-QX. This correlation indicates that a second substitute at the aromatic ring is not only tolerated, but even necessary for good binding properties.

References: [1] S.M. Ametamey, M. Kokic, N. Carrey-Rémy et al. Bioorg. Med. Chem. Letters, **2000**, *10*, 75-78. [2] J. Ohmori, S. Sakamoto, H. Kubota et al. *J. Med. Chem.* **1994**, 467-475.

Keywords: Quinoxalinedione, AMPA, PET, Fluorine-18

P074 A SIMPLE AUTOMATED SYSTEM FOR CLINICAL PRODUCTION OF ^{11}C-LABELED CHOLINE, ACETATE AND METHIONINE USING DISPOSABLE KITS

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[1]Bioscan, Inc., Washington, DC, USA; [2]Department of Radiology, Medical College of Virginia, Richmond, VA, USA

Introduction: Bioscan has developed the ReFORM-Plus™ module with sterile, disposable kits to perform a number of critical radiochemical tasks under cGMP conditions. The principle design goal was to provide a unit that could transform HPLC purified products in organic mobile phase into saline based injectables which meet regulatory purity requirements. In addition, the unit's flexible programming system makes it an ideal system for the routine production of such useful compounds as [^{11}C]-choline, [^{11}C]-acetate, and [^{11}C]-methionine.

Experimental: [^{11}C]-acetate is produced with [^{11}C]-CO_2 released in a flow of 2-5mL/min from a molecular sieve or a cold trap into a special v-vial reactor containing 200μL of 0.75M Grignard reagent in diethyl ether. The product is purified using a series of Sep-Pak cartridges based on the system developed by Le Bars et al (J. of Radiolabeled Compounds 2006; **49**: 263-267). The process is completed in 11-15 minutes, and produces yields of 30-40% at EOS.

[^{11}C]-choline is produced with [^{11}C]-methyl iodide distilled in a flow of 2-5mL/min from the Bioscan MeI-Plus system into a special v-vial reactor containing 200μL of a 50/50 mixture of diethanolamine and DMF. The product is purified using an SCX cation exchange column based on the system developed by Smith et al (Abstract, 36th Annual Scientific Meeting of the Australia and New Zealand Society of Nuclear Medicine).

[^{11}C]-methionine is produced with [^{11}C]-methyl iodide distilled in a flow of 2-5mL/min from the Bioscan MeI-Plus system into a special v-vial reactor containing 20 mg KF on alumina (Al_2O_3) and 2 mg L-homocysteine in 1 mL of ethanol using the method described by Mitterhauser et al. (Applied Rad. and Isotopes 2001; **55**: 17-22) The product is purified using C18 and Alumina Sep-Paks and a 0.22 micron filter to remove the Al_2O_3 particles.

Results and Discussion: The set up of the synthesis system and disposable kit for [^{11}C]-acetate production is shown in Figure 1. Data from both "hot" and "cold" runs will be presented.

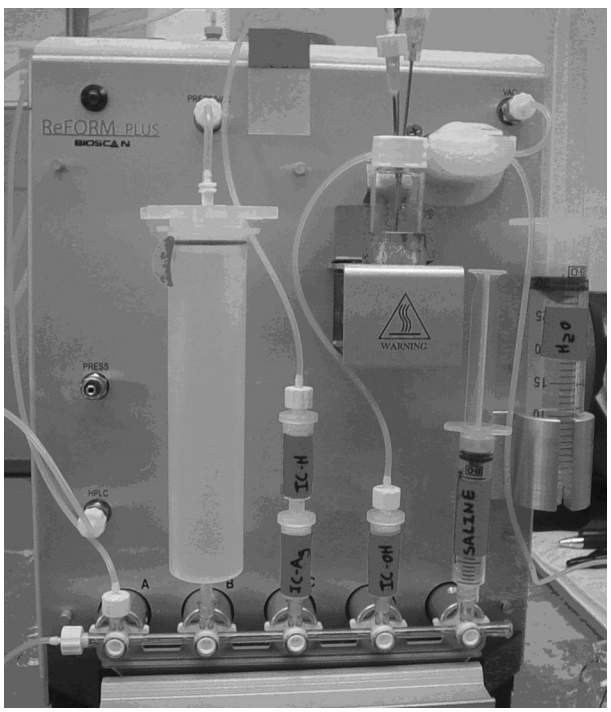

Fig. 1

Conclusion: The simple production and purification procedures result in high yield, high purity products with fast, simple chemistry and Sep-Pak purification. The availability of sterilized disposable kits for these processes allows producers to readily meet cGMP requirements for clinical use.

Keywords: Acetate, Choline, Methionine, ^{11}C Automated Synthesis, Disposable Kit

P075 SYNTHESIS OF 2-(^{18}F)FLUOROESTRADIOL FOR IMAGING OF ER+ TUMORS

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[1]Chemistry, Univ. of Illinois, Urbana, IL, USA; [2]Nuclear Medicine, Seoul National University Hospital, Seoul, Korea

Introduction: Early detection of breast cancer is critical for effective antitumor therapies, and accurate determination of breast tumor estrogen receptor (ER) levels is needed to make appropriate choices between endocrine vs. conventional radiation or cytotoxic chemotherapy. To determine ER levels in breast tumors in vivo using PET imaging, we have developed various radiolabeled high affinity ER ligands. An attractive compound for this purpose is 2-fluoroestradiol (**I**) (Figure 1), which has a binding affinity equivalent to that of estradiol (**II**) for ERα. The affinity of **I** for sex-hormone binding globulin (SHBG) is ca. 40 times that of **II**, which could facilitate its target tissue uptake.

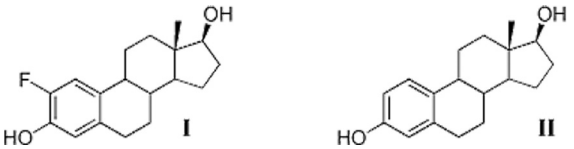

Fig. 1

Experimental: The aromatic fluorine in compound **I** provides an opportunity for the direct labeling of this compound by aromatic radio fluorination with fluorine-18. However, while nucleophilic aromatic substitution with F-18 fluoride ion is effective for radio-fluorination of electron-poor aromatic rings, it is not effective with electron-rich arenes. The diazonium ion decomposition methods for arene fluorination (e.g., the Balz-Schiemann-like reactions) are not effective in producing high specific activity products, and they work poorly on electron-rich systems. We have investigated the use of the diaryl iodonium salt approach for the preparation of F-18 **II** (Figure 2).

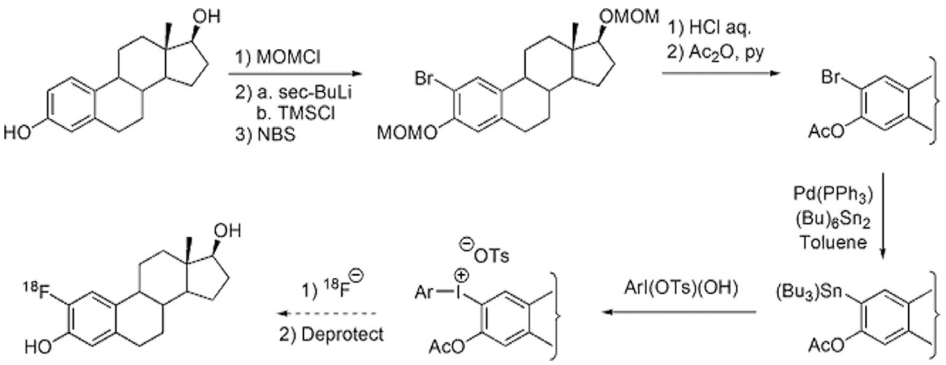

Fig. 2

Results and Discussion: Various diaryl iodonium salt precursors to compound **II** and to other complex systems have been prepared, and their conversion to fluorine-substituted products has been investigated. Initial results indicate that members of this class of iodonium salts are easily prepared, stable under most conditions, and in some cases are reactive towards fluoride ion.

Conclusion: The diaryl iodonium salt approach to radio fluorination of aromatic rings appears to be a possible route for the production of high specific activity 2-fluoroestradiol.

Acknowledgement: We would like to thank the National Institute of Heath and Department of Energy for funding.

Keywords: Radio Fluorination, Nuclear Receptor, Iodonium Salts

P076 NUCLEOPHILIC AROMATIC (^{18}F)FLUORINATION IN MOLTEN SALTS VIA DENITROFLUORINATION OR DISPLACEMENT OF ANILINIUM SALTS

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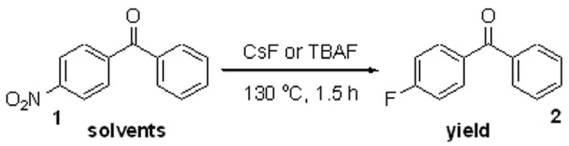
[1]Department of Chemistry, Inha University, Inchon, Korea; [2]Department of Nuclear Medicine, Asan Medicine Center, University of Ulsan College of Medicine, Seoul, Korea

Introduction: Especially, in electron deficient aromatic system, nucleophilic aromatic [^{18}F]fluorination provides direct F-18 labeled radiotracer as well as prosthetic groups such as 4-[^{18}F]fluorobenzoate, 4-[^{18}F]fluorobenzaldehyde and 4-[^{18}F]fluorobenzonitrile, which have been utilized to label proteins and small peptide fragments.[1,2] In this study, we introduce TBAOMs as a novel class of reaction media for an effective aromatic [^{18}F]fluorination of nitrobenzene and anilinium salt compounds, substituted with several EWGs at *para*-position.

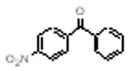
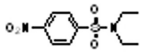
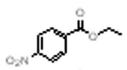
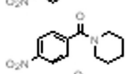
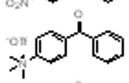
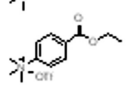
Results and Discussion: TBAOMs and TBAOTf are stable and neutral ammonium salts, melting at 78°C and 112°C, respectively, can act as a solvent at fluorination temperature (130°C). They are also thermally more stable than common imidazolium-based ionic liquids, in particular, under basic condition. For the comparison of these molten to other typical solvents, denitrofluorination of 4-nitrobenzophenone (**1**) was performed using CsF or TBAF in three categories of solvents; a) aprotic solvents, b) ionic liquids, and c) molten salts (Scheme 1). Reactions in ionic liquids such as [bmim][OMs], and [bmim][OTf] readily and entirely decomposed **1** with no product. However, reactions in aprotic solvents and molten salts yielded up to 59% and 82% of **2**, respectively.



solvents	yield
aprotic solvents; CH_3CN, DMF, DMSO	up to 59%
ionic liquids; [bmim][OMs], [bmim][OTf]	no product
molten salts; TBAOMs, TBAOTf	up to 82%

Fluorination of several electron deficient aromatic compounds was performed with CsF or TBAF in TBAOMs solvent at 130°C for 70 min, to give 74%, 34%, 19%, and 2% of fluorinated compounds (Table 1). Hot reaction in TBAOMs solvent successfully gave 76-94% radiolabeling yields within 10 min (entry 1-3, 5, 6) and 65-82% radiochemical yields. Less activated amide compound showed 18% radiolabeling yield.

Table 1. Aromatic Fluorination with Various Substrates.

entry	substrate	F-19 Time (min)	F-19 yield (%) CsF	F-19 yield (%) TBAF	F-18 Time (min)	F-18 TLC (%)	F-18 RCY (%)
1		70	74	57	5	94	80
2		70	34	53	15	91	82
3		70	19	1	5	82	70
4		70	2	2	15	18	8
5		70	47	67	5	94	74
6		70	47	15	5	76	65

Conclusion: We were able to obtain aromatic [^{18}F]fluorinated compounds in high yield using TBAOMs as a reaction solvent. Our result will be further investigated in connection with development of prosthetic group.

References: [1] Wilbur DS. *Bioconjugate Chem.* 1992; **3**: 433-470. [2] Okarvi SM. *Eur J Nucl Med* 2001; **28**: 929-938.

Keywords: Nucleophilic Aromatic [^{18}F]Fluorination, Molten Salts

P077 NOVEL RECIPE FOR F-18 COCKTAIL; FAST AND MILD (^{18}F)FLUORINATION

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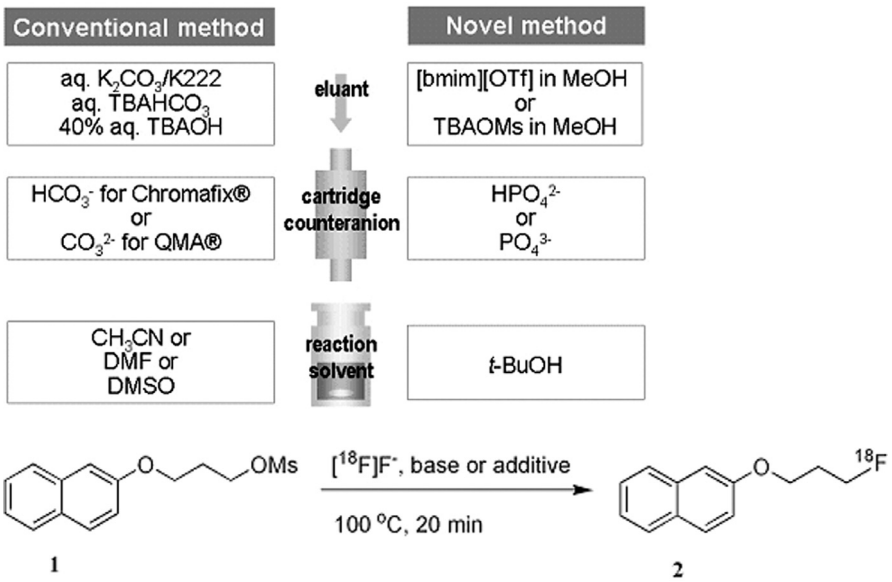
Introduction: Nucleophilic [^{18}F]fluorination is one of the most common method to prepare PET imaging agent. In many cases, polymer cartridges are utilized not only to obtain pure F-18, but also to recycle expensive [^{18}O]H_2O in capture-release manner, in which captured F-18 in polymer cartridges is released by elution with aqueous TBAOH, $TBAHCO_3$, or K_2CO_3/K_{222}. We have paid attention to overcome several inherent disadvantages of such conventional method, which attempted us to modify this procedure as follows.

Results and Discussion: 1) Anhydrous neutral ionic liquids such as [bmim][OTf] and TBAOMs solution in MeOH were used to wash F-18 out of polymer cartridge → *Results*: Most F-18 was released out from cartridge, and evaporation of MeOH took only 2 min.

2) The counter anions in polymer cartridge were changed to other alternative bases including di- or tribasic phosphate → *Results*: By-products including olefin and alcohol were dramatically reduced.

3) Finally, the commonly-used polar aprotic solvents were substituted with polar protic *t*-BuOH as recently reported in our laboratory [1]. → *Results*: Most precursors remained intact without decomposition.

All [^{18}F]fluorination were performed under the same condition, at 100°C for 20 min. % Area of starting molecule **1** in HPLC profile was used as a criterion of reaction mildness and selectiveness. Conventional [^{18}F]fluorination using TBAOH or K_2CO_3/K_{222} gave 83% and 79% radio-TLC yield, respectively, and showed complex mass pattern on HPLC analysis, in which only 15% and 7% of **1** was survived. In contrast, our method resulted in 76-99% radio-TLC yield, and 76-94% of starting material remained.



Conclusion: Our result is practically favorable, and expected to be a general method and applicable to more complicated precursors. In addition, remarkable suppression of by-product formation will reduce the quantity of precious precursor and make purification of F-18 labeled product much easier, promising high specific activity.

Reference: [1] Kim DW, Chi DY, et al. *J Am Chem Soc* 2006; **128**: 16394-16397.

Keywords: Polymer Cartridge, Ionic Liquids

P078 AUTOMATED SYNTHESIS OF THE CHOLINE ANALOG, (^{18}F)FLUOROMETHYLALLYLCHOLINE (FMAC)

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Introduction: In recent years positron-emitter choline has become established as particularly attractive tracer for cancer detection using positron emission tomography (PET) imaging. The aim of this study was to develop an automated synthesis for the new ^{18}F-labeled choline analog, [^{18}F]fluoromethylallylcholine ([^{18}F]FMAC).

Experimental: [^{18}F]FMAC was synthesized using commercial modules (FBM, F-Methyl, Tracera, Zionsville, IN). The [^{18}F]fluorination of dibromomethane was performed in acetonitrile for 5 min at 120°C with K^{18}F/Kryptofix 2.2.2. The produced [^{18}F]fluorobromomethane (FBM) was isolated by gas chromatography (Porapak Q, 80/100 mesh, 7.8 x 700 mm, 100°C, helium flow = 20 cc/min), converted to [^{18}F]fluoromethyl triflate (FMT) by passing it through a heated silver triflate column then it was trapped in the second reactor at -5°C with 0.5 mL solution of acetone and the *N*-allyl-*N*-methyl-*N*-hydroxyethylamine (20 mg). The reactor was heated for 15 min at 40°C. The product was held up on a cation-exchange cartridge, isolated from the amine precursor using rinses with ethanol (10 mL) and water (5 mL). Finally, [^{18}F]FMAC was eluted form the cartridge with 0.5mL of sterile isotonic saline. All synthesis steps were monitored and controlled by a laptop computer. A disposible manifold system used in the final isolation of [^{18}F]FMAC makes the setup procedure simple and reproducible, employing all new materials for each run.

Results and Discussion: [^{18}F]FMAC was produced in good overall radiochemical yields (20-26% uncorrected) and high radiochemical purities (>98%). Radiochemical yields of [^{18}F]FMAC decreased at temperatures above 40°C due to decomposition of the product. The use of the alkyltriflate, FMT, as opposed to the alkylbromide, FBM, greatly improved the fluoromethylation reaction rate and lowered the mass requirement for amine precursor.

Conclusion: A fully automated synthesis was developed for the ^{18}F-labeled choline analog, [^{18}F]FMAC, to allow further evaluation of this tracer in human clinical trials.

Acknowledgement: Supported in part by NIH grant (HL-63771, CA-108620).

Keywords: Fluoromethylallylcholine, Automated Synthesis, Choline. Fluorine-18

P079 HIGHLY STEREOSELECTIVE ALPHA-AMINO ACIDS SYNTHONS FOR PREPARATION OF (^{18}F)-FDOPA AND ALPHA-(^{11}C)METHYL AMINO ACIDS. EVALUATION OF CHIRAL NICKEL COMPLEXES BEARING C_2-SYMMETRICALLY SUBSTITUTED BENZYL GROUP

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Introduction: Radiochemistry of short-living isotopes for radiodiagnostic imaging is a growing field for application of α-amino acids synthons. A number of efficient approaches have been developed both for specialised asymmetric syntheses and application of universal chiral precursors. Our development of metallocomplex synthons is based on disclose of factors influencing intramolecular interactions in the complexes and shielding of one side of (pro)chiral centre. Data of X-ray structure determinations and mapping of differential electron density, NMR studies of conformations of the complexes in solutions and solid state, *ab initio* MP2 modelling followed by topological analysis let us to create a lead structure: a complex carrying a C_2-symmetric benzyl group with electron-donating groups at least in both *ortho*-positions. Third generation structures allowing to achieve stereospecific alkylation by alkylhalogenides (*e. g.* substituted [^{18}F]fluorobenzylbromide in FDOPA synthesis) or highly stereoselective [^{11}C]methylation in preparation of α-[^{11}C]methyltyrosine and α-[^{11}C]methylDOPA will be presented.

Results and Discussion: Stereochemistry of alkylation of analogues of Ni(II) complexes of Schiff base of (*S*)-*N*-(2-benzoylphenyl)-1-benzylpyrrolidine-2-carboxamide and α-amino acids bearing a symmetrically substituted benzyl group was studied in thermodynamically and kinetically controlled model reactions mimicking real preparation of FDOPA or α-[^{11}C]methyl amino acids. Derivatives containing 9-anthrylmethyl, pentamethylbenzyl or 3,5-bis-*tert*-butylbenzyl groups were found to be the most efficient synthons for preparation of both target radiotracers. For these three compounds one may estimate that in thermodynamically controlled reactions like preparation of FDOPA, stereospecific formation of the chiral centre will be achieved. No chromatographic separation of stereoisomers will be necessary. Kinetically controlled model α-[^{13}C]methylation run with 69-78% d. e.

Acknowledgement: The authors acknowledge the support by the Ministry of Education, Youth and Sports of the Czech Republic (grants MSM0021627501 and MSM0021627502).

Keywords: Carbon-11, Fluorine-18, Amino Acids, Asymmetric Synthesis, Chiral Nickel Complexes

P080 PREPARATION OF *O*-(2'-^{18}F-FLUOROETHYL)-L-TYROSINE VIA DIRECT N.C.A. FLUORINATION OF Ni-BPB-*(S)*-TYRO-CH_2CH_2OX AS A SYNTHETIC PRECURSOR

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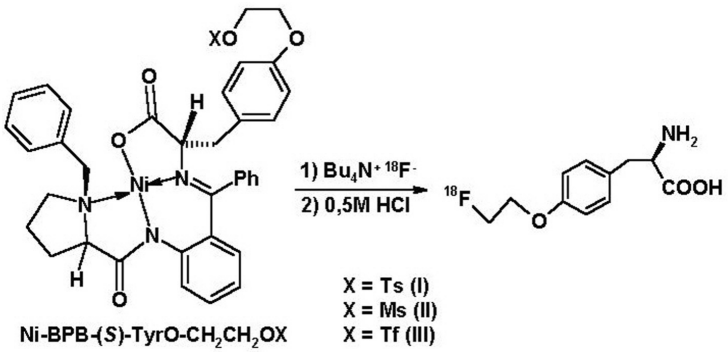
Introduction: An intense application of amino acid tracer *O*-(2'-^{18}F-fluoroethyl)-L-tyrosine ([^{18}F]FET) in clinical practice is to a great extent due to introduction of a simple synthetic method, direct n.c.a ^{18}F fluorination of *O*-(2-tosyloxyethyl)-N-trityl-L-tyrosine tert-butylester [Hamacher and Coenen, 2002]. Recently we have suggested a novel chiral enantiomerically pure precursor for [^{18}F]FET, Ni^{II} complex of a Schiff's base of *(S)*-[N-2-(N'-benzylprolyl)amino]benzophenone with *(S)*-tyrosine; Ni-BPB-*(S)*-TyrO-CH_2CH_2OTs (**I**) [Kuznetsova et al, 2006]. Nucleophilic displacement of tosyl group with [^{18}F]F^- in the presence of TBAC followed by deprotection and HPLC purification afforded the [^{18}F]FET in radiochemical yield of 25% (EOB) and enantiomeric purity 95-97%. Based on this leading structure the precursors with mesyl (**II**) and triflate (**III**) leaving groups were prepared. Here we aimed to compare these precursors for their efficiency in radiolabeling using TBAC and cryptate complex [K/K2.2.2]CO_3.

Experimental: Nucleophilic fluorination was performed in acetonitrile (80°C, 5 min, 4-5 mg of precursor) in the presence of TBAC or [K/K2.2.2]CO_3. Incorporation rate of ^{18}F into (**I-III**) was evaluated by TLC of reaction mixture diluted by water. After deprotection (0.5 M HCl, 5 min, 110°C) [^{18}F]FET was isolated by RP HPLC (CH_3COONH_4, pH 4/EtOH 92/8). Total synthesis time was 55 min.

Results and Discussion: For practical reasons we were interested in implementation of novel precursor into [^{18}F]FET production using cryptate complex, [K/K2.2.2]CO_3. Incorporation rate of ^{18}F into (**I**) was in range of 55-60%. In case of (**II**) fluorination efficiency was 55% in the presence of TBAC and 28% in the presence of kryptofix. For triflate-based precursor (**III**) radiolabeling yield was lesser than 10% in both cases. With the use of (**I**) and (**II**) in combination with kryptofix formation of non-identified labeled by-product (14-20%) was observed via TLC analysis of hydrolysis reaction mixture. Enantiomeric purity of [^{18}F]FET derived from kryptofix mediated fluorinations was only 93-94% which is crucial for PET application.



Conclusion: In conclusion, to apply Ni-BPB-*(S)*-TyrO-CH_2CH_2OX as a precursor for the synthesis of [^{18}F]FET, the use of TBAC could be recommended in radio fluorination step.

Acknowledgement: This work was supported by ISTC grant 2780 and RFBR grant OFI 06-03-08089.

Keywords: Fluorine-18, O-(2'-18F-Fluoroethyl)-L-Tyrosine, Kryptofix, TBAC

P081 OPTIMIZATION OF A ^{18}F-FLUOROETHYL-L-TYROSINE SYNTHESIS METHOD

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Introduction: In our hospital, ^{18}F-Fluoroethyl-L-Tyrosine (FET) is used for clinical imaging of brain tumors by positron emission tomography. The FET is produced regularly since 2001 using a method analogous to that of Wester et al. (1999). Because other PET scanning centers in Switzerland also started to request FET, we needed to improve our yields in order to keep up with the demand.

Due to time limitations, we decided to improve the existing method stepwise rather than establishing a completely new method. Here, we report about the methodological changes and the resulting improvements in yield and simplification of the method.

Experimental: The basic method is described in Späth et al. (2004).

Results and Discussion: Switching from Kryptofix(2.2.2)/K_2CO_3 to tetrabutylammonium (TBA) as phase transfer catalyst of the first labeling reaction increased the yield of FET by 18% (n = 6, each). For this quantitative comparison we used only productions, which were performed consecutively in an alternating way to minimize the influence of underlying uncontrolled parameter shifts. Higher radiochemical yields with TBA instead of Kryptofix was also reported by Hamacher and Coenen (2002) for their synthesis route using O-(2-tosyloxyethyl)-N-trityl-L-tyrosine tert.butylester as precursor.

Reducing the drying time of the polystyrene cartridge (LiChrolut EN; Merck) from 12 to 3 min increased the yield of FET by 34% (n = 3, each). Obviously, it is not necessary to remove all traces of methanol and water remaining on the EN cartridge from the mobile phase of the first preparative HPLC.

Substituting a self-prepared dipotassium salt of L-tyrosine by a commercially available disodium salt simplified the preparation of the synthesis. The solubility of the tyrosine salt in DMSO was improved by adding it as a solution in NaOH directly to the reactor. At the same time, we increased the temperature of the second labeling reaction from 100 to 120°C. Therefore; we cannot differentiate between the effects of those changes on the yield of FET. However, after establishment of all changes the yield is now between 6 - 8 GBq FET compared to 2 - 4 GBq before. The method is also shorter (drying of the EN cartridge) and easier (no preparation of the dipotassium salt).

Since the single changes were relatively small, each of them could be established in short term and revalidated concurrently with the regular productions for patients.

Conclusion: The improved yield allows us to satisfy the demand for FET for all of Switzerland with one production per week. Since we are expecting a still increasing demand, work is in progress to further increase the overall yield by replacing the first HPLC clean-up by a simple cartridge clean-up and by increasing the yield of the second labeling reaction by further optimizing the reaction parameters.

Keywords: 18F-Fluoroethyl-L-Tyrosine (FET), Tetrabutylammonium

P082 HIGH RADIOCHEMICAL YIELD AUTOMATIC SYNTHESIS OF 3'-DEOXY-3'-(^{18}F)FLUOROTHYMIDNE SYNTHESIS WITH PROTIC SOLVENT PLUS MODIFIED (^{18}F)FLUORIDE DRY METHODS

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Introduction: Conventional Drying procedure of [^{18}F]fluoride needed long time and high temperature for completely drying because [^{18}F]fluorination was performed under anhydrous condition. And [^{18}F]fluorination also performed under high pressure to increase radiochemical yield. In this experiment, we modified elution solvent for [^{18}F]fluoride elution from general H_2O and CH_3CN mixture to MeOH, EtOH and CH_3CN solution without H_2O for fast drying. We also modified [^{18}F]fluorination condition to reduce reaction time without loss of radiochemical yields.

Experimental: The synthesis was performed with GE TracerLab MX module. We prepared three kinds of elution buffer. They were 20 μL $TBAHCO_3$ with EtOH, MeOH and 600 μL CH_3CN, respectively. After trapping of 185 MBq/0.5 mL [^{18}F]F^- on PS-HCO_3 cartridge, [^{18}F]F^- was eluted with these buffer to the reactor. For drying step, we have 60 sec of drying time for MeOH buffer and 90 sec of drying time for EtOH and CH_3CN buffer. After drying, we added 20 mg of the precursor, 5'-*O*-DMTr-2'-deoxy-3'-*O*-nosyl-β-D-threo-pentofuranosyl)-3-*N*-BOC-thymine (**1**) or 5'-*O*-Tr-precursor (**2**) with 100 μL CH_3CN and 2 mL t-amyl alcohol. For [^{18}F]fluorination, we have 120°C and 7.5min. Compare with conventional high pressure [^{18}F]fluorination condition, we opened the valves which were connected to the reaction vessel. With this system, the reaction solvent evaporated automatically by high internal pressure of the reactor and we could increase the reaction mixture concentration for high [^{18}F]fluorination yield. After [^{18}F]fluorination, hydrolysis was performed with 1 N HCl 3 mL and 0.2 mL CH_3CN mixture solution at 85°C. After neutralization, we purified the product by HPLC.

Results and Discussion: The recovery ratio of [^{18}F]F^- was 98.7±1.1 and 97.4±2.5% with EtOH and MeOH buffer, respectively but we only obtained 75.4±1.8% with CH_3CN elution buffer. (n=6 for each condition) The radiochemical yields were 65.3±5.8, 64.3±6.7 and 35.4±5.8% for MeOH, EtOH and CH_3CN elution buffer with DMTr-protected precursor (**1**), respectively. With Tr-protected precursor (**2**), we obtained 63.8±7.2, 60.2±5.7 and 30.5±7.6% for MeOH, EtOH and CH_3CN elution buffer. (n=3 for each condition) The residual radioactivity on the cassette were < 5%. The preparation time was 35.8±5.7 min for three conditions. We have 20.8±5.7 min for the synthesis procedure and 15 min used for HPLC purification.

Conclusion: We developed new [^{18}F]F^- dry and [^{18}F]fluorination method for fast synthesis of [^{18}F]FLT. Our methods showed high and similar radiochemical yield compared with conventional drying and [^{18}F]fluorination method with dramatically reduce the preparation time.

Keywords: [^{18}F]Fluoride, [^{18}F]Fluorothymidne, Protic Solvent, Dry Method, Automation

P083 SYNTHESIS OF ([18]F)SETOPERONE USING THE NANOTEK MINUTEMAN® MICROFLUIDIC SYSTEM

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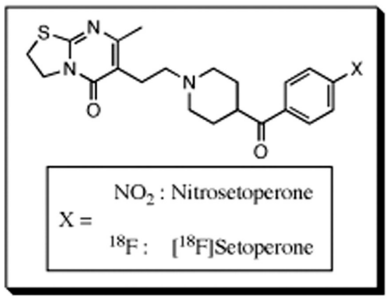
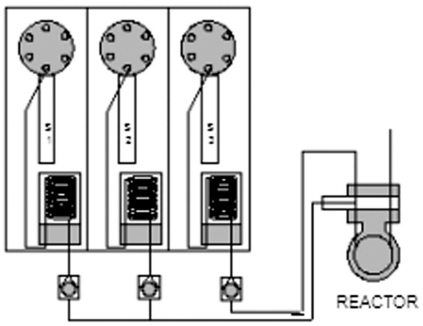
Introduction: NanoTek and others have demonstrated microfluidic platforms to synthesize PET tracers, where processing time and reagent usage decreases 30 to 100 times from that of conventional automation [1–3]. Microfluidic channels of ~100 μm increase reaction speeds by dramatically reducing diffusion distances and times (e.g. [18]F]FDG >98% rcy and [18]F]FLT 94% rcy in < 2 min). An important facet of microreactor systems for research compound development is rapid optimization of radiochemistry yields, minimizing use of precursor and time; reaction volumes of 10-100 μl and times of a few min.

We demonstrate the use of the NanoTek Minuteman® microreactor to provide improved synthesis of [18]F]Setoperone, a potent PET serotonin antagonist with moderate dopaminergic activity [4]. Due to the high cost and limited availability of the precursor (nitrosetoperone), microfluidic preparation of [18]F]Setoperone was seen as an attractive alternative for the production of this radiopharmaceutical.

Experimental: [18]F]Fluoride trapped on a resin column, released and dried with K_{222}/K_2CO_3, and resolubilized in 500μl DMSO was loaded into syringe pump 3 of 3. Nitrosetoperone (4mg, 9μmol) was loaded into pump 2 with 500μl DMSO. Pump 1 was filled with DMSO. The reactor cartridge (100μm by 4 metres, 36μl volume) was heated at 200°C. The delivery lines were primed, flow rates were set at 10μl/min and reaction volumes ranging from 10 to 200μl collected. RC yields were 70 to 80% by radioTLC. Non-optimized final product yields after HPLC purification were 35-40% with a RC purity >95%, as compared to production yields at TRIUMF of 10-20%.





Conclusion: Microfluidics provides higher yields, faster synthesis and requires only micrograms of precursor providing access to multiple compounds at a significantly reduced cost. Work is in progress to optimize the reaction parameters and product yield for [18]F]Setoperone. These results clearly indicate that [18]F]Setoperone can be synthesized substituting commonly available DMSO for the conventional solvent sulfolane [4].

References: [1] Matteo, J., et al. 53rd Society of Nuclear Medicine Annual Meeting. 2006. [2] Yu, M., et al. 53rd Society of Nuclear Medicine Annual Meeting. 2006. [3] Lu, S-Y., et al. Lab on a Chip., 2004, 523-525. [4] Crouzel C., et al. J. Lab. Compd. Radiopharm., 1988, 403.

Acknowledgement: The authors wish to thank CIHR and TRIUMF Life Sciences for support.

Keywords: [18]F]Setoperone, Microfluidics

P084 (^{18}F)/^{19}F EXCHANGE OF FLUORINE CONTAINING COMPOUNDS

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Introduction: The purpose of this study was to investigate the behaviour of fluorinated compounds in the presence of [$^{18}F^-$]. The study is aiming to increase our understanding of the impact of polyfluorinated compounds in selecting our labeling strategy. There is an increased interest in this approach, since there are drugs now containing more than one fluorine.

Experimental: [^{18}F]Fluoride and low concentration of different organofluorine compounds, shown in Figure 1, were used in a nucleophilic aromatic [^{18}F]fluorination. In this study several parameters, such as solvent, concentration, conventional and microwave heating were explored, to improve the radiochemical yield and still achieve a reasonable specific radioactivity.

Results and Discussion: Compounds **1** and **2** were labeled in 44±1 (n=2) and 29% (n=2) analytical radiochemical yield respectively, (22°C, 15 min reaction time, 1.86 mM concentration, *N*,*N*-dimethylformamide (DMF) as solvent). Compounds **3** and **4** required heating at 150°C for exchange reaction to occur and they were labeled in 8±2 (n=2) and 95 (n=2) % respectively, (15 min, 56 mM concentration, DMF). Specific radioactivity of compound **1** was determined to 5 GBq μmol^{-1}.

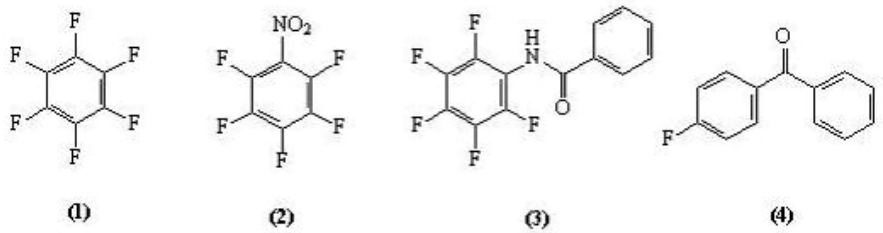

Fig. 1. Examples of compounds used in this study.

Conclusion: [^{18}F]/^{19}F exchange can be used as labelling method when the need for specific radioactivity is not a limiting factor, as in for example in straightforward drug distribution studies.

Acknowledgement: This work was conducted in collaboration with Imanet, GE Healthcare.

Reference: [1] Zhang W., Tetrahedron 59 (2003) 4475-4489.

Keywords: ^{18}F, Halogen Exchange, Organofluorine Compounds

P085 A NEW AND RELIABLE RADIOSYNTHESIS OF N.C.A. (^{11}C)RACLOPRIDE

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Introduction: Raclopride is a 2-methoxybenzamide (orthopramide) that has antipsychotic properties and acts as a potent and selective antagonist at dopamine D_2/D_3 receptors. [^{11}C]Raclopride has become a valuable tool for examining striatal dopamine receptors with PET [1].

Experimental: Several papers [2–6] dealing with the synthesis of [^{11}C]raclopride have appeared using various norraclopride precursors (HBr salt, HOTf salt, or free amine) in combination with either [^{11}C]CH_3I in DMSO or DMF or [^{11}C]MeOTf in ketonic solvents. All methods have in common, that the phenolic precursor is transformed *in situ* into a more nucleophilic phenoxide salt with either NaOH or NaH prior to the labelling reaction.

Some preliminary labelling experiments using the free precursor base and [^{11}C]MeOTf [2,3] in our hands gave low radiochemical yields and many labelled by-products. Therefore we examined in closer detail the "classical" radiosynthesis with [^{11}C]CH_3I in DMSO and different alkali metal salts with the intention to fine-tune the nucleophilicity of the precursor phenolate.

Results and Discussion: Using the free amine precursor, varying amounts of hydroxide or carbonate salts of Li, Na, and K with DMSO as the reaction solvent again gave only trace amounts of [^{11}C]raclopride accompanied by many radioactive by-products. Finally lithium methanolate (LiOMe) was found to be the base of choice. Dissolving the amine precursor in three molar equivalents of 0.1M methanolic LiOMe followed by evaporation to dryness under a stream of helium gave a glassy solid of the lithium phenolate which was dissolved in DMSO and directly subjected to methylation (80°C, 3 min).

In the reaction with [^{11}C]methyl iodide a volatile radioactive by-product always formed, which showed an almost identical chromatographic behaviour to that of [^{11}C]raclopride under standard RP HPLC conditions [5]. To the best of our knowledge this by-product has never been reported before. This impurity could, however, successfully be removed by purging helium gas through the warm (80°C) reaction mixture.

Conclusion: Using this simple technique, [^{11}C]raclopride was prepared from the preformed lithium salt of norraclopride by radiomethylation in DMSO with a radiochemical yield of 50 ± 4%, a (radio)chemical purity exceeding 99% and a specific activity of 67 ± 22 GBq/μmol, ready for injection in a synthesis time of 40 min after EOB.

References: [1] Brooks D.J. Ann. N.Y. Acad. Sci. 2003, 991, 22-35. [2] Langer O., Nagren K., Dolle F. et al. J. Labelled Cpd. Radiopharm. 1999, 42, 1183-1193. [3] Iwata R., Pascali C., Bogni A. et al. Appl. Radiat. Isot. 2001, 55, 17-22. [4] Ishiwata K., Ishii S., Senda M. Ann. Nucl. Med. 1999, 13, 195-197. [5] Ehrin E., Gawell L., Hogberg T. et al. J. Labelled Cpd. Radiopharm. 1986, 24, 931-940. [6] Fei X., Mock B.H., DeGrado T.R. et al. Synthetic Communications 2004, 34, 1897-1907.

Keywords: Raclopride, Carbon-11, PET

P086 3,4,6-TRI-O-ACETYL-2-DEOXY-2-(^{18}F)FLUOROGLUCOPYRANOSYL-1-PHENYLTHIOSULFONATE: A THIOL-REACTIVE AGENT FOR THE CHEMOSELECTIVE ^{18}F-GLYCOSYLATION OF PEPTIDES

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Introduction: Glycosyl 1-phenylthiosulfonates are agents for the site-specific glycosylation of cysteine-containing peptides. The aim of this study was to develop a chemoselective ^{18}F-glycosylation method based on a suitable ^{18}F-labeled glycosyl donor. Herein, we present the radiosynthesis of 3,4,6-tri-O-acetyl-2-deoxy-2-[^{18}F]fluoroglucopyranosyl phenylthiosulfonate (Ac_3-[^{18}F]FGlc-PTS) and its application for bioconjugation using the model peptide CAKAY and the $\alpha_v\beta_3$ targeting c(RGDfC). Furthermore, we studied the in-vitro binding affinity of the glycosylated RGD peptide.

Experimental: Peptides were synthesized by Fmoc-assisted solid-phase synthesis including microwave irradiation and analyzed by ESI-MS and LC-MS. Glycosylation of CAKAY and c(RGDfC) with Ac_3-FGlc-PTS were carried out in Tris buffer (pH 7.7, rt). Ligations were monitored by titration of residual free thiol groups with Ellman's reagent. Both S-glycosylated peptides were isolated by HPLC and characterized by NMR and ESI-MS. Receptor binding assays were performed using immobilized $\alpha_v\beta_3$ integrin and human endothelial cells (HUVEC) with disintegrin ^{125}I-echistatin. ^{18}F-glycosylated peptides were synthesized by ligation with Ac_3-[^{18}F]FDG-PTS and isolated by semipreparative radio-HPLC.

Results and Discussion: The β/α anomeric ratio of Ac_3-FGlc-PTS was >4:1 (^{19}F NMR) being maintained during the glycosylation process that afforded glycosylated c(RGDfC) or CAKAY in 90% yield. $\alpha_v\beta_3$-binding affinity of the glycosylated c(RGDfC) remained uninfluenced in comparison with c(RGDfC) and c(RGDfS) as determined by competition binding studies versus ^{125}I-echistatin (Ki = 68±10 nM ($\alpha_v\beta_3$) versus Ki = 77±4 nM (HUVEC)). Optimization of the two-step radiosynthesis of Ac_3-[^{18}F]FDG-PTS led to a RCY of 40% after 60 min (related to tetra-acetylated [^{18}F]FDG). The ligation of Ac_3-[^{18}F]FDG-PTS with both cysteine-containing peptides proceeded quantitatively in 15 min (RCY >95%). The chemoselective ^{18}F-glycosylation of c(RGDfC) provided c(RGDfC(S,S'-Ac_3-[^{18}F]FGlc)) in a decay-uncorrected RCY of 13% (EOB) within 130 min.

Conclusion: Ac_3-[^{18}F]FGlc-PTS represents a novel ^{18}F-labeling reagent for the mild chemoselective ^{18}F-glycosylation of peptides indicating its potential for the design and development of ^{18}F-labeled bioactive S-glycopeptides suitable to study their pharmacokinetics in vivo by positron emission tomography.

Keywords: F-18, Glycosylation, Peptide Labeling, PET

P087 ROLE OF (^{11}C)CH_3I PRODUCTION METHOD (GAS VS. LIQUID PHASE) ON RADIOLABELING YIELDS AND SPECIFIC ACTIVITY OF RADIOTRACERS

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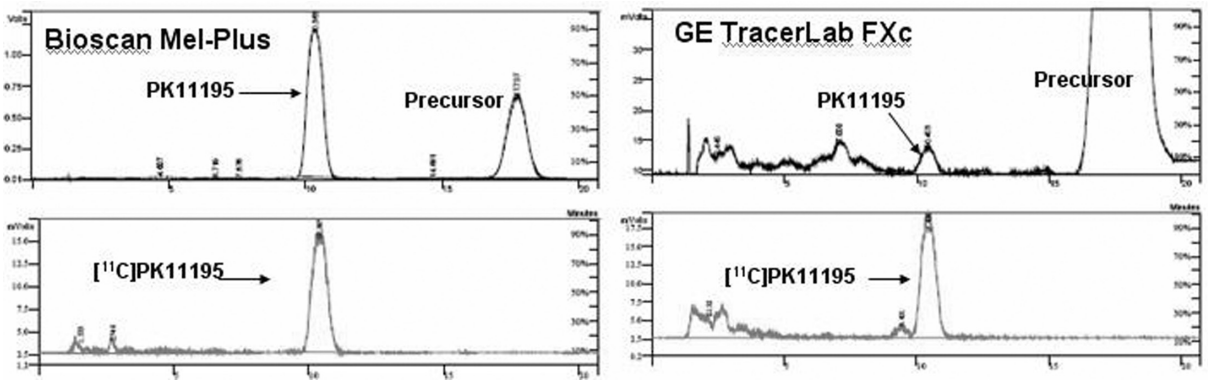
Introduction: [^{11}C]Methyl iodide (MeI) can be generated using automated synthesis modules based on gas phase or liquid phase method. The purity and specific activity (SA) of MeI may determine the radiolabeling yield and final SA of ^{11}C labeled radiotracers. Therefore, using two synthesis modules, we compared the a) quality of MeI and b) the effect of MeI quality on the synthesis, radiolabeling yields and specific activity of [^{11}C]PK11195 and [^{11}C]Alanine.

Experimental: GE Tracerlab FXc (modified version 2006) and Bioscan MeI-Plus were used to generate MeI. Based on HPLC, the UV absorbance and radioactivity profiles were analyzed. to determine the quality of MeI. [^{11}C]PK11195 was prepared by incubating a mixture of desmethyl PK11195; 1mg in 0.4 mL DMSO/DMF (3:1), KOH (15 mg) and MeI at RT for 4-5 min and purified by HPLC. [^{11}C]Alanine was prepared by incubating a mixture of N,N-(Diphenylmethylene)glycine t-butyl ester in 0.3 mL of DMF, KOH and MeI 80°C for 2 min. Following purification, acid hydrolysis and evaporation, a dry residue of [^{11}C]Alanine was obtained.

Results and Discussion: Compared to gas phase MeI, the liquid phase MeI, shows a chemical impurity (ethyl iodide) and greater mass of MeI. The MeI produced by both methods, however, do show some labeling of solvent DMF. The SA of MeI at EOB produced by the gas phase method (6-20 Ci/μmole) is much higher compared to that with liquid phase method (1-2 Ci/μmole. The radiolabeling yields of [^{11}C]PK11195 were slightly higher with liquid phase MeI. But the SA was significantly higher with MeI generated by gas Phase (4-10 Ci/μmole) compared to that with liquid phase (0.5-1.0 Ci/μmole). Figure-1 shows the relative differences in the mass of precursor and PK11195. With [^{11}C]Alanine, the radiolabeling yields were significantly higher with the gas phase MeI (70 $\pm$ 10%) compared to that with MeI produced by the liquid phase method (12 $\pm$ 5%).



Conclusion: The gas and liquid phase methods to generate MeI have been well established. However, the automated synthesis modules that are being used to generate this important ^{11}C precursor, do not appear to produce MeI of similar chemical and radiochemical quality. Careful evaluation of the purity and SA of the [^{11}C]CH_3I is absolutely necessary in order to select an appropriate automated MeI synthesis module for routine production of ^{11}C radiotracers.

Keywords: Methyl Iodide, Specific Activity, Radiolabeling Yield

P088 ENZYMATIC SYNTHESIS OF 5-HYDROXY-L-(^{11}C)TRYPTOPHAN (5-HTP)

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Introduction: 5-HTP can be used as a universal imaging method for detection of neuroendocrine tumors [1]. Tryptophanase (TRP) can be used to synthesize 5-HTP from [^{11}C]pyruvic acid, 5- hydroxyindole and ammonia. In 1989, Bjurling, et al [2] reported the preparation of [^{11}C]pyruvic acid from racemic [^{11}C]alanine using glutamic-pyruvic transaminase (GPT), D-amino acid oxidase (DAO) and catalase. Because of low heat stability of GPT, a new synthesis of [^{11}C}pyruvic acid using alanine racemase (AR) was reported in 1998 by Ikemoto et al [3]. We have combined both these techniques and optimized the multi-enzymatic synthesis of 5-HTP.

Experimental: [^{11}C]Alanine was first synthesized by heating a mixture (at 80°C for 2 min) of [^{11}C]methyl iodide, N,N-(diphenylmethylene)glycine t-butyl ester (3 mg) and 2μL KOH (5M) in 0.3 mL DMF. The reaction mixture was diluted with 20 mL water and passed through C-18 Sep-pak cartridge and washed with water. The [^{11}C] intermediate was then eluted with 2 mL of dichloromethane into a glass tube. Following hydrolysis with 0.3 mL HCl (6M), the DL-[3-^{11}C]alanine solution was evoparated to dryness at 165-170°C within 5 min. The dry residue was then dissolved in a solution containing 80 μL TRIS/HCl (0.5M, pH 9.0), 100 μL ammonium sulfate (0.15M) and 80 μL of water. To study pH effect, the pH was adjusted 8-10 using a microelectrode. Subsequently, 30 μL DAO, 100 μL AR, and 30 μL of TRP enzymes and 10 μL of pyridoxal phosphate and flavine adenine nucleotide were added. The mixture was incubated at 45°C for 15 s before the addition of 10 μL of 5-hydroxyindole (0.5M). After 3 min incubation, the reaction was quenched by the addition of 0.2 mL of HCl (6M), passed through 5 μ filter and the filtrate was injected into HPLC to separate 5-HTP from [^{11}C]pyruvate.

Results and Discussion: Radiolabeling yield of DL-[^{11}C]Alanine was 60-70% within 12 min. Careful control of temperature during hydrolysis and evoparation was critical for the synthesis of alanine. The optimal pH for 5-HTP synthesis is between 9.0-9.5 and the radiolabeling yields were 17±5% (n=22). The formation of 5-HTP was minimal at pH 8.5. The total synthesis time was 45-50 min. The use of 2-3 units of tryptophanase was optimal. Using 5-HTP-PET, we have successfully performed serial imaging studies in patients (n=20) with neuroendocrine tumors in order to understand kinetics of biodistribution and to dermine radiation dosimetry.

Conclusion: Enzymatic synthesis of 5-HTP with high radionuclidic and chemical purity appears to be both feasible and safe for routine clinical PET studies.

References: [1] Orlefors H, et al. J Clin Endocrinol Metab 2005;90:3392-3400. [2] Bjurling P, et al. J Chem Soc Perkin Trans 1989;1:1331-1334. [3] Ikemoto M, et al. Appl Radiat Isot 1998;49:1557-1562.

Keywords: [^{11}C]5-Hydroxytryptophan, 5-HTP, Enzymatic Synthesis

P089 A FACILE SYNTHESIS OF N-SUCCINIMIDYL 4-(^{18}F)FLUOROBENZOATE FOR PROTEIN LABELING

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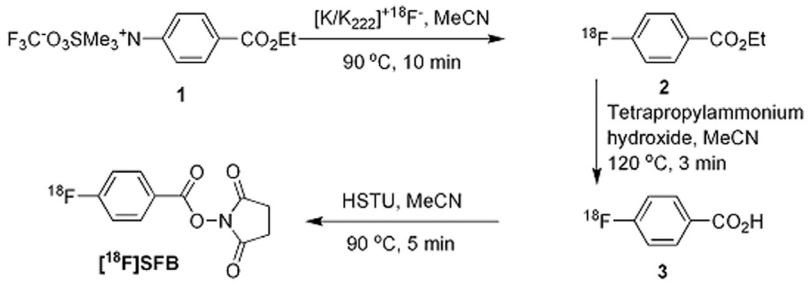
Introduction: N-Succinimidyl 4-[^{18}F]fluorobenzoate ([^{18}F]SFB) is one of the most versatile used ^{18}F-labeling agents used for labeling biomarkers such as monoclonal antibodies and peptides for PET imaging. It exhibits excellent *in vivo* stability and can be produced in good radiochemical yields. However, the current radiosynthesis of [^{18}F]SFB involves a laborious three-step procedure. Here we reported a simplified, one-pot synthesis of [^{18}F]SFB and its use in the labeling of Avastin™ (Bevacizumab), a FDA approved monoclonal antibody against VEGF as an antiangiogenesis cancer therapy.

Experimental: Ethyl 4-(trimethylammonium triflate)benzoate (**1**) (5 mg) in anhydrous MeCN (1 mL) was added to a complex of anhydrous [K/Kryptofix$_{222}$]$^{+}$^{18}F^{-}. The reaction mixture was heated at 90°C for 10 min to produce ethyl 4-[^{18}F]fluorobenzoate (**2**). The ethyl ester was subsequently hydrolyzed to form **3** using 20 mL of tetrapropylammonium hydroxide at 120 °C for 3 min and then the mixture was azeotropically dried with MeCN (1 mL). Subsequently, a solution of *N*,*N*,*N*′,*N*′-tetramethyl-O-(N-succinimidyl)uronium hexafluorophosphate (HSTU) (12 mg) in MeCN (1 mL) was added and the solution was heated at 90 °C for 5 min. After cooling, 5% acetic acid (9 mL) and H_2O(15 mL) were added. The reaction mixture was passed through a C18 Sep-Pak cartridge and a Lichrolut SCX cartridge. After the cartridge was washed with 10% MeCN (15 mL), the product [^{18}F]SFB was eluted from the cartridge with MeCN (2 mL). The solvent was then removed by a stream of nitrogen at 60 °C. Avastin (0.20-0.50 mg) solution and 0.1 M aqueous Na_2HPO_4 (0.2 mL) were added to the dried [^{18}F]SFB residue and the mixture was allowed to react at room temperature for 15 min. At the end of reaction, the mixture was purified by passing it through self-made Sep-Pak Gel Filtration cartridges.

Results and Discussion: The uncorrected radiochemical yield of [^{18}F]SFB was approximately 30% and the radiochemical purity was over 95%. The synthesis time was 60 min. [^{18}F]Avastin was produced in an uncorrected radiochemical yield of (10-35)% in 33 min from [^{18}F]SFB.



Conclusion: An efficient preparation of [^{18}F]SFB has been developed using tetrapropylammonium hydroxide in place of NaOH to reduce the total synthesis time. [^{18}F]Avastin was successfully produced utilizing the [^{18}F]SFB.

Acknowledgement: This research is supported by SNM/Mallinckrodt Seed Grant 2006.

Keywords: [^{18}F]SFB, Avastin, Positron Emission Tomography

P090 NUCLEOPHILIC AROMATIC SUBSTITUTION BY (^{18}F)FLUORIDE IN THE PRESCENCE OF A METHOXY AND A FORMYL SUBSTITUENT

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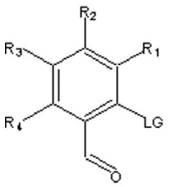
Introduction: In the context of synthesis of ^{18}F-fluorinated aromatic amino acids, the nucleophilic aromatic substitution by ^{18}F in presence of both electron donating (-OMe) and electron withdrawing (-CHO) groups has been attracting continuous interest [1–9]. The aim of the present study was to evaluate the contrary influence of –OMe and –CHO for different leaving groups.

Experimental: Nucleophilic ^{18}F-fluorination was performed in the common Kryptofix 222/potassium carbonate system (140°C, 10 mg/ml, 20 min) and analyzed by TLC and HPLC (all exp. n = 3).

Results and Discussion: For compound **1a** and **2a** in DMSO similar results were found as reported in the literature. However, in DMF substitution mainly showed enhanced yields. In presence of the methoxy substituent labeling yields were also clearly higher in DMF (55–87%) than in DMSO (4–75%). Moreover depending on the substitution pattern, compound **1c**, **1e** and **2c** gave higher RCYs than **1b**, **1d**, **2b** where the electron donating methoxy group was in *meta* position to the LG.



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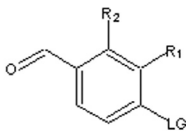

2

	LG			
	NO_2		Cl	Br
	DMF (DMSO)	Lit.	DMF (DMSO)	DMF (DMSO)
1a (R_{1-4}=H)	73±0.3 (68±0.4)	53-87 [1-7]	65±1 (1±0.3)	73±0.2 (2±0.5)
2a ($R_{1,2}$=H)	82±6 (40±3)	53-75 [1,3-8]	70±3 (1±0.8)	76±1 (1±0.6)
1b (R_1=OMe)	67±3 (6±0.6)	16.8-23 [2]		
1c (R_2=OMe)	87±3 (74±4)	75-87 [2,4]		
1d (R_3=OMe)	55±5 (4±0.7)	5 [2]		
1e (R_4=OMe)	79±4 (41±0.6)	–		
2b (R_1=OMe)	77±3 (23±1)	29-55 [2,4,5]		
2c (R_2=OMe)	83±3 (75±8)	75 [5]		

Conclusion: Nucleophilic substitution of formyl activated aromatic compounds was improved using DMF instead of DMSO, the solvent effect was strongest for the halogen exchange (LG = Br, Cl). A single methoxy group in *ortho* or *para* position to the LG resulted in lower RCYs. Future synthetic approaches for the synthesis of ^{18}F-fluorinated aromatic amino acids should avoid this substitution pattern.

References: [1] Maeda et al., Appl Radiat Isot 43, 1992, 1035. [2] Ding et al., J Fluorine Chem 48, 1990, 189. [3] Ekaeva et al., Appl Radiat Isot 46, 1995, 777. [4] Lemaire et al., Appl Radiat Isot 43, 1992, 485. [5] Rengan et al., J Label Compds Radiopharm 33, 1993, 563. [6] Hwang et al., Appl Radiat Isot 42, 1991, 1043. [7] Stone-Elander et al., Appl Radiat Isot 44, 1993, 889. [8] Lemaire et al., Appl Radiat Isot 38, 1987, 1033. [9] Tierling, Berichte des Forschungszentrums Juelich, JUEL-3952 (2002).

Keywords: Nucleophilic Aromatic Substitution, Formyl Arenes, [^{18}F]Fluoride, Denitrofluorination

P091 MODEL COMPOUNDS FOR THE NUCLEOPHILIC ^{18}F-LABELING OF TYROSINE

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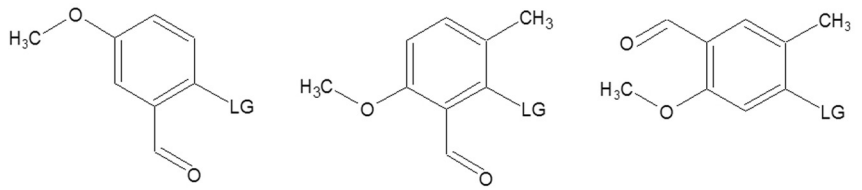
Introduction: With regard to the synthesis of [^{18}F]-*m*-tyrosine and [^{18}F]-*p*-tyrosine via nucleophilic ^{18}F-fluorination of carbonyl activated aromatic compounds, model compounds were synthesized to examine the influence of the substitution pattern on the RCY in order to systematize previous results[1-5]. Dependency on solvent, temperature and concentration was also examined.

Experimental: The nucleophilic ^{18}F-fluorination was performed with [K/2.2.2.]/$^{18}F^-$. The RCY was monitored by TLC after 1, 3, 7, 10, 20 and 30 minutes. Given RCYs are the maximum observed yields within this time period. Unless stated otherwise, all reactions were carried out in 1 ml DMF, 120°C, 0.05 mmol/ml, n=5.

Results and Discussion: Compounds **1** (LG = F, Br, Cl, I, NO_2) were synthesized as models for *m*-tyrosine. RCYs varied from 17 to 83%. Isotopic exchange showed best results (RCY 83%, n=1), followed by ^{18}F-substitution of NO_2 (RCY 55 ±5%, n=3).



1 **2** **3**

2 and **3** (LG = F, Br, Cl, NO_2) were applied as model systems for *p*-tyrosine. RCYs varied from 9 to 85% for **2** and 32 to 80% for **3**. Independent on the position of the electron withdrawing formyl group (*o* in **2**, *p* in **3**), isotopic exchange showed best results (RCY 85 ±5% for **2**, RCY 80 ±8% for **3**), followed by ^{18}F-substitution of NO_2 (RCY 52 ±6% for **2**, RCY 72 ±8% for **3**).

For **2** (LG = NO_2) the influence of the reaction conditions on the RCYs was investigated. In the range of 60–140°C, RCYs ranged from 6 to 62%, with maximum yield at 140°C (RCY 62 ±8%). As in our previous study [4], a strong solvent dependency was observed. DMSO, DMF and DMA were tested at 120°C. The most commonly used solvent in the literature, DMSO led to a considerably lower yield (36 ±6%) than DMF (52 ±6%). Changes of the concentration of **2** (0.5 - 20 mg/ml) resulted in RCYs between 18% (0.5 mg) and 52 ±6% (10 mg).

Conclusion: Future synthetic approaches for the nucleophilic ^{18}F-fluorination of aromatic compounds should target structures with NO_2 as leaving group in the *p*-position to the electron withdrawing formyl substituent. Labeling should be carried out in DMF at a temperature of 140°C.

References: [1] Ding et al., J. Fluorine Chem., 48, **1990**, 189-205. [2] Lemaire et al., Appl. Radiat. Isot., 43, **1992**, 485-494. [3] Tierling, Ber. Forsch.zentr. Jülich; 3952 (**2002**). [4] Al-Labadi et al., J. Rad. Nuc. Chem 270(2), **2006**, 313-318. [5] Rengan et al., J. Label. Compds. Radiopharm., 33, 7, **1993**, 563-572.

Keywords: Nucleophilic Aromatic Substitution, Tyrosine, Denitrofluorination, Formyl Arenes, ^{18}F-Labeled Aromatic Aminoacids

P092 SYNTHESIS AND EVALUATION OF ^{18}F-LABELED BENZOXAZOLE AND BENZOTHIAZOLE DERIVATIVES WITH HIGH AFFINITY TO β-AMYLOID PROTEIN

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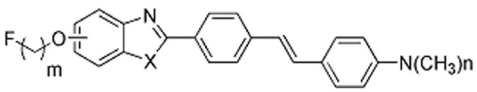
Introduction: Formation of β-amyloid (Aβ) plaques in the brain is a major contributing factor in the pathogenesis of Alzheimer's Disease (AD). Detection of Aβ plaques in the brain can be used in early diagnosis and monitoring the progression of AD. Herein we describe synthesis and evaluation of 5-, or 6-substituted-2-(4-aminostilbene)benzoxazole and benzothiazole derivatives, potential diagnostic imaging agents for Aβ plaques in AD brain.

Experimental: Synthesis of the desired 5-, or 6-fluoroalkyloxy-2-(4-aminostilbene)benzoxazole and benzothiazole derivatives(**I**) was achieved via cyclization reaction, nitro groups reduction and reductive amination of methylamino/dimethylamino groups. The unlabeled and precursor compounds were prepared by substitution reaction of 5-, 6-OH-2-(4-aminostilbene)benzoxazoles or benzothiazoles with 2-fluoroethanol-*p*-tosylate or di-*p*-tosylate ethylene glycol. For *in vitro* binding assays, the pre-formed Aβ42 aggregates were employed to assess the binding affinities of these derivatives competing against [^{125}I]TZDM. K_d of [^{125}I]TZDM and IC_{50} values of synthesized unlabeled compounds were measured. K_i values were calculated using the Cheng-Prusoff equation ($K_i = IC_{50}/(1+[L]/K_d)$). After selection of promising compounds with excellent K_i values, radiolabeling was performed by reacting the tosylated precursors with TBA^{18}F in CH_3CN/t-amylalcohol. Biodistribution studies of the labeled compounds were carried out via micro-PET in normal mice after iv injection.



m = 2, 3 X = O, S n = 0, 1, 2

I

Results and Discussion: The synthesis of the desired 24 unlabeled compounds and 4 [^{18}F]labeled compounds was successfully achieved. According to the binding assays targeting Aβ42 aggregates, the unlabeled derivatives competed well against [^{125}I]TZDM, displaying lower K_i values (K_i = 0.32-0.68 nM) than PIB compound (K_i = 0.77 nM). The radiochemical yield gave about 30%.

Conclusion: Most of the synthesized compounds showed excellent binding affinities to Aβ aggregates compared to PIB compound. Taken together, the data suggest that the novel [^{18}F] labeled compounds can be used as PET tracers for imaging Aβ aggregates in the brain of AD patients.

Acknowledgement: We are grateful to the Ministry of Science and Technology (MOST) and Ministry of Commerce, Industry and Energy (MCIE) of Korea for financial support.

Keywords: β-Amyloid, [^{18}F], Inhibition Constant (Ki), Aβ42

P093 DESIGN AND APPLICATION OF A GENERAL-PURPOSE AUTOMATIC LIQUID HANDLING MODULE FOR PET TRACERS

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Introduction: Flexible module system with easy programming backbone is necessary for intensive research on PET tracer development. Commercially-available automatic synthesizers are mechanically stable and reliable, but have various limitations such as high cost, low flexibility, complex programming, and so on. In preliminary steps of PET tracer synthesis, flexible modules with simple programming backbone are strongly desired. Recently, micro-computer technology allows us to assemble miniatured humanoid robots even in hobby level. Using this technology, we developed flexible modules including automatic three-way valves, syringes and I/O unit for controlling external devises. Applicability and reliability was confirmed with some applications of the system, such as Cu-64 production, HPLC purification, and so on.

Experimental: The automatic modules were designed to control a sterilized disposable three-way valve or syringe, to realize sterility as well as disposability even in basic research. In addition, this concept allowed us to avoid cross-contamination of the reagents. A main board had a capacity of controlling 32 modules simultaneously. Programming was based on "manual positioning + teaching", so that no special engineering knowledge was required. To confirm the usefulness of the system, we developed an automatic Cu-64 separation and purification system from Ni-64 solid target as an example. The system consisted with two syringes, 11 three-way valves and one heater with temperature controller through I/O unit. The separation between Ni and Cu was used the disposable ion exchange column (Poly-Prep column AG1-X8, Bio-rad). The evaluation of the module was performed using the non-radioactive Ni/Cu and the Cu-64 which was produced with Ni-64 (p, n) Cu-64 reaction using a cyclotron (Eclipse RD/HP, 11 MeV, Siemens).

Results and Discussion: In the cupper purification trials, we confirmed that this system accomplished to collect and purify the Cu in both cold and hot runs with sufficient reproducibility. This system may realize trial research synthesis under one tenth of the cost of commercially available synthesizers without an engineering knowledge.

Conclusion: We designed a new flexible automatic module system. This convenient system may help the research of the PET tracer development.

Keywords: Automatic Module, Low Cost and Flexible Synthesizer, Sterilyzed and Disposable Kit, PET Tracer

P094 A NOVEL RAPID ONE-STEP SYNTHESIS OF (^{18}F)FLT USING MICROFLUIDIC REACTOR

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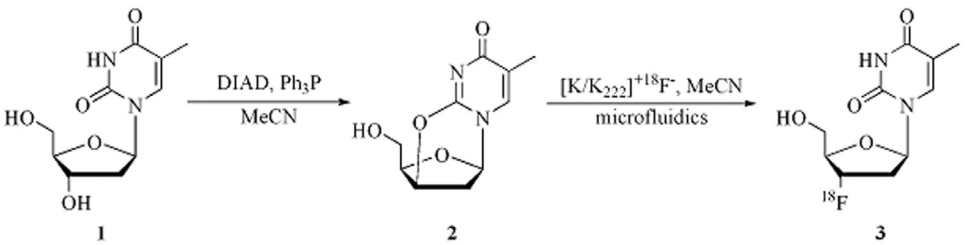
Introduction: Labeled thymidine is the preferred radiopharmaceutical for indicating cellular proliferation. The radiosynthesis of [^{18}F]FLT recently described by Grierson *et al.*, started with the labeling precursor 3-*N*-(2,4-dimethoxylbenzyl)-1-[5-*O*-(4,4'-dimethoxyltrityl)-3-*O*-nosyl-2-dexy-β-D-lyxofuranosyl]thymine, which requires a seven-step route starting from thymidine and two radiosynthesis steps – labeling and hydrolysis. Here, we describe a novel one-step precursor synthesis procedure for the conversion of thymidine into 2,3'-anhydrothymidine, and a one-step microfluidic labeling method to improve the labeling efficiency, including improved yield and fast production.

Experimental: A mixture of thymidine (0.76 g), and triphenylphosphine (1.65 g) was azeotropically dried with portions of acetonitrile (15 mL). The residual was suspended in MeCN (20 mL) and then cooled to –20°C. To the rapidly stirred mixture, a solution of DIAD (diisopropylazodicarcarboxylate, 1.27 g) in MeCN (7 mL) was added dropwise, while maintaining the temperature between –15°C and –20°C. The resulting cold mixture was stirred for 1.5 h and then allowed to slowly warm to 10°C over 5 h. A light brown solution was present. This solution was rapidly stirred at room temperature and then treated with water. The addition led to the quick formation of a thick suspension which was filtered after 30 min. The collected white solid was washed with MeCN and vacuum dried to afford 0.95 g (yield: 85%) of anhydrothymidine (**2**). A MinuteMan LF (NanoTek), liquid-flow microfluidic reactor system, was used to convert **2** to [^{18}F]FLT (**3**). Reagent solutions were prepared and loaded into the MinuteMan LF: reagent cartridge #1 was loaded with **2** dissolved in anhydrous MeCN, reagent cartridge #2 was loaded with no-carrier-added [^{18}F]fluoride ion in MeCN, produced from [^{18}O]-enriched target water, trapped on a micro MP-1 ion exchange column and released with a solution of kryptofix$_{222}$ and K_2CO_3 in 10% water in MeCN followed by the azeotropic removal of water at 110°C.

Results and Discussion: The uncorrected radiochemical yield of [^{18}F]FLT was 10-20% and the radiochemical purity was over 95%.



1 2 3

Conclusion: An efficient preparation of [^{18}F]FLT has been developed using one-step synthesis of 2,3'-anhydrothymidine and one-step microfluidic labeling.

Acknowledgement: This research is supported by DOE Grant No: DE-FG02-05ER84290.

Keywords: [^{18}F]FLT, Microfluidic, Positron Emission Tomography

P095 THE ROLE OF BASE IN ([18]F)FLT SYNTHESIS

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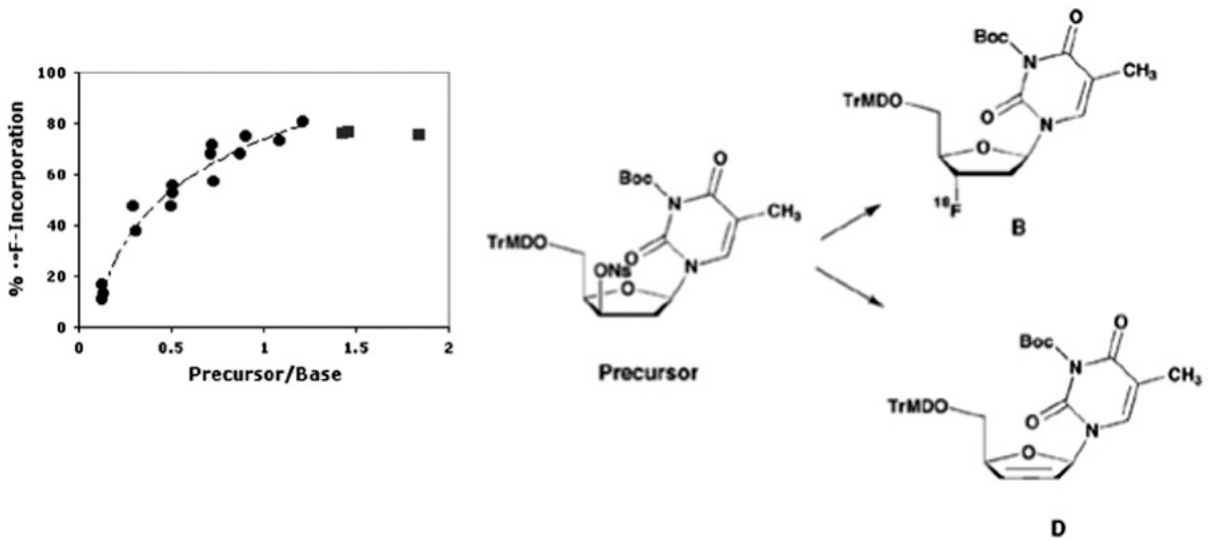
Introduction: Synthesis of 3'-deoxy-3'-[^{18}F]fluorothymidine, [^{18}F]FLT, via nucleophilic substitution of the nosyl group with ^{18}F has been previously reported (1-3). Since we were unable to reproduce some of the results presented in the literature, we have further investigated critical factors influencing the ^{18}F-fluorination reaction.

Experimental: 3-N-Boc-1-[5-O-(4,4[apos]-dimethoxytrityl)-3-O-nosyl-2-deoxy-β-D-lyxofuranosyl]-thymine was used as the precursor. The substitution reaction with ^{18}F under different conditions with various amounts of the precursor (6-20mg), Kryptofix 222 (K222) (3.8-28mg) and K_2CO_3 (1-5mg) was studied by analyzing the reaction in acetonitrile using HPLC.

Results and Discussion: The rate of ^{18}F incorporation into the [^{18}F]FLT intermediate (B) by nucleophilic substitution dramatically changed with the basicity of the reaction medium, which was derived from the K222/K_2CO_3 complex. Starting with 6-13 mg of the precursor (average 8.8±2.2mg: 11 μmole), 60-70% of ^{18}F (average 64.4±10.5%) was incorporated into the intermediate in the presence of 14 μmole of the base after 5 minute heating at 100°C. In contrast, a 5-fold increase of the base to 74 μmole resulted in a remarkable drop of ^{18}F incorporation to 13.4±2.8%. Furthermore, most of the precursor (>97%) was found decomposed. The rate of ^{18}F incorporation depended upon the precursor-to-base ratio (Figure 1) and reached a plateau of approx 80% when the ratio approached 1.2-1.5. These findings suggest that in the presence of an excess amount of the base, the precursor is consumed quickly by the E2 elimination mechanism (Figure 2) before the substitution reaction is complete. Under optimal conditions, where the precursor-to-base ratio was controlled, an overall [^{18}F]FLT yield of 30-40% was achieved even if the precursor amount was as small as 8-13 mg.



Conclusion: Control of basicity of the reaction medium, where ^{18}F is incorporated into the [^{18}F]FLT intermediate by nucleophilic substitution, is one of the key factors determining the yield of [^{18}F]FLT.

References: [1] Grierson JR et al. Nucl Med Biol (2000) 27:143-156. [2] Martin SJ et al. Nucl Med Biol (2002) 29:263-273. [3] Yun M et al. Nucl Med Biol (2003) 30:151-157.

Acknowledgement: We thank Mr. Howard Sheh and Mr. Calvin Lom of Sloan-Kettering Institute for ^{18}F production essential for this work.

Keywords: [^{18}F]FLT, 3'-Fluorothymidine, Elimination and Substitution

P096 ^{18}F-LABELLED METOMIDATE ANALOGUES AS ADRENOCORTICAL IMAGING AGENTS

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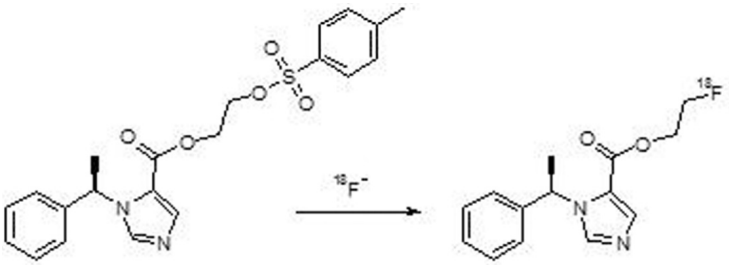
Introduction: ^{11}C-Metomidate and its ethyl analogue were synthesized with the purpose to develop a PET imaging agent for tumors of adrenal cortex[1]. Although ^{11}C-MTO has good biological properties the high uptake in the liver sometimes disturbs the interpretations of the images. The search for an alternative led to the development of ^{18}F-labelled analogues. We have created a small library of ^{18}F-MTO labelled analogue compounds.

Experimental: In the two-step synthesis of for example 2-[^{18}F]fluoroethyl 1-(1-phenylethyl)-1H-imidazole-5-carboxylate, ([^{18}F]ETO), (**B**), 1,2-bis(tosyloxy)ethane was used to yield 2-[^{18}F]fluoroethyl 4-methylbenzenesulfonate. The fluoro derivative was then reacted with the pre-treated MTO-precursor to yield (**B**). A more rapid and efficient labelling method, with a potential to be automized was accomplished by performing a one-step nucleophilic fluorination according to scheme 1. Precursors like 2-{[(4-methyl-phenyl)sulfonyl]oxy}ethyl 1-[(1*R*)-1-phenylethyl]-1*H*-imidazole-5-carboxylate (**A**), was synthesized and then reacted with [^{18}F]fluoride, to yield (**B**).

Results and Discussion: A convenient two-step synthesis of ^{18}F-labelled Metomidate analogues, compaired to the literature[2], was developed and the products were obtained in 17 ± 1% decay-corrected radiochemical yields. In the one step labelling synthesis of compound (**B**) The specific radioactivity was measured at 328 GBq/μmol (6.92×10^{-4} μmol total mass) after 4 μAh bombardment and 75 min synthesis.



Scheme 1. One-step labelling synthesis of [^{18}F]ETO.

Conclusion: The ^{18}F-labelled analogues provides tracers which are easily synthesized and results in high specific radioactivity.

Acknowledgement: This work was conducted in collaboration with Imanet, GE Healthcare

References: [1] Bergstrom, M., Bonasera, T.A., Lu, L., Bergstrom, E., Backlin, C., Juhlin, C., Langstrom, B. *Society of Nuclear Medicine*, **1998**, 39, 982. [2] Wadsak, W., Mitterhauser, M. *Journal of Labelled Compounds & Radiopharmaceuticals* **2003**, 46(4), 379.

Keywords: [^{18}F]Fluorination, [^{18}F]Alkyl MTO Analogues

P097 UTILIZING A VERSATILE INEXPENSIVE CATALYST 5 ROBOT TO SYNTHESIZE ^{18}F-FLUORODIHYDROTESTOSTERONE (^{18}F-FDHT)

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Introduction: Commercially available robot systems have been utilized at Washington University for over 20 years for the preparation of positron-emitting (PET) radiopharmaceuticals. In 2004 a CRS Catalyst 5 robot (Thermo Electron Corp.) replaced a CRS M1A (Hudson Corp.) robot used to make ^{18}F-fluorodeoxyglucose, ^{18}F-fluoroestradiol (^{18}F-FES). We will discuss the preparation of ^{18}F-flurodihydrotestosterone (^{18}F-FDHT).

Experimental: Currently, the Catalyst 5 robot is used to synthesize ^{18}F-FDHT, ^{18}F-FES, ^{18}F-fluorothymidine, and 9-[(4-[^{18}F]-fluoro)-3-hydroxymethylbutyl]guanine (^{18}F-FHBG). All items that come into contact with reagents used by the robot are disposable with the exception of the preparative HPLC. Visual Basic was used to develop the user interface, the kernal for communication with the robot arm and all RS-232 compatible external hardware used in each synthesis. Commercially available syringe pumps(Hamilton) have been purchased for reagent additions and solid phase extractions. All other synthesis components have been designed and fabricated "in house".

Results and Discussion: The initial set-up and first synthesis of ^{18}F-FES was completed within four months and subsequent syntheses have been developed in less than two weeks. Manually produced ^{18}F-FDHT radiochemical yields have been 47.6±13.5%, >95% radiochemical purity and a synthesis time of 100 minutes. Robotically produced radiochemical yields have been 44.3±4.3%, >95% radiochemical purity and a synthesis time of 120 minutes. Typical starting activity range from 150-250 mCi(5.5TBq-9.2TBq) with 28-41mCi(1.0TBq-1.5TBq) of final product.

Conclusion: Radiochemical yields of ^{18}F-FDHT and the other three robotically produced syntheses (^{18}F-FES, ^{18}F-FHBG, ^{18}F-FLT) are comparable with the reported manual yields and have lower standard deviation. The robot is a valuable asset for the production of multiple ^{18}F labelled syntheses.

Acknowledgement: This work was supported by Department of Energy grant DE FG02 84ER60218.

Keywords: Automation, Robot

P098 RADIOSYNTHESIS OF (^{11}C)6-OH-BTA-1 IN DIFFERENT MEDIA AND CONFIRMATION OF REACTION BY-PRODUCTS

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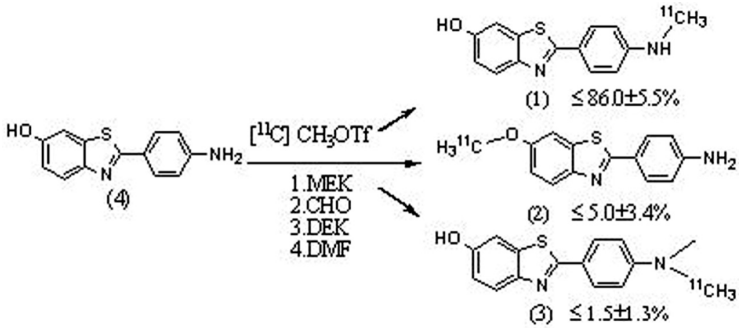
Introduction: [^{11}C]6-OH-BTA-1 ([*N*-methyl-^{11}C]2-(4'-methylaminophenyl)-6-hydroxybenzothiazole, **1**), a β-amyloid imaging agent for the diagnosis of Alzheimer's disease in PET, can be labeled with higher yield by a simple loop method. During the synthesis of [^{11}C]**1**, we found formation of by-products in various solvents, such as methylethylketone (MEK), cyclohexanone (CHO), diethylketone (DEK), and dimethylformamide (DMF), and confirmed those by-products.

Experimental: In automated radiosynthesis module, 1 mg of 4-aminophenyl-6-hydroxybenzothiazole (**4**) in 100 μl of each solvent was reacted with [^{11}C]methyl triflate in HPLC loop at room temperature (RT). The reaction mixture was separated by a semi-preparative HPLC. Aliquots eluted at 14.4, 16.3 and 17.6 min were collected and analyzed by analytical HPLC and mass spectrometery.

Results and Discussion: The labeling efficiencies of [^{11}C]**1** were 86.0±5.5%, 59.7±2.4%, 29.9±1.8%, and 7.6±0.5% in MEK, CHO, DEK and DMF, respectively. Specific activity of [^{11}C]**1** was 2.5±2.3 x 10^5 (Ci/mol) in MEK. The mass spectra of three products eluted at 14.4, 16.3 and 17.6 mins showed peaks of m/z 257.3 (M+1), 257.3 (M+1) and 271.3 (M+1) indicating their structures as 1, 2-(4'-aminophenyl)-6-methoxybenzothiazole (**2**) and 2-(4'-dimethylaminophenyl-6-hydroxybenzothiazole (**3**), respectively. Ratios of labeling efficiencies for the three products ([^{11}C]**1**:[*O*-methyl-^{11}C]**2**:[*N*-methyl-^{11}C]**3**) were 86.0±5.5%:5.0±3.4%:1.5±1.3% in MEK, 59.7±2.4%:4.7±3.2%:1.3±0.5% in CHO, 9.9±1.8%:2.0±0.7%:0.3±0.1% in DEK and 7.6±0.5%:0.0%:0.0% in DMF, respectively.



Conclusion: The labeling efficiency of [^{11}C]**1** was the highest when MEK was used as a reaction solvent. O-methylated and dimethylated by-products were also confirmed by mass spectrometry and HPLC.

Keywords: Alzheimer's Disease, PIB, PET, β-Amyloid Plaque

P099 AUTOMATED PRODUCTION OF (^{18}F)FLUORODOPA INJECTION, USP

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Introduction: For several years Fluorodopa F 18 Injection, USP (6-[^{18}F]fluorodopa; [^{18}F]FD) has been produced for research studies of brain pathology using a remotely-operated synthesis system (1) based on a [^{18}F]fluorodestannylation pathway (2). [^{18}F]Fluorine for this method was produced via the ^{20}Ne(d,α)^{18}F reaction using the Washington University JSW 16/8 cyclotron, and typical batch yields were 10-15 mCi after a total production time of 180 min.

We have developed a new radiopharmaceutical production system that complies with the more stringent requirements mandated by USP Chapter 797, as well as to meet additional clinical demand for use of [^{18}F]FD in PET oncology studies (3). This system applies the same synthetic pathway as the remotely-operated system, but utilizes [^{18}F]F_2 produced via the double-shot ^{18}O(p,n)^{18}F method (4) using the Washington University RDS Eclipse cyclotron. The stannylated labeling substrate is obtained from ABX (Radeberg, FRG).

Experimental: A fully-automated [^{18}F]FD Module was constructed for the very competitive price of less than $15,000. All supplies used in the synthesis are disposable, including tubing and reagent containers. This greatly simplifies cleaning and maintenance of a sterile, pyrogen-free drug production environment. Preparative HPLC, (stationary phase: Whatman Partisil 10 ODS-3 M9/25; mobile phase: Sterile Water for Injection, USP/Acetic Acid, glacial, 99.99+% (999/1 v/v) 4 mL/min) was used to isolate the drug product. Terminal sterilization of the product was achieved using an in-line 0.22 μ filter, which was checked for membrane integrity prior to drug release.

Results and Discussion: This module routinely produces 50 mCi (1.85GBq) batches of [^{18}F]FD from a 30-min 40μA bombardment, and 10 minute passivation run (4). This batch yield corresponds to a radiochemical yield of 25$\pm$5%, which is similar that of more expensive commercial devices marketed for production of [^{18}F]FD. The overall production time is only 110 min including bombardment, and the entire procedure is automated to minimize radiation burden to personnel.

Conclusion: The [^{18}F]FD produced with this automated module has a radiochemical purity exceeding 95%, a specific activity greater than 1000 mCi/mmol, (37 GBq/mmol) and meets all USP requirements for drug purity.

Acknowledgement: Research Supported by NS04056.

P100 ^{18}F-GLYCOSYLATION USING KOENIGS-KNORR CONDITIONS: A COMPARATIVE STUDY

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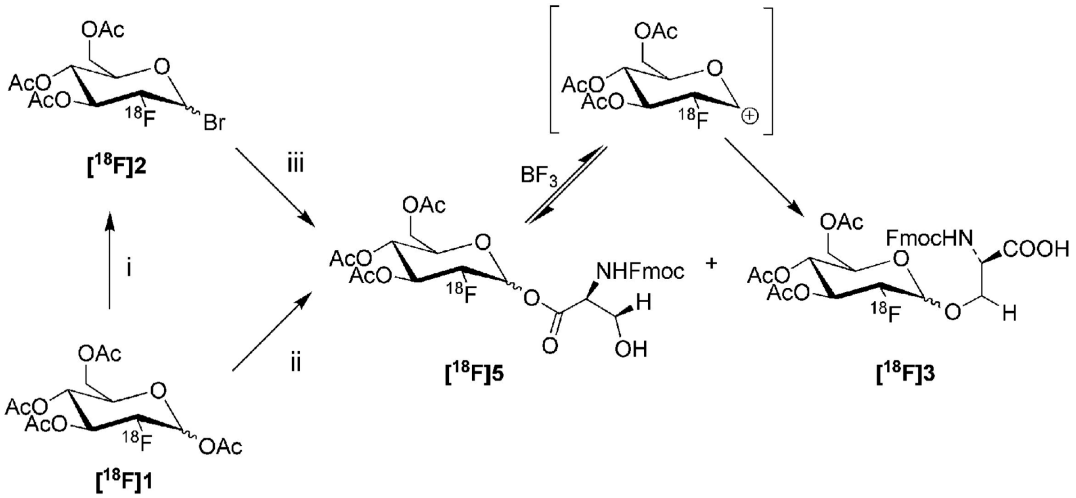
Introduction: The use of prosthetic groups for ^{18}F-labelling of biomolecules has gained considerable importance for the synthesis of radiopharmaceuticals for positron emission tomography. We recently examined the applicability of tetra-O-acetylated [^{18}F]FDG (**[^{18}F]1**) as ^{18}F-glycosylation agent. We herein report a comparison of **[^{18}F]1** with 3,4,6-tri-O-acetyl-2-deoxy-2-[^{18}F]fluoroglucopyranosyl bromide (**[^{18}F]2**) as an alternative ^{18}F-glycosyl donor under Koenigs-Knorr conditions.

Experimental: **[^{18}F]2** was synthesized by bromination of **[^{18}F]1** with HBr/AcOH in dichloromethane at room temperature (rt). ^{18}F-glycosylation using BF_3 was accomplished by adding the labelling precursor (10 mM) in 200 µl MeCN and 5 µl BF_3 to dry **[^{18}F]1** at 80°C. ^{18}F-glycosylation applying Koenigs-Knorr conditions using AgOTf was optimized with respect to the choice of solvent, AgOTf/labelling precursor ratio and reaction temperature. Both ^{18}F-glycosylation methods were performed by using the N-protected amino acid Fmoc-Ser-OH and fully protected Z-Ser-OBn to obtain the corresponding products **[^{18}F]3** or **[^{18}F]4**. All reference compounds were synthesized by Lewis-Acid promoted glycosylation (including **3** or **4**, and glycoester **5**), characterized by NMR and MS, and used for the analysis of radioactive product distribution by HPLC.

Results and Discussion: The BF_3-method using BF_3 and Fmoc-Ser-OH or Z-Ser-OBn as glycosyl acceptors gave a decay-uncorrected radiochemical yield (RCY) of 23% for **[^{18}F]3** and 11% for **[^{18}F]4** after HPLC-separation in 60 min. Studying the reaction of **[^{18}F]1** with Fmoc-Ser-OH for early reaction time points we observed the formation of glycoester **[^{18}F]5**, which was converted into **[^{18}F]3** during the progress of the reaction. Applying the optimized Koenigs-Knorr conditions to the ^{18}F-glycosylation of Fmoc-Ser-OH, the RCY of **[^{18}F]3** decreased to 21%, due to irreversible formation of glycoester **[^{18}F]5**. In the case of Z-Ser-OBn the Koenigs-Knorr method revealed an improved RCY of 67±6% in comparison with 27±4% obtained by the BF_3-method. Contrary, the serinyl precursor containing a free carboxyl group (Fmoc-Ser-OH) was advantageously labelled by ^{18}F-glycosylation applying the BF_3-method.



i: HBr/AcOH; ii: boron trifluoride, MeCN, Fmoc-Ser-OH; iii: AgOTf, DCM, Fmoc-Ser-OH

Conclusion: Applying Koenigs-Knorr reaction conditions, **[^{18}F]2** proved its suitability for the AgOTf-activated ^{18}F-glycosylation of Z-Ser-OBn with improved RCY. Therefore, the ^{18}F-glycosylation agent **[^{18}F]2** should be preferentially applied to O-glycosylation reactions on suitably protected biomolecules.

Keywords: F-18, Glycosylation, FDG, Koenigs-Knorr

P101 DESGIN, SYNTHESIS AND EVALUATION OF NEW TRACERS FOR NON-INVASIVE IMAGING OF AMYLOID PLAQUES

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Introduction: Amyloid-plaque formation is one of the earliest and most relevant physiological processes in the development of Alzheimer's disease (AD). We present a report on our efforts to develop a tracer applicable for both, PET and SPECT, with enhanced selectivity for Aβ42 and improved in vivo properties, i.e. metabolic stability. The lead structure, phenylimidazo-1,2-a-pyridine (IMPY) was decorated with various substituents and substitution pattern.

Experimental: Apart from altered substitution pattern on the aromatic rings, the extent and nature of N-anilino alkylation was varied. In addition, structures have been selected allowing for C-11 and radiohalogenation. Affinity was determined using competition binding assays (Ki) on synthetic Aβ40 and Aβ42 amyloid fibrils. Together with structural overlays and modeling calculations, the affinity and selectivity data were used for the identification and assessment of relevant substructures and their influence on Aβ-binding.

Results and Discussion: Twenty-two new derivatives of IMPY were synthesized and tested. The binding experiments to fibrils of synthetic Aβ42- and Aβ40-peptides showed up to 92% inhibition of binding of the 3H-labeled reference at the 100 nM level to Aβ42 and up to 83% inhibition to Aβ40 resulting in Aβ42-to-A β40-selectivity ratios of up to 41. The lipophilicity (logPoctanol/PBS) of the compounds was in the range of 0.5 to 3.5. By overlays and trend analyses four distinct substructures with differentially pronounced impact on the binding were identified (Fig.1). Apparently these substructures independently determine binding and thus allow subtle adjustment of molecular properties. In addition, as recently demonstrated for a series of BTA-analogues, this model enables tailoring of lipophilicity, brain uptake, plasma half-life and in vivo stability.

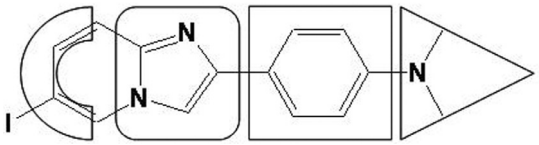

Fig. 1

Conclusion: Twenty-two novel IMPYs substituted with radiohalogens or C-11 in different positions have been synthesized and evaluated as Aβ-ligands. Changes of the substitution pattern can be used to improve the selectivity for the two relevant Aβ-proteins. Work is in progress to further explore the identified key molecular descriptors for further optimization of the combination of radiolabel and the identified lead structures. Verification of the in vitro data is currently being performed in a double transgenic mice model ex vivo and in vivo and compared with aged-matched controls.

Acknowledgement: Funded by the DFG (HE 4560/1-2).

Keywords: Alzheimer's Disease, Amyloid Beta Plaque, Non-Invasive Imaging, IMPY, PET

P102 DIRECT PRODUCTION OF (^{18}F)FLUOROMETHANE FROM AQUEOUS (^{18}F)FLUORIDE ION

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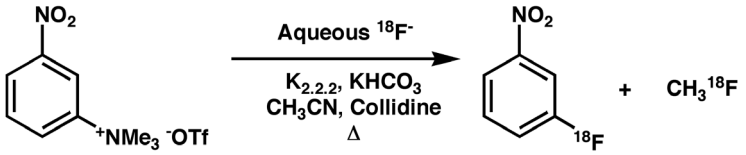
Introduction: Fluorine-18 labeled fluoromethane (18FCH3) is an inert, low toxicity diffusible tracer that has been applied to measure cerebral (Holden et al., JNM 1981; Herholz et al., Nuklearmedizin 1990) and tumoral blood flow (Miller et al., Clin Can Res 2006). The synthesis of 18FCH3 has been predominantly achieved by the nucleophilic displacement of iodine (Gatley et al., Appl. Rad. Isot. 1991) or sulfonate esters (Block et al., JLCR 1987). Banks et al. (Appl. Rad. Isot. 1994) reported the preparation of 18FCH3 by the displacement of a methyl group from a trimethylammonium triflate leaving group. Similarly, our group noted the production of 18FCH3 during the preparation of 3-fluoro-nitrobenzene (VanBrocklin et al., JCLR Supp 1, 2001). We describe herein the preparation of 18FCH3 directly from fluoride ion using 3-nitro-N,N,N-trimethyanilinium triflate requiring no resolubilization, applying the instant fluorination technique reported by Windhorst et al. (JLRC Supp 1, 2001).

Experimental: A thick walled glass v-vial was charged with 6.25 mg (16.6 μmol) kryptofix and 1.66 mg (16.6 μmol) potassium bicarbonate and sealed with a septum. To this vial was added aqueous 18F-fluoride ion. The volume of aqueous fluorde was varried. In a separate vial 5 mg (15.1 μmol) of 3-nitro-N,N,N-trimethyanilinium triflate was dissolved in 0.3 mL acetonitrile and 0.4 mL 2,4,6-collidine. The dissolved triflate salt is then added to the fluoride v-vial. The mixture was heated for 10 minutes at 160 degC. The fluoromethane was removed from the vial headspace using a syringe.

Results and Discussion: The amount of aqueous fluoride ion was varied from 50-200 μL. Using 50 μL, the yield of 18FCH3 ranged from 35-60% ndc for a total reaction time of 15-20 minutes. The fluoromethane was analyzed by gas chromatography versus non-radioactive fluoromethane. Increasing the amount of water proportionally decreased the amount of 18FCH3 produced.



Conclusion: Fluorine-18 fluoromethane was produced in good yield directly from aqueous fluoride ion without the need to remove the water and resoubilize the fluoride into organic solvent. The 18FCH3 was extracted directly from the headspace of the reaction vial into a gastight syringe. This methodology will permit the facile production of gaseous fluoromethane for a variety of uses with minimal synthetic equipment required and at sites without access to an onsite cyclotron.

Acknowledgement: This work was supported by the UCSF Department of Radiology and the NIH under grant no. CA79823.

Keywords: Fluoromethane, Fluoride Ion, Perfusion

P103 RAPID SYNTHESIS OF (^{18}F)SETOPERONE BY MICROWAVE HEATING AND SIMPLE PURIFICATION

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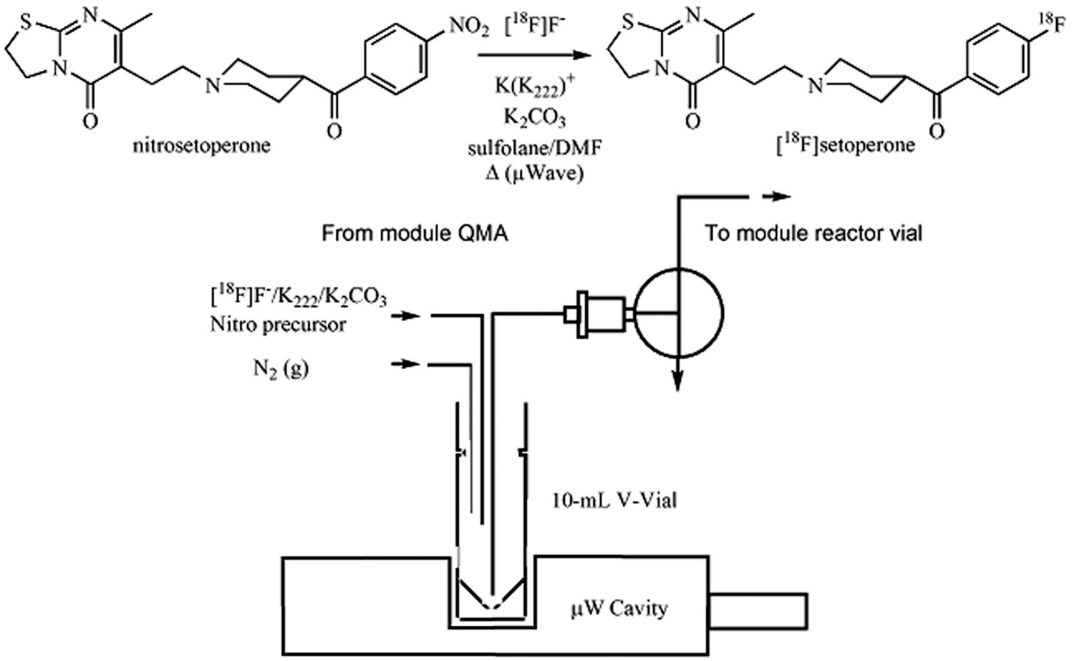
Introduction: A simple method was developed for radiolabeling and purification of the serotonin 5-HT_{2A} receptor radiotracer [^{18}F]setoperone[1] from its 4-nitro precursor using a single-mode microwave accelerator and a modified commercial fluorination module.

Experimental: Fluorine-18 was obtained by proton bombardment of H_2[^{18}O]O (1.8 mL Ta target; 30 mA) on a CTI/Siemens RDS 12 cyclotron. The aqueous [^{18}F]fluoride was trapped on anion exchange (QMA, Waters) and eluted with Kryptofix-222/K_2CO_3/CH_3CN using a GE TRACERlab® FX-FN module, then directed to a 10-mL V-vial in a conformal single-mode microwave cavity (Resonance Instruments 521). The solution was dried by N_2(g) flow with microwave heating (3x2 min 80W). Nitro-setoperone precursor (1 mg) in 400 mg sulfolane + 250 mL DMF was added and reaction was induced by two 10-sec 80-watt microwave pulses. The reaction mixture was diluted with 10 mL 0.1 M NH_4OH and trapped on a C_{18} solid phase extraction (SPE) cartridge (Waters C_{18} plus) to remove DMF and sulfolane, then eluted with 1.5 mL EtOH into the reaction vessel of the GE module, concentrated to 1/3 volume with He(g) flow, diluted with 3.5 mL H_2O and purified by semi-prep HPLC (Lichrosorb RP-Select B, 250 x 10 mm, MeOH/ THF/ (10 mM NaOAc pH 4.5), 9/21/70, at 4 mL/min), retention times setoperone 12.3 min, nitro precursor 16.4 min. The collected product was isolated on a 2nd C-18 SPE and eluted with EtOH and normal saline, followed by 0.22 mm membrane filtration into a sterile vial using the module's apparatus.

Results and Discussion: On a scale of 10-119 GBq [^{18}F]fluoride, [^{18}F]Setoperone was obtained by this process in average radiochemical yield from [^{18}F]F^- of 37±15% (mean ± SD, n = 8, radiochemical purity >98%, and specific activity 653 ± 237 TBq/mmol (15,130 Ci/mmol), in a synthesis time of 100 min from EOB. By applying reversed phase HPLC conditions similar to those used for [^{18}F]altanserin,[2] the product eluted before the precursor, resulting in less likelihood of precursor contamination of the labeled product and increasing the isolated specific activity.



Conclusion: Application of a single-mode microwave cavity coupled with a commercial PET chemistry module resulted in efficient preparation of [^{18}F]setoperone in high specific activity in a semi-automated process.

Acknowledgement: This work was supported by US National Institutes of Health (5R21MH073800-02) and Vanderbilt Department of Radiology & Radiological Sciences.

Keywords: Fluorine-18, [^{18}F]Setoperone, Microwave Acceleration, Solid Phase Extraction, HPLC

P104 USE OF BORONIC ACID BIOCONJUGATES AS PRECURSORS FOR RAPID AQUEOUS RADIOFLUORINATION OF BIOMOLECULES

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Introduction: A rapid and convenient labeling of relatively large and often relatively fragile biomolecules (e.g. oligonucleotides, peptides) is a desirable concept. Such is illustrated by the preparation of DOTA conjugates that are stable precursors that await ^{64}Cu wash in. The same approach would be desirable for the incporpration of ^{18}F. Nevertheless, such has not been easy to address with ^{18}F because of the properties of fluoride. Electrophilic ^{18}F is produced in low specifc activity and is too reactive for treating a biomolecule such as an oligonucleotide. Anionic ^{18}F is readily produced with very high specific activity however its nucleophilicity is neglible in the presence of water in which most biomolecules are soluble and native. Thus most ^{18}F labeling approaches involve the production of a small organofluoride (usually an aryl or pyridyl) under anhydrous conditions that in subsequent steps is converted to the bioconjugate. We have been exploring the use of arylboronic acids as fluoride acceptors that can be synthetically coupled to a biomolecule (oligonucleotide) that can be then labeled in a direct, one-step, aqueous labeling reaction to afford relatively high specific activity. This new approach and some of the limitations in terms of chemistry and the need to add carrier will be discussed.

Experimental: In our approach we have prepared a phosphoramidite that is appended with a boronic acid. This amidite can be used for solid phase synthesis of an oligonucleotide with one boronic acid or ten boronic acids. Standard tetrazole, I_2 oxidation, NH_3 deprotection, and PAGE purification are involved in producing this conjugate. Labeling takes place by the addition of $KH^{18/19}F_2$ at pH 4 followed by a bicarbonate quench and a spin column for clean-up. The labeled oliognucleotide can be resolved by PAGE and subjected to phosphor-screen autoradiography.

Results and Discussion: The results are a rapid, fast, simple one-step direct fluorination of a biomolecule under aqueous conditions. The current limitations are the need to add carrier ^{19}F and radiochemical yields that have been variable - mainly due to working with trace fluoride. These limitations are discussed in the contect of the new chemistry of producing ^{18}F-containing aryltrifluoroborates and can be overcome by using higher amounts of ^{18}F and a microscale reactions.

Conclusion: Using boronic acids as fluoride acceptors allow for the preparation of bioconjugate precursors that can be labeled in one direct simple and often high yielding aqueous step and thus represent a novel approach to labeling a biomolecule as a aryltriflluoroborate.

Acknowledgement: We acknowledge the CIHR for financial support.

Keywords: Bioconjugates, Radiopharmaceuticals, New Fluorination Methods, Boronic Acid

P105 NOVEL APPROACH FOR THE SYNTHESIS OF DIETHYL ([11]C-*CARBONYL*) MALONATE AND ITS APPLICATION AS AN INTERMEDIATE

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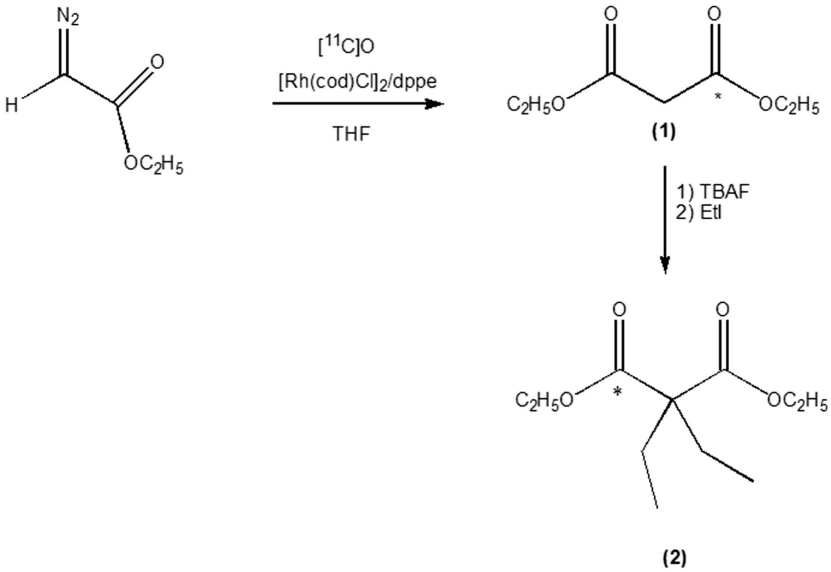
Introduction: The malonic esters have widely been used in organic synthesis as a two-carbon nucleophilic synthon and are of interest for synthesizing more complexed structures and biological active molecules. Several malonic esters have been labeled with [^{11}C]H_3I, but this synthesis was limited to compounds containing the ^{11}C-label on an alkyl group[1]. The presented synthetic method deals with the characteristics of Rhodium complexes[2] to react with [^{11}C]carbon monoxide[3] and diazo compounds to form C-C double bond releasing N_2 gas[4]. The carbene produced from diazo and [^{11}C]carbon monoxide in the presence of rhodium complex[5] allows the formation of [^{11}C]ketene, which can undergo several transformations.

Experimental: The model reaction was the synthesis of diethyl[*carbonyl*-^{11}C]malonate, starting from ethyl diazoacetate and ethanol mixed in THF together with the complex formed by the mixture of chloro(1,5-cyclooctadiene)rhodium(I) dimer ([Rh(cod)Cl]$_2$) and 1,2-bis(diphenylphosphino)ethane (dppe), in the presence of [^{11}C]carbon monoxide. The reaction was performed at 100°C for 5 min.



Results and Discussion: Diethyl[*carbonyl*-^{11}C]malonate**(1)** was obtained with a radiochemical yield of 20 ± 7% and a [^{11}C]O trapping efficiency of 90%. An alkylation reaction on this compound was performed using ethyl iodide and tetrabutyl ammonium fluoride. Diethyl diethyl[*carbonyl*-^{11}C]malonate **(2)** was obtained in 50% radiochemical yield.

Conclusion: The availablity of diethyl[*carbonyl*-^{11}C]malonate as a potential precursor and intermediate for biologically active PET-tracers was tested. We are now in the process of utilizing this synthetic pathway towards labelling of series of [*carbonyl*-^{11}C]malonate compounds with the potential in the development of new PET tracers.

References: [1] Gee T and Långström B, *Appl. Rad. Isot.*, 1991, 42, 1195-1198. [2] Doi H, Barletta J, Suzuki M, Noyori R, Watanabe Y and Långström B, *Org. Biomol. Chem.* 2004; 2; 3063-3066. [3] Kilhberg T and Långström B; *Method and apparatus for production and use of [^{11}C]carbon monoxide in labeling synthesis*, PCT-International patent. Application number: PCT/SE02/01222. [4] Cohen R, Rybtchinski B, Gandelman M, Rozenberg H, Martin J and Milstein D, *J. Am. Chem. Soc.*, 2003, 125, 6532-6546. [5] Marsden SP and Pang WK, *Chem. Comm.* 1999, 1199-1200.

Keywords: Diethyl[Carbonyl-11C]Malonate, [^{11}C]Carbon Monoxide, Rhodium-Mediated Carbonylation Reaction, Ketene

P106 SYNTHESIS OF ([11]C)HYDROXYUREA – A BIOLOGICAL APPLICATION OF ([11]C-*carbonyl*)ISOCYANATE AS A REACTION INTERMEDIATE

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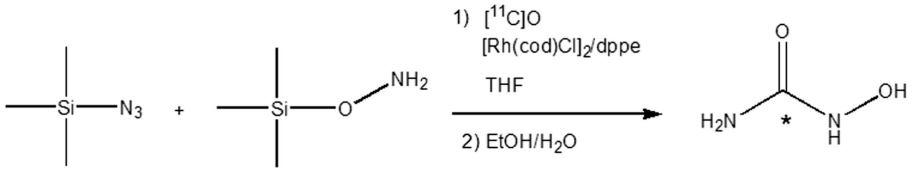
Introduction: Previous work showed the possibilities to use a rhodium-mediated carbonylation starting from azide compound and [^{11}C]carbon monoxide [1], to prepare [^{11}C]isocyanate or an [^{11}C]isocyanate-coordinated Rh complex as intermediates [2]. The model synthesis of *N*,*N*'-diphenyl[^{11}C]urea and ethyl phenyl[^{11}C]carbamate could be performed in respectively 82% and 76% radiochemical yields.

A similar protocol was designed for the synthesis of a biological active compound, hydroxyurea [3].



Experimental: This synthesis was performed using azidotrimethylsilane, mixed in THF with the rhodium complex made *in situ* by the mixture of chloro(1,5-cyclooctadiene)rhodium(I) dimer ([Rh(cod)Cl]$_2$) and 1,2-bis(diphenylphosphino)ethane (dppe), in the presence of [^{11}C]carbon monoxide, followed by the action of *o*-(trimethylsilyl)hydroxylamine. The reaction occurred at 120°C for 5 min. Deprotection was performed by action of ethanol, water 70:30 for 1 min at room temperature.

Results and Discussion: The desired product was obtained in 38 ± 3% decay-corrected radiochemical yield (78 ± 2% analytical decay-corrected radiochemical yield), and 90 ± 5% trapping efficiency, within a total synthesis. The identity and the confirmation of the labelling position were confirmed by ^{13}C-NMR analysis of ^{13}C-labelled hydroxyurea. The ^{13}C-NMR signal at 162 ppm corresponds to the carbonyl carbon of authentic hydroxyurea.

Conclusion: Work is in progress to apply the tracer [^{11}C]hydroxyurea in various biological studies especially with respect to access to tumors and normal organs, including transport over the BBB. Furthermore there is an interest in the evaluation of possible pharmacokinetic interactions by other pharmacological agents, e.g. acting on the efflux systems.

References: [1] Kilhberg T; Långström B; *Method and apparatus for production and use of [^{11}C]carbon monoxide in labeling synthesis*, PCT-International patent. Application number: PCT/SE02/01222. [2] Doi H, Barletta J, Suzuki M, Noyori R, Watanabe Y and Långström B, *Org. Biomol. Chem.* 2004; 2; 3063-3066. [3] Dogruel M, Gibbs JE and Thomas SE, *J. Neurochem.* 2003; 87; 76-84.

Keywords: [^{11}C]Hydroxyurea, [^{11}C]Isocyanate, [^{11}C]Carbon Monoxide, Rhodium-Mediated Carbonylation Reaction, Efflux Systems

P107 SYNTHESIS AND EXPEDITED REFORMULATION OF (^{11}C)DASB USING FXc MODULE

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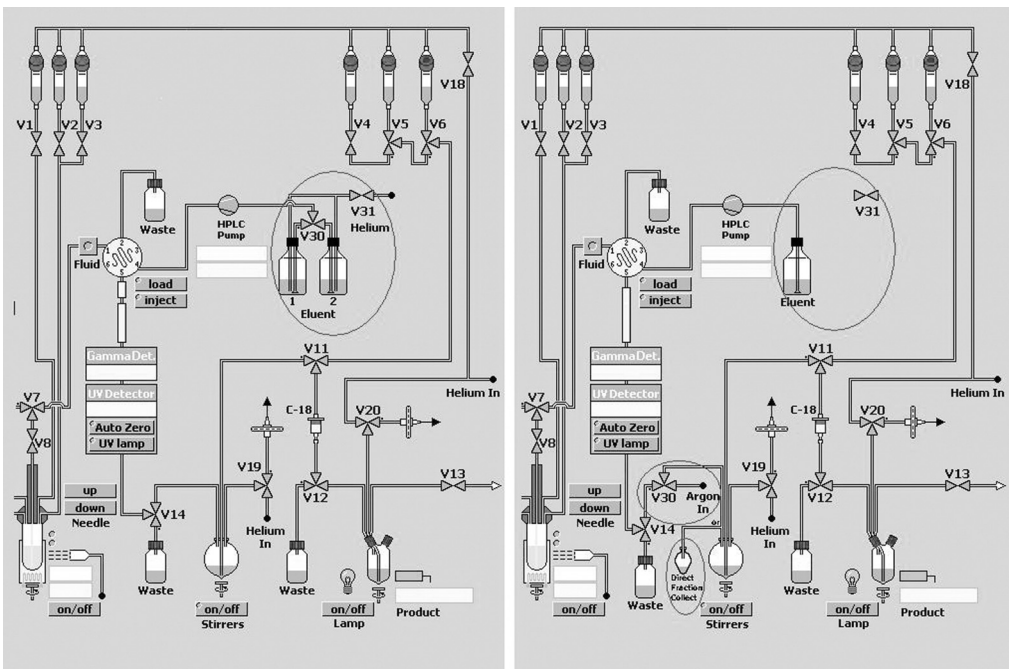
Introduction: We prepare DASB, a SERT ligand using TRACERlab FXc module. Despite a short synthesis time, reformulation step remained a slow step. The system configuration takes several minutes to pass entire bolus thru sep-pak and remained prone to mixing solvent from lines to the reformulated product. We made modifications to increase production efficiency and to decrease processing time. Herein, we report routine production of DASB using FXc and modifications made to reformulation steps.

Experimental: The [^{11}C]CO_2 delivery time and pressures from RDS 112 cyclotron were optimized. The [^{11}C] CO_2 was first converted to [^{11}C]MeI and then to [^{11}C]MeTf using an in-line triflate column/furnace. DASB was prepared by bubbling [^{11}C]MeTf in the reaction vial containing the precursor. After the bubbling of [^{11}C]MeTf (~1-2 min), the reaction mixture was auto-loaded on to HPLC column for purification.

Modifications were made to the module (shown as circles in figure) by adding helium flush to the collection vessel using a previously unused valve V30. This valve was relocated between V14 and fraction collection vial. The argon pressure through V30 was maintained at 50 psi to help load the Sep-Pak.

Results and Discussion: DASB was synthesized using slight modification to the standard time list. To increase Ni-column life, we used 0.25% oxygen in nitrogen as the target gas. This formulation helped extend Ni-column life everal fold. The [^{11}C]CO_2 delivery time and pressures from RDS 112 cyclotron were optimized, converted to [^{11}C]MeI, and then converted to [^{11}C]MeTf using an in-line triflate column/furnace. The reaction was completed by bubbling on-line generated [^{11}C]MeTf in to the reaction vial containing the precursor. After the bubling of [^{11}C]MeTf (~1-2 min), the DASB was isolated using HPLC.

Modifications were made to the module (shown as circles in figure) by adding helium flush to the HPLC collection vessel by using a previously unused valve V30. This valve was placed between V14 and the fraction collection via and was designed to deliver helium at a static pressure of 50 psi. This helium pressure provided a quicker loading of the Sep-Pak, requiring shorter times than earlier. This shorter times improved the overall yields.



Conclusion: The use of TRACERlab FXc provided a convenient and reliable synthesis of multiple back-to-back production of DASB with reliability and consistency. Added modification to the reformulation step provided added efficiency and shorter synthesis times.

Acknowledgement: This project was in part supported by a grant from the NIH CA105382.

Keywords: C-11 Radiotracer, C-11 Choline, FXc Module, Repeat Synthesis, Optimization

P108 IMPROVED RADIOCHEMICAL YIELDS, CONSISTANCY, AND RELIABILITY OF C-11 METHYL IODIDE PRODUCTION ACHIEVED THROUGH BATCH MODE USING GE'S FXc SYNTHESIS MODULE

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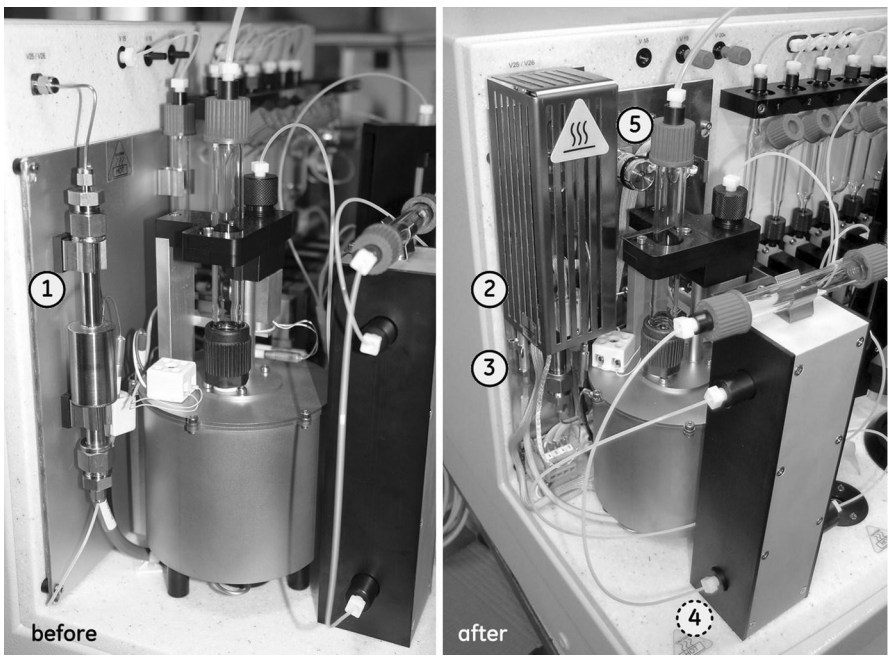
Introduction: For routine production of C-11 ligands, we use TRACERlab FXc module. This module converts cyclotron produced $[^{11}C]CO_2$ to $[^{11}C]CH_4$ in a continuous mode (CM) followed by the iodination to produce $[^{11}C]MeI$. Therefore, the yields, specific activity, and reliability of this module remained dependent on numerous factors including target design, target gas composition, and cyclotron delivery system. In addition, a longer wait time between subsequent runs hindered our efforts to use this module for more than two or three synthesis a day. A 'batch mode' (BM)was introduced to address some of these issues. Herein, we report our experience with BM process and its affect on overall quantity and quality of $[^{11}C]MeI$ produced.

Experimental: Two major modifications were made to this module. A molecular sieve-Ni catalyst combination column was added and 48V heater was replaced with a 220V (attached figure). We performed eighty four $[^{11}C]MeI$ productions using CM (pre-modification module) and thirty seven synthesis using the BM. In CM, soon after the delivery, CO_2 was processed through a Ni-catalyst column to generate $[^{11}C]CH_4$. The column was heated to release $[^{11}C]CH_4$ and was converted to $[^{11}C]MeI$ by passing through an iodine column. In BM, the $[^{11}C]CO_2$ was trapped on a molecular sieve-catalyst column, flushed for 1-2 min with hydrogen and hydrogen was added to the oven. After flushing, the hydrogen delivery valve was closed, the sieves were heated to release $[^{11}C]CO_2$, converted to $[^{11}C]CH_4$, and reacted with iodine to give $[^{11}C]MeI$.

Results and Discussion: The average conversion to $[^{11}C]CH_4$ was 386 ± 128 mCi for CM and 416 ± 74 mCi for theBM. Conversion to $[^{11}C]MeI$ was 112 ± 35 mCi and 146 ± 32 mCi for the CM and BM. The BM provided ~6% more $[^{11}C]MeI$. The in-line continuous cooling of the heaters and increased heater power decreased wait time between subsequent runs from 90 min to ~30 min. Although, low oxygen contents in target gas has always provided longevity to our Ni-catalyst column, BM has further increased number of runs performed before column replacement.



Conclusion: The batch mode significantly improved the reliability and reproducibility to produce $[^{11}C]$ MeI. The wait times between syntheses was significantly decreased.

Acknowledgement: This project was in part supported in part by a grant from the NIH CA105382 (to PKG).

Keywords: C-11 Methyl Iodide, TRACERlab FXc Module, Optimization

P109 AVOID DMF WHEN LABELING WITH ^{11}C-METHYL TRIFLATE

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Introduction: DMF (dimethylformamide) is a commonly used solvent for methylation reactions with ^{11}C-methyl iodide, in part because it is an aprotic solvent with a high boiling point. We present evidence, however, that DMF is not a good reaction solvent when ^{11}C-methyl triflate (MeOTf) is used instead.

Experimental: Three different types of ^{11}C-methylation reactions were examined using MeOTf derived from gas-phase [^{11}C]CH_3Br (BH Mock, et al., *Nuc Med Biol* 26:467-471, 1999): *O*-methylation of β-CFT acid, *N*-methylation of Nor-β-CFT and *O*-methylation of des-methyl raclopride. All β-CFT reactions were initially performed in pure DMF, while Raclopride labeling was typically performed in acetone. Over time, the concentration of DMF in the β-CFT reaction mixture was reduced as we tried to increase and/or maintain adequate radiochemical yields. Since Raclopride yields were much more consistent than with β-CFT, we then deliberately added DMF to the raclopride precursor solution to confirm the negative effects noted in the β-CFT reactions. Yield and specific activity (SA) were routinely determined for each reaction series by "on-the-fly" conversion of the radioactivity and UV profiles of eluted tracer to mCi (EOB) and total mass (nmoles) as soon as the product exited the HPLC column (BH Mock et al., *J Label Compd Radiopharm* 48:S224, 2005). Numerous control studies were also conducted to characterize the side-products produced when MeOTf reacted with the different solvent mixtures *sans* precursor.

Results and Discussion: Radiochemical yields of ^{11}C-β-CFT were consistently low and unreliable when DMF was present in the reaction solvent, especially with base-catalyzed *O*-methylation, because a large variable portion of the MeOTf was consumed by direct reaction with DMF and/or its hydrolysis products - formic acid and dimethylamine. Large volatility losses were often observed, most likely due to formation of ^{11}C-trimethylamine. All β-CFT reactions are now done in pure acetonitrile. On the other hand, ^{11}C-Raclopride production in acetone was much more consistent, both in radiochemical yield and SA. The major side product is ^{11}C-methanol, produced post-reaction by hydrolysis of unreacted MeOTf. However, when 15% DMF was deliberately added to the precursor solution, the negative effect on ^{11}C-Raclopride yield was dramatic; *e.g.,* dropping from 213 mCi to 25 mCi in back-to-back syntheses with the same amount of incoming MeOTf radioactivity.

Conclusion: A significant portion of MeOTf reacts directly with DMF, even when present at <5% in the precursor solution. When base is added to enable *O*-methylation, even more radioactivity is lost to the hydrolyzed DMF by-products. DMF should be avoided in MeOTf reactions, especially if high temperatures or strong bases are required.

Acknowledgement: Supported in part by INGEN of Indiana University.

Keywords: Dimethylformamide, C-11 Methyl Triflate, Methylation Reaction Solvents

P110 EXPANDING THE UTILITY OF THE FLUOROUS LABELING METHOD. TRIALKYLSTANNYLATION OF FUNCTIONALIZED ARYL AND VINYL HALIDES WITH A FLUOROUS DISTANNANE

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Introduction: The removal of unreacted starting material and related impurities from a labeling reaction in order to obtain the desired product in high effective specific activity (ESA) presents a challenge that is increasingly relevant to the development of targeted radiopharmaceuticals. This is especially true for agents designed to target receptors expressed in low concentrations. Routes to labeled compounds with high ESA which avoid lengthy and inconvenient HPLC purification have therefore attracted significant interest [1]. Fluorous tags, such as the tris(2-perfluorohexylethyl)stannyl group, R^f_3Sn, are analogous to solid-phase supports in that the unlabeled substrate can be rapidly separated from the product by solid-phase extraction. In the case of the fluorous method, the substrates can be readily purified and characterized by techniques used for small molecules.

Methods for introducing the R^f_3Sn group into molecules have been described which are based on organozinc and organolithium-based synthetic approaches [1]. A more functional-group-tolerant method of introducing the R^f_3Sn group would facilitate the synthesis of fluorous precursors to highly functionalized radiopharmaceuticals. The methodology under development is based on a palladium cross-coupling reaction between a fluorous distannane, $R^f_3SnSnR^f_3$, and an aryl or vinyl halide [2,3].

Experimental: A fluorous distannane was prepared in effectively quantitative yield from a commercially available fluorous trialkyltin hydride *via* a palladium-catalyzed dehydrogenative coupling [4]. The distannane was formed at room temperature prior to the cross-coupling reaction, which was conducted at reflux. The methodology was amenable to parallel synthesis and the products were readily purified by column chromatography.

Results and Discussion: The scope of the methodology was examined by preparing a library of twelve fluorous trialkylarylstannanes from 15 aryl bromides and iodides. Various catalysts and reaction conditions were investigated in an attempt to optimize reaction yields. Depending on the substituent, yields from 10% to 59% were obtained in THF and with $Pd(PPh_3)_4$ as the catalyst. Products were characterized by ^1H, ^{13}C, ^{19}F and ^{119}Sn NMR, IR and MS.

Conclusion: The new palladium cross-coupling methodology allows for the synthesis of fluorous-tagged precursors bearing functional groups that are incompatible with present synthetic approaches thereby expanding the general utility of the fluorous labeling method.

References: [1] Donovan, A.; Forbes, J.; Dorff, P.; Schaffer, P.; Babich, J.; Valliant, J.F. *J. Am. Chem. Soc.* **2006**, *128*, 3536-3537. [2] Azizian, H.; Eaborn, C.; Pidcock, A. *J. Organomet. Chem.* **1981**, *215*, 49-58. [3] Curran, D.P.; Hoshino, M. *J. Org. Chem.* **1996,** *61*, 6480-6481. [4] Braunstein, P.; Morise, X. *Chem. Rev.* **2000**, *100*, 3541-3552.

Keywords: Specific Activity, Iodine, Fluorous, Discovery

P111 DEVELOPMENT OF COST EFFECTIVE REMOTE SYNTHESIS MODULE FOR (^{11}C)METHYLATION

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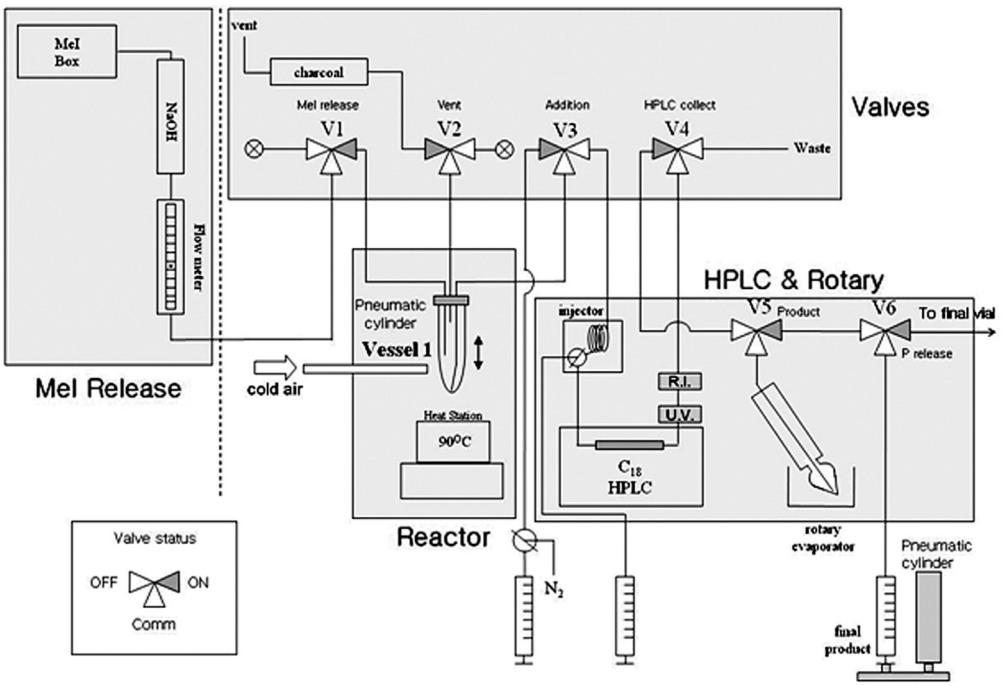
Introduction: PET studies with [^{11}C]radiotracer require radiosynthesis system built in the same facility, because of short $t_{1/2}$. We also can buy commercialized synthesizers which are programmable and routine production oriented. However, we still need "the homemade synthesis module" because of cost and easy modification. In addition, it is reasonably recommended to have separated synthesis modules dedicated for each [^{11}C]radiotracer in order to avoid yield reduction and radiation overexposure. In this report, we describe building the [^{11}C]methylation module to produce [^{11}C]Carfentanil with relatively low budget.

Experimental: [^{11}C]CO_2 (~1600 mCi) was generated by bombardment (40 min) from cyclotron (CTI-ZIEMENS) following the nuclear reaction of ^{14}N(p,n)^{11}C. [^{11}C]MeI (~800 mCi) was synthesized from reduction of [^{11}C]CO_2 in $LiAlH_4$ solution at a commercialized module (CTI-ZIEMENS). [^{11}C]MeI trapping into reaction vial was performed by using of compressed air cooling prior to methylation reaction. The product fraction combined from HPLC was collected into rotary evaporator and dose formulation was carried out in the module by pneumatic cylinder operated pump. Product was analyzed with HPLC for authenticity and specific activity and GC for residual solvents concentration.

Results and Discussion: Total synthesis time was about 60 min included [^{11}C]MeI synthesis, HPLC purification and formulation of dose. Radiochemical yields were above 25% (D.C.) and radiochemical purity was over than 98% by HPLC. Most chemistry works were carried out in the module with acrylic body case. Compressed air stream cooled reaction vessel down slightly lower than room temperature and showed relatively high trapping yield comparing to that of trapping on the water bath. Pneumatic cylinder, built in module body, efficiently drove a 50 ml syringe to push and withdraw radioactivity between rotary evaporator and final sterile vial. The flow monitor, the illustrator of flow status by LED lamps associated with valves, was useful to help a chemist to operate synthesis easily without any mistake while production of [^{11}C]Carfentanil.



Conclusion: We built and tested a cost efficient synthesis module with some novel ideas about cost and performance for the synthesis of [^{11}C]Carfentanil. It costed about 1,100 US dollars to build a new homemade [^{11}C]methylation module (MeI module, HPLC and rotary evaporator were not estimated). The size optimized module including [^{11}C]MeOTf application will be stuied.

Keywords: C-11, MeI, Radiolabeling, Module, [C-11]Carfentanil

P112 (^{18}F)-N-2-FLUOROETHYLATION OF WEAK NUCELEOPHILES WITH HIGH RADIOCHEMICAL YIELDS: OPTIMIZED SYNTHESIS OF THE MODEL COMPOUND (^{18}F)-N-2-FLUOROETHYLANILINE

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Introduction: [^{18}F]-Fluoroethylation is a commonly used two step reaction sequence for the introduction of n.c.a. [^{18}F]-Fluoride in molecules bearing OH-, NH- or SH-groups. However, [^{18}F]-Fluoroethylation of weak nucleophilic amines often results in low radiochemical yields (rcy), even at under relative drastic alkylation reaction conditions. Using the approach (1) of direct labelling of the 2-bromoacetyl-derivative of the aniline derivatives followed by the selective reduction of the carbonyl group could be an alternative for the synthesis of some [^{18}F]-Fluoroethylated-radioparmaceuticals. Our initial aim in this approach was the optimization of the synthesis of [^{18}F]-N-2-Fluoroethylaniline (^{18}FEt-Ani).

Experimental: The labelling of ^{18}FEt-Ani was carried out by a two step synthesis (according to (1)), nucleophilic substitution on N-2-Bromoacetylaniline with n.c.a. [^{18}F]-Fluoride followed by reduction with BH_3 to ^{18}FEt-Ani. The reaction conditions for the nucleophilic substitution were optimized with respect to different PTC/bases combinations, solvent, time, temperature and the addition of small traces of water. Before reduction the solvent was exchanged by a cartridge procedure. The reduction of [^{18}F]-N-2-Fluoroacetylaniline with BH_3 was evaluated in different solvents.

Results and Discussion: Rcy up to 70 to 90% of radioactivity in solution could be achieved with the several PTC-base-combinations (kryptofix-222 or 18-crown-6 with $KHCO_3$or K_2CO_3). However, the overall rcy decreased partially drastic to only 15% resulting from adsorption of high amounts of [^{18}F]-Fluoride on the wall of the reaction vessel. The solubility of the [^{18}F]-Fluoride complexes in acetonitrile is $\leq$50%. This could be increased to $\sim$60% by addition of small amounts of water. Because of the higher solubility of the [^{18}F]-Fluoride, DMSO gave in combination with the system K222/K_2CO_3 the highest overall rcy (for the SN-step) of up to 65-70%. After separation of the solvent by a C18-cartridge the reduction with BH_3 in acetonitrile of [^{18}F]-N-2-Fluoroacetylaniline to ^{18}FEt-Ani was nearly quantitatively (>90%).

Conclusion: The [^{18}F]-Fluorination of N-2-Bromoacetylanilide followed by reduction to yield the desired ^{18}FEt-Ani allows standard reaction conditions for the SN-step. Using this synthetic pathway we were able to label the model compound ^{18}FEt-Ani with high overall rcy of 60-65%. This strategy is thus an alternative to get hold of [^{18}F]-2-Fluoroethylated-radiopharmaceuticals in high rcy, if the N-2-Bromoacetylamide derivative is available as precursor and the molecule is stable under reduction conditions.

Reference: [1] E. Briard and V.W. Pike, J Label Compd Radiopharm 2004, 47, 217.

Acknowledgement: This study was supported by a grant from Graduate College GRK 677 of the DFG.

Keywords: Fluorine-18, Fluoroethylation, [^{18}F]-N-2-Fluoroethylaniline

P113 RADIOSYNTHESIS OF ([11]C)MNPA AND ([3]H)MNPA FROM THE PRECURSOR (*R*)-2-HYDROXY-10,11-ACETONIDE-NPA

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Introduction: *In vivo* imaging of the dopamine D_2 receptor with agonist radioligands and PET has recently been reported by several groups [1–5]. We earlier described the development of the dopamine D_2-like receptor agonist radioligand (*R*)-2-$^{11}CH_3O$-*N*-propylaporphine ([^{11}C]MNPA, [^{11}C]***1***) [1,3]. [^{11}C]***1*** was initially prepared by direct methylation of the precursor (*R*)-2-hydroxy-NPA and selective labeling at the 2-position was tested by derivatization of [^{11}C]***1*** into the ^{11}C-labeled (*R*)-2-methoxy-10,11-methylendioxy-NPA and (*R*)-2-methoxy-10,11-diaceto-NPA [1,3]. We now present a new approach for ^{3}H- and ^{11}C-labeling of ***1***, starting from the precursor (*R*)-2-hydroxy-10,11-acetonide-NPA (***2***).

Experimental: The precursor ***2*** was prepared according to an eight step synthesis starting from codeine. [^{3}H]-methoxy-10,11-acetonide-NPA ([^{3}H]***3***) and [^{11}C]***3*** were prepared by methylation of ***2*** in DMSO and NaOH with [^{3}H]- and [^{11}C]methyl iodide, respectively. For [^{11}C]***1***, the reaction mixture was heated for 5 min at 80°C, whereas for [^{3}H]***1*** the mixture was stirred for 30 minutes at room temperature. [^{11}C]***1*** was obtained by addition of hydrochloric acid (6M) to the reaction mixture and subsequent heating for 5 min at 150°C. [^{3}H]***1*** was obtained by heating the semi-preparative purified [^{3}H]***3*** fraction at 50°C for 3 days after addition of methanol and sulfuric acid (3 M). Semi-preparative reversed phase HPLC was used for purification of [^{11}C]***1*** and [^{3}H]***1***.

Results and Discussion: [^{11}C]***3*** and [^{3}H]***3*** were obtained in good yields of about 60% from precursor ***2***. Cleavage of the acetonide group of [^{11}C]***3*** was obtained in a yield of 90%, resulting in an overall yield of about 54% of [^{11}C]***1***. ^{3}H-labeling yielded a 70% conversion of [^{3}H]***3*** into [^{3}H]***1*** resulting in an overall yield of 42%. Specific radioactivity obtained for [^{11}C]***1*** and [^{3}H]***1*** were >2000 and 38 Ci/mmol, respectively.

Conclusion: [^{11}C]***1*** and [^{3}H]***1*** were prepared in good yields and with high specific activity. This new synthetic route was found to give reproducible results and is preferred due to specific labeling in the 2-position.

References: [1] Halldin et al. (**1992**) *J. Labelled Compd. Radiopharm.* 35, S265-S266. [2] Hwang et al. (**2000**) *Nucl. Med. Biol.* 27, 533-539. [3] Finnema et al. (**2005**) *Nucl. Med. Biol.* 32, 353-360. [4] Wilson et al. (**2005**) *J. Med. Chem.* 48, 4153-4160. [5] Hwang et al. (**2003**) *J. Nucl. Med.* 44, 294P.

Keywords: Dopamine, Agonist, PET, Carbon-11, Tritium

P114 DEVELOPMENT OF VERSATILE SYNTHESIS EQUIPMENT FOR MULTIPLE PRODUCTION OF PET RADIOPHARMACEUTICALS

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Introduction: Positron emission tomography (PET) technique has been one of the most useful methods for imaging of various in vivo biological functions with a wide variety of radiopharmaceuticals labeled with positron emitters. To visualize various in vivo functions, demands for diverse PET radiopharmaceuticals have been increasing. However most of commercially available synthesis systems have been specialized and optimized for only one PET radiopharmaceuticals or several radiopharmaceuticals produced by the same type of chemical reaction. In order to produce various PET radiopharmaceuticals, we developed versatile synthesis system which enables to produce PET radiopharmaceuticals according to various chemical reactions by combination of "main body" and synthesis module" which is specialized in particular labeling reaction.

Experimental: "Main body" is comprised of commonly used parts in the production such as air heater, radiation sensors and pneumatic cylinder. Other parts depending on the chemical reaction type such as solenoid valves, tubing, vessels are assembled in "synthesis modules", which are used by mounting on the "main body". "Synthesis modules" for ^{18}F-fluoroalkylation reaction, ^{18}F fluorination by $^{18}F^-$, ^{11}C-methylation reactions by $^{11}CH_3I$ or $^{11}CH_3OTf$ were developed. [^{18}F]Fluoroethyl DAA 1106, [^{18}F]FLT, [^{18}F]FMISO, [^{11}C]Ro 15-1788 and [^{11}C]FLB 457 were prepared using this synthesis system to evaluate the performance.

Results and Discussion: Table 1 summarized results of PET radiopharmaceutical productions using this system. [^{18}F]Fluoroethylation reaction, [^{18}F]fluorination and [^{11}C]methylation reactions by [^{11}C]CH_3I and [^{11}C]CH_3OTf yielded corresponding PET radiopharmaceuticals in satisfactory radiochemical yields. Replacement of synthesis module was easy and repeated PET radiopharmaceutical productions were possible using this apparatus.

Synthesis of PET radiopharmaceuticals by varsatile synthesis system

Compound	Reaction type	Radiochemical yield (% EOS)
[^{18}F]fluoroethy DAA 1106	[^{18}F]fluoroethylation	40
[^{18}F]FLT	[^{18}F]fluorination	40
[^{18}F]FMISO	[^{18}F]fluorination	70
[^{11}C]Ro 15-1788	[^{11}C]methylation via [^{11}C]CH_3I	26
[^{11}C]FLB 457	[^{11}C]methylation via [^{11}C]CH_3OTf	24

Conclusion: Using versatile synthesis apparatus, ^{18}F-fluorinated compounds and ^{11}C-labeled compounds were prepared by replacement of synthesis module. Other PET radiopharmaceuticals would be produced by developing corresponding new synthesis modules (e.g. Grignard reaction, ^{18}F-fluorination by [^{18}F]F_2). This versatile synthesis system is a powerful device for the various PET radiopharmaceutical productions.

Keywords: Versatile Synthesis Apparatus, PET Radiopharmaceuticals, Automated Synthesis

P115 SYNTHESIS OF S-(2-(^{18}F)-FLUOROETHYL)-L-METHIONINE FOR TUMOUR IMAGING

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Introduction: Radiolabelled amino acids and in particular *S*-(2-[^{11}C]-methyl)-L-methionine (MET) has been extensively used in PET tumour imaging in both animals and man. However, the short half life of ^{11}C ($T_{1/2}$ = 20 min) has prompted the development of ^{18}F-labelled amino acids of which *O*-(2-[^{18}F]-fluoroethyl)-L-tyrosine (FET)[1] has been a lead candidate. More recently, a new amino acid analogue of MET, S-(2-[^{18}F]-fluoroethyl)-L-methionine (FEM)[2,3], was synthesised in a two step process using 2-[^{18}F]-fluoroethyltosylate. FEM was reported to exhibit similar characteristics to FET in differentiating neoplasms and inflammation in rodents. The aim of this study was to develop an efficient one step radiolabelling method for the synthesis of FEM.

Experimental: For this purpose, S-(2-bromoethyl)-L-methionine and S-(2-chloroethyl)-L-methionine were synthesised as precursors (figure 1). Radiolabelling was achieved by classical fluorine-18 nucleophilic substitution (figure 2) followed by acid hydrolysis. Attempts to prepare the corresponding S-(2-tosyoxylethyl)-L-methionine were unsuccessful.

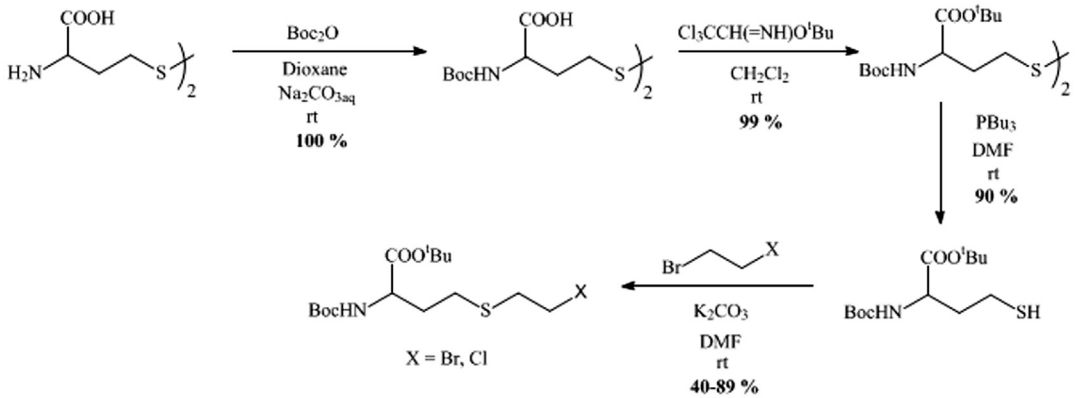

Fig. 1

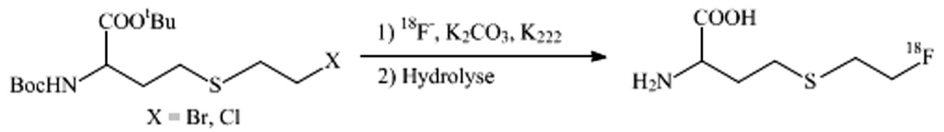

Fig. 2

Results and Discussion: Nucleophilic displacement on the protected FEM bromo-analogue with fluorine-18 resulted in a higher radiochemical yield (30-40% in 5 min at 100°C) compared to the chloro-precursor (20-25% in 15min at 100°C). The hydrolysis of protected [^{18}F]-FEM with hydrochloric acid was carried out at 100°C for 5 min. However, preliminary QC results indicate that [^{18}F]-FEM in aqueous systems displayed only limited stability. Comparative studies on the non-radioactive FEM by 1H-NMR and HPLC suggests that the fluorine is displaced to give the corresponding alcohol.

Conclusion: These results on the radiosynthesis and stability of [^{18}F]-FEM will be presented.

References: [1] Wester H.J., Herz M., Weber W., Heiss P., Senekowitsch-Schmidtke R., Schwaiger M., Stöcklin G., *J. Nucl. Med.*, **1999**, *40*, 205-212. [2] Tang G., Wang M., Tang X., Luo L., Gan M., *Nucl. Med. Biol.*, **2003**, *30*, 509-512. [3] Tang G., Wang M., Tang X., Luo L., Gan M., *Acta PharmaceuticaSinica*, **2003**, *38*, 915-918.

Acknowledgement: This work is supported by the CRC in Biomedical Imaging Development.

Keywords: Fluorine-18, PET, [^{18}F]-FEM, Tumour Imaging

P116 SYNTHESIS OF (^{18}F)FLUORINE LABELLED IMIDAZO(1,2b) PYRIDAZINE AS POTENTIAL PROBES FOR THE STUDY OF PERIPHERAL BENZODIAZEPINE BINDING SITES USING PET

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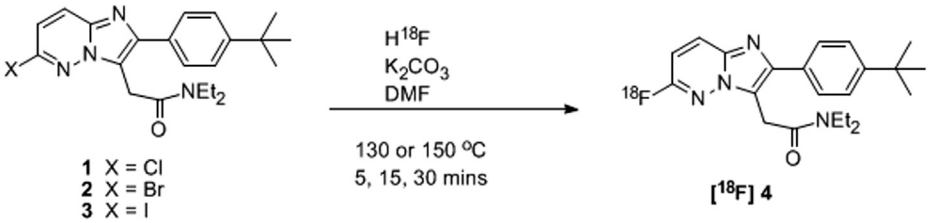
Introduction: As an extension of our work in developing compounds that target peripheral benzodiazepine binding sites (PBBS), we have synthesised several imidazo[1,2-b] pyridazine PBBS ligands that have the versatility of being labelled with ^{123}I and ^{18}F for SPECT and PET imaging. We have already reported our success with labelling these pyridazines with [^{123}I]iodine by using a copper assisted halogen exchange in the presence of acetic acid and sodium bisulfate at 200°C.[1,2] Other research groups have shown that chloro pyridazines can be radiolabelleled with [^{18}F]fluorine.[3,4] Here we report our study on the radiolabelling of imidazo[1,2-b] pyridazines **1–3** with nucleophilic [^{18}F]fluoride and investigate the effect of radiochemical yield versus the halogen leaving group.

Experimental: The pyridazine type PBBS ligands were synthesised as described by Katsifis *et al.*[1,2] followed by halogen exchange to produce the appropriate halogen leaving group. Compounds **1–3** were radiolabelled with ^{18}F using K_2CO_3 and K222 in DMF at 130°C and 150°C using established procedures.

Results and Discussion: Kinetic studies using 5 mg of precursor indicated that the bromo analogue (**2**) gave the best yields ranging from 60–80% at 150°C and 50–60% at 130°C at 5 and 15 mins while both the Cl and I analogues (**1** and **3**) gave 40–50% at both 150°C and 130°C at 5 and 15 mins. Lower yields were obtained with longer reaction times (10 – 30%) and when less than 5 mg of precursor was used, which was related to the decomposition of both the precursor and the radiolabelled product.



Conclusion: Pyridazines are a viable option for nucleophilic substitution with [^{18}F]fluorine giving moderate to high yields with the bromo leaving group giving the better yields. Consequently we were able to prepare compound **4** in 70–80% radiochemical yield and with radiochemical purity >98% suitable for biological evaluation.

References: [1] Katsifis, A.; Barlin, G.; Mattner, F and Dikic, B. *Radiochim Acta*, 92, 305–309, **2004**. [2] Katsifis, A.; Najdovski, L.; Mardon, K.; Mattner, F.; Barlin, G.; Davis, L.; Kassiou, M.: *J. Lab. Comp. Radiopharm.* 40, 623–625, **1997**. [3] Mourad, A; Kilbourn, M.R. *J Label Compd. Radiopharm*, 30, 140, **1991**. [4] Zeng, F.; Southerland, R.J.; Voll, J.R.; Votaw, J.R.; Williams, L.; Ciliax, B.J.; Goodman, M.M. *J Label Compd. Radiopharm*, 48, S1–S341, **2005**.

Keywords: Pyridazines, PET, Peripheral Benzodiazepine Binding Sites, [^{18}F]Fluorine

P117 METHOD FOR ^{11}C-LABELLING OF IRREVERSIBLE EGFR INHIBITORS VIA PALLADIUM-MEDIATED CARBONYLATION

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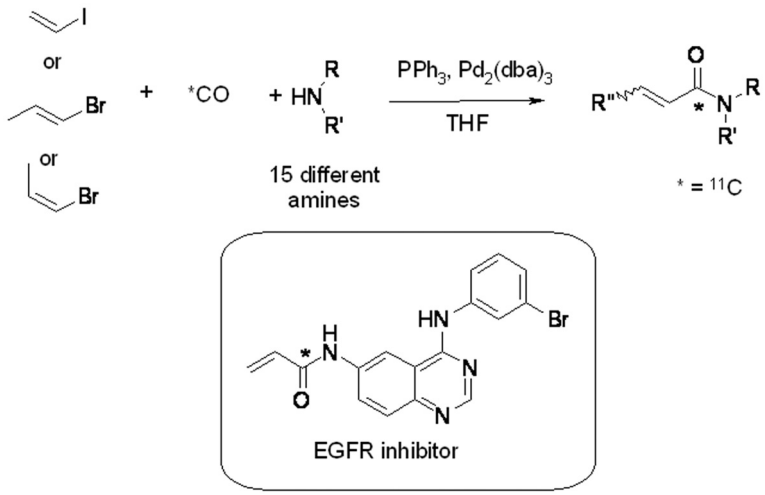
Introduction: Transition metal catalyzed carbonylation is useful in the synthesis of carbonyl compounds via incorporation of carbon monoxide and has also been adopted in labelling reactions with very low concentrations of [^{11}C]carbon monoxide. Previously reported syntheses of ^{11}C-labelled amides using [^{11}C]carbon monoxide have not included acrylamides, a functional group present in irreversible EGFR inhibitors. Two methods are presented for synthesizing acrylamides labelled with ^{11}C and ^{13}C in the carbonyl position.

Experimental: In the first method [1-^{11}C]acrylic acid was synthesized using [^{11}C]carbon monoxide via palladium-mediated hydroxycarbonylation of acetylene. The labelled carboxylic acid was converted to acid chloride and subsequently treated with amine to yield *N*-[*carbonyl*-^{11}C]benzylacrylamide. The second method utilized [^{11}C]carbon monoxide in palladium-mediated carbonylative cross-coupling of vinyl halides and amines in THF.

Results and Discussion: Higher radiochemical yield was achieved with the latter method and the amount of amine needed was decreased to 1/20. In total 20 different ^{11}C-labelled acrylamides were synthesized and were isolated in up to 81% decay corrected radiochemical yield. Starting from 10±0.5 GBq of [^{11}C]carbon monoxide, *N*-[*carbonyl*-^{11}C]benzylacrylamide was obtained in 4 min with a specific radioactivity of 330±4 GBq/μmol. Co-labelling with ^{11}C and ^{13}C enabled confirmation of the labelled position by ^{13}C-NMR spectroscopy. The latter method was used to label an irreversible binding epidermal growth factor inhibitor in 67% decay corrected radiochemical yield within 25 min from EOB.



Conclusion: An efficient one pot single step method for ^{11}C-labelling of acrylamides in the carbonyl position with retention of the configuration over the C=C double bond has been developed. The method has successfully been used to label an irreversible binding EGFR inhibitor in high radiochemical yield with high specific radioactivity.

Acknowledgement: This work was conducted in collaboration with Imanet, GE. Financial support from The Swedish Science Research Council and Lennanders stiftelse, Uppsala University is gratefully acknowledged.

References: [1] Eriksson, J., Åberg, O., Långström, B., *Eur. J. Org. Chem.*, **2007**, in press. [2] Ben-David, I., Rozen, Y., Ortu, G., Mishani, E., *Appl. Rad. Iso*, **2003**, 209-217.

Keywords: Carbonylation, Amides, [^{11}C]Carbon Monoxide, Carbon-11, EGFR

P118 OPTIMIZATION OF PHOTOSENSITIZED CARBOXYLATION USING (^{11}C)O

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Introduction: Aliphatic carboxylic and related functional groups are potential sites for introducing ^{11}C-labels. We have reported one-pot protocols for labeling this type of groups using ^{11}CO via radical-mediated reactions. Bases or photosensitizers are generally required for facilitating such reactions involving water (or alcohols) as a nucleophile in labeling acids (esters). Recently, when developing a process for labeling a functionalized carboxylic acid, we faced the problem that bases induced a rapid side reaction. Using sensitizers partly solved the problem but further optimization has proved difficult because initiation mechanism was not well defined.

Experimental: Series of experiments were conducted to elucidate relationships between radiochemical yields and reaction variables using a simplified model reaction (Fig. 1). The reactions were carried out in a 270 μL reactor using 10–20 nmol of [^{11}C]O. 1-Iodopentane (0.2 M) and a ketone (0.01M) were dissolved in CH_3OH/THF mixture (1:1). The reactor was pressurized to 39 MPa and irradiated with Xe lamp for 6 min at 35°C.

Results and Discussion: Among studied sensitizers a group of ketones were found more effective. Generally, the efficiency of energy transfer photosensitizers is determined by their lowest excited state energy (E_T). In the carbonylation reaction (1), however, the radiochemical yields appeared as unrelated to E_T (Table 1): some high-energy sensitizers were not efficient. The observed dependence of outcome on the concentration of a nucleophile also could not be readily explained (Fig. 1). These observations seem characteristic of the co-solvent participation in the reaction mechanism. This hypothesis was further studied computationally and the results come in good agreement with the experimental data.

Table 1. Radiochemical yields of [^{11}C]esters using different sensitizers

Sensitizer	E_T[a], kJ/mol	Yield[b], %
xanthone	310	44
2-methoxyacetophenone	299	14
benzophenone	289	55
2-acetylnaphthalene	249	1
biacetyl	236	1
benzil	227	25

[a]Triplet energy. [b]Deacay corrected.

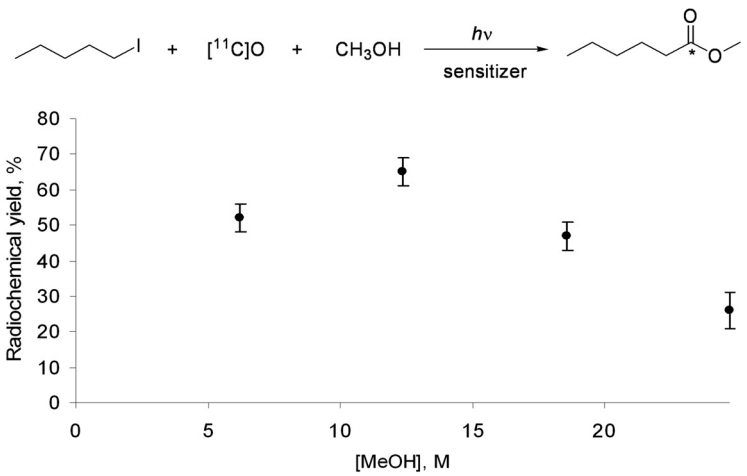

Fig. 1

Conclusion: Available data enables us to suggest that atom transfer mechanism is operative, rather than energy transfer. In practice, these findings are immediately transferable to the synthesis of imaging agents for PET.

Acknowledgement: This work was conducted in collaboration with Imanet, GE Healthcare.

Keywords: ^{11}C, Carbon Monoxide, Radicals, Carbonylation

P119 MICRO-SYNTHESIS OF 2-(^{11}C)-THYMIDINE TO IMPROVE YIELD

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Introduction: The highly variable yields for [^{11}C]-thymidine, its half-life and rapid metabolism to thymine and ultimately CO_2 prompted development of [^{18}F]-fluorothymidine (FLT) as an alternative for imaging cellular growth. Despite continuing enthusiasm for FLT, recent work shows that the selectivity of nucleoside transporters and thymidine kinase leads to images that are dominated by transport rather than the salvage pathway. Thus FLT images are difficult to interpret, leading us to improve the synthesis of 2-[^{11}C]-thymidine, the gold standard for PET imaging of proliferation.

Experimental: 2-[^{11}C]-thymidine has been made from [^{11}C]$COCl_2$ or cyanide. The CN reaction steps are trapping [^{11}C]-cyanide, conversion to cyanate and then to urea. [^{11}C]-Urea is filtered to remove salts, dried, cyclocondensed to thymine, purified and enzymatically converted to thymidine [J Label Cmpd Radiopharm 37:610, 1995]. Production of [^{11}C]-urea and filtration/drying before cyclocondensation have been the most difficult steps.

We make [^{11}C]-urea by bubbling $NH_4{}^{11}CN$ into 70 μL of $KMnO_4$ in KOH in a 1 mL autoinjector vial. After trapping, the vial is warmed at 110°C for 1 min to achieve quantitative oxidation to cyanate and 25 μL NH_4Cl is added, followed by 12 μL EtOH. The vial is capped and heated to 175°C for 3.25 min to make [^{11}C]-urea. A small headspace and high P are critical to maximize urea yield. Salts are not removed prior to drying. Removal of reduced Mn salts was a major limitation of the earlier method. The urea is dried at 125°C and a gentle Ar stream in <5min and 100 μL oleum is added followed by 9μL 2-methyl-3-methoxy-2propenoic acid methyl ester for the cyclocondensation reaction, 5 min at 125°C. The product is neutralized by passing it through a small column of AG11x8 and buffered with TRIS. Deoxyribose is added, along with thymidine phosphorylase, to make the final product which is purified by HPLC (1x25 cm C18, 5% EtOH in water).

Results and Discussion: With miniaturization conversion to urea improved from 15% to ~90%. Cyclocondensation yields varied depending on the freshness of the acrylate precursor which polymerizes with time. NMR is not adequate to detect this degradation. With older precursor the total decay-corrected yield ranged from 0 to 10% (7±4%); with fresh precursor from the freezer the yield ranged from 18 to 28% (22±4%). The radiosynthesis and purification of 2-[^{11}C]-thymidine is complete within 40 min EOB with a 23±4% decay corrected yield in a two-pot process.

Conclusion: Miniaturization of the radiosynthesis of ring-labeled [^{11}C]-thymidine from cyanide via urea is now a robust, high-yield synthesis with fewer steps. Miniaturization is likely to play an important role in optimizing many radiochemical syntheses.

Acknowledgement: This research was supported by CA42045 and RR17229.

Keywords: [^{11}C]-Thymidine, [^{11}C]-Urea, Proliferation Imaging, Microsynthetic Methods

P120 A NOVEL METHOD FOR THE SYNTHESIS OF ^{11}C-RACLOPRIDE USING A MICROREACTOR

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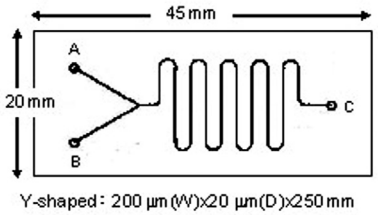
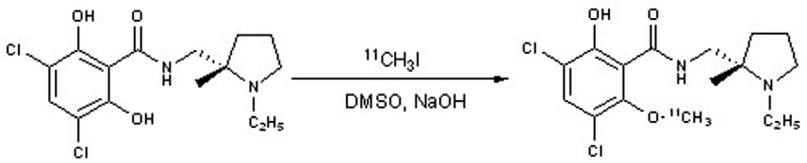
Introduction: Carbon 11-labelled raclopride ([^{11}C]raclopride) is a central D2-dopamine receptor imaging reagent for PET. [^{11}C]CH_3OTf has recently been used in the the synthesis of [^{11}C]raclopride. However, this method was limited because of difficulties in handling of a silver triflate (AgOTf) column. To solve this problem, microreactor was introduced as a novel method for the radiosynthesis. Microreactor devices, consisting of a network of micron-sized channels (typical dimensions in the range 10-300 μm) etched into a solid substrate such as glass, are capable of controlling and transferring tiny quantities of liquids and would offer the advantage of applying to radiochemical reactions. Here, an efficient, rapid synthesis of [^{11}C]raclopride using [^{11}C]CH_3I with a microreactor is described.

Experimental: The microreactor is a Y-shaped channel [200 μm(W) x 20 μm(D) x 250 mm(L); total volume ~ 1 μl](Figure 1). A solution of *O*-desmethylraclopride in DMSO (2.5 mg/ml) was injected into a inlet A and a solution of [^{11}C]CH_3I in DMSO was injected into a inlet B. The reaction mixture was collected from outlet C. A portion of the reaction mixture was injected into a HPLC system. Then [^{11}C]raclopride was fractioned and the radioactivity was measured with an auto well gamma counter. After the decay correction, the radiochemical yield was calculated.

Results and Discussion: The radiochemical yields of [^{11}C]raclopride was 11.7±4.3% for the infusion rate of 1.5 μl/min (reaction time 20 sec) at 25°C and 14.5±2.3% for the infusion rate of 0.5 μl/min (reaction time 60 sec) at the same temperature. By increasing the temperature to 60°C, [^{11}C]raclopride was obtained in higher yields (20 sec: 20.3±2.0%). This study showed more reproducible yields than conventional methods.





Conclusion: We developed a novel method for the systhesis of [^{11}C]raclopride using a microreactor. Since [^{11}C]raclopride were prepared in over 20% yields (20 sec, 60°C), this technique could be applied for simple and efficient routine production of carbon 11-labelled compounds. The microreactor technology would be useful for PET radiolabelling reactions.

Acknowledgement: This work was financially supported by NEDO P05001.

Keywords: 11C-Methylation, [^{11}C]Raclopride, Microreactor

P121 SIMPLE RADIOSYNTHESIS OF 5-BROMO-2'-(^{18}F)FLUORO-2'-DEOXYURIDINE VIA A NEW ANHYDROTHYMIDINE PRECURSOR

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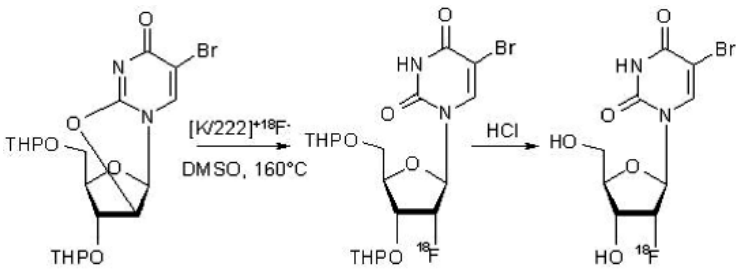
Introduction: Several radiolabelled thymidine analogs were identified to enable in vivo imaging of deregulated proliferation using PET. The most prominent representative is [^{18}F]FLT which can be used to image a number of different tumor types. The molecular target of thymidine analogs is thymidine kinase (TK1) whose activity is increased in the DNA synthetic phase of the cell cycle. Retention of these analogs reflects therefore a measure of cell proliferation. In 2-position fluorinated thymidine analogs are of special interest because they have the potential to be incorporated into DNA. 5-[^{76}Br]Bromo-2'-fluoro-2'-deoxyuridine ([^{76}Br]FBRU) was reported to be a suitable tracer for the assessment of tumor proliferation. Therefore a tow-step synthesis approach was developed which enables a facile introduction of ^{18}F in a corresponding anhydro-thymidine precursor to form [^{18}F]FBRU.

Experimental: Precursor synthesis of 1-(2'-deoxy-2'-anhydro-3'-5'-tetrahydropyranyl-β-D-arabinofuranosyl)-5-bromo-uracil: Starting from uridine 2,2'-anhydro-1-β-D-arabinofuranosyluracil was obtained by reaction with diphenyl carbonate and sodium bicarbonate in DMA. N-Bromosuccinimide bromination was used to introduce Br in 5-position. The hydroxyl groups were protected with tetrahydropyranyl (THP) groups.

Radiosynthesis: The anhydro precursor was treated with [K$^+$[suB]2.2.2]^{18}F$^-$ for various times (5–60 min) at temperatures between 100–180°C. THP protecting groups were cleaved applying 1 N HCl for 10 min at 55°C. After addition of phosphate buffer the reaction mixture was analysed using polystyrene RP HPLC. Synthesis of [^{18}F]FBRU was confirmed by coinjection of unlabelled FBRU standard and [^{18}F]FBRU.

The manually optimized synthesis was adapted to an automated synthesis module (TRACERlab FXFN, GE Medical Systems).

Results and Discussion: The conditions of [^{18}F]fluorination of the anhydro precursor were systematically investigated and optimized. Optimal reaction conditions were: 20 mg precursor in 0.5 ml DMSO at 150°C for 10 min. Radiochemical yields of 54.5% could be achieved. Thus, in the automated synthesis yields of 25% could be obtained after 60 min preparation time.



Conclusion: A new anhydro precursor for the synthesis of [^{18}F]FBRU was developed. The two-step radiolabelling method enabled the production of [^{18}F]FBRU in an automated synthesis module in high radiochemical yields for further biological evaluation.

Acknowledgement: Research was supported by Grant KFO120 from the German Research Foundation (DFG).

Keywords: Fluorine-18, Thymidine Analogs, TK1, PET

P122 NUCLEOPHILIC AROMATIC (^{18}F)FLUORINATION OF ELECTRON-RICH AROMATIC SYSTEM USING IODONIUM SALT

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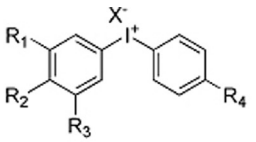
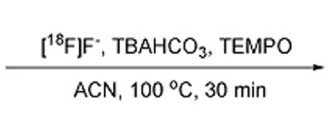
Introduction: The incorporation of [^{18}F]fluoride into electron poor or electron rich arenes under no-carrier-added (n.c.a) condition has been a challengeable research project in PET study.[1] Of several methods, aromatic fluorination of iodonium salts is thought to be a fascinating method to directly obtain biologically active [^{18}F]fluoro-compound. However, there have been no reports mentioned the electron rich system with high specific activity. Thus, herein, more reactive and selective aromatic fluorination was investigated on both asymmetrical and symmetrical electron rich diaryliodonium salts systems.

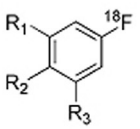
Experimental: A series of electron rich diaryliodonium salts (**1a**-**d**) was prepared by the coupling reaction of appropriate (diacetoxy)iodoarenes with arylboronic acid or aryltrialkylstannanes in 34-90% yields. [^{18}F]Fluorination of 3,4,5-trimethoxyphenyl-(4'-methoxyphenyl)iodonium trifluoroacetate salt (**1a**) was carried out as a model reaction with $TBAHCO_3$ and 70 mol% of TEMPO (tetramethylpiperidine-*N*-oxide, a radical scavenger preventing radical mediated decomposition) at 100°C for 30 min in a sealed vial.

Results and Discussion: Radio TLC showed 41±2% (n=3) conversion and RCY was 26±3% (n=3). Comparison of retention time on HPLC analysis (HPLC condition; acetonitrile/H_2O (4/6), 4.0 mL/min) has confirmed the formation of 1-[^{18}F]fluoro-3,4,5-trimethoxybenzene (**2a**). We thought that this regioselective reaction might be controlled by the combined consideration of electronic effect and steric effect (so-called *ortho*-effect).[2] Further [^{18}F]fluorinations of other iodonium salts such as 3,4-dimethoxyphenyl(4'-methoxyphenyl)iodonium trifluoroacetate (**1b**), 3-methoxyphenyl(4'-methoxyphenyl)iodonium triflate (**1c**), and 4-methoxyphenyl(4'-methoxyphenyl)iodonium triflate (**1d**) were performed under the same condition and gave 26%, 34%, and 9% conversion to the corresponding [^{18}F]fluoroarenes **2b-d**, respectively.



1a : R_1-R_4 = OCH_3, X=CF_3CO_2
1b : R_1 = OCH_3, R_2 = OCH_3, R_3 = H, R_4 = OCH_3, X=CF_3CO_2
1c : R_1 = H, R_2 = H, R_3 = OCH_3, R_4 = OCH_3, X=CF_3SO_3
1d : R_1 = H, R_2 = OCH_3, R_3 = H, R_4 = OCH_3, X=CF_3SO_3





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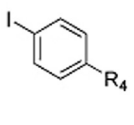

2a : R_1-R_3 = OCH_3
2b : R_1 = OCH_3, R_2 = OCH_3, R_3 = H
2c : R_1 = H, R_2 = H, R_3 = OCH_3
2d : R_1 = H, R_2 = OCH_3, R_3 = H

3a : R_4 = OCH_3
3b : R_4 = OCH_3
3c : R_4 = OCH_3
3d : R_4 = OCH_3

Conclusion: Although regioselective [^{18}F]fluorination of **1b**-**d** was not optimized yet, we were able to validate both asymmetrical and symmetrical nucleophilic aromatic [^{18}F]fluorination of electron rich aromatic systems. Our results may open several possibilities of incorporation of [^{18}F]fluoride to electron rich and biologically active molecules within a few step.

Keywords: Aromatic Fluorination, Iodonium Salt, F-18

P123 NUCLEOPHILIC RADIOFLUORIDATION USING SIMPLE MICROFLUIDIC DEVICES

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Introduction: Microfluidic devices offer several significant benefits for PET radiotracer synthesis. These benefits include reduced radiation shielding requirement, fast reaction times, increased control of reaction conditions and reduced reagent consumption. Several authors have previously reported the use of microfluidic devices for the radiosynthesis of 2-[^{18}F]FDG where the radiolabelling and deprotection reactions were performed using simple microfluidic 'T'-mixers. To date, only one group has implemented the more challenging [^{18}F]fluoride phase transfer process.

We present an elegant microscale solution for conducting [^{18}F]fluoride phase transfer and subsequent radiosynthesis of 2-[^{18}F]FDG that eliminates the azeotropic drying process.

Experimental: [^{18}F]Fluoride solution (1 mL) was passed at differing flowrates (100–1000 μL/min) through a volume of resin (1-15 μL, Chromabond, Macherey-Nagel) contained within a microscale device. [^{18}F]Fluoride was eluted from the resin at flowrates up to 250 μL/min using a mixture of K_2CO_3/K2.2.2 in CH_3CN/water (10,000 ppm, 500-1000 μL). The elution mixture was reacted with a solution of mannose triflate using a microfluidic 'T'- mixer heated to 85°C. The reaction mixture was collected in a solution of NaOH (0.3M) and analysed by radioHPLC for 2-[^{18}F]FDG. All solutions were transferred using programmable syringe pumps (Harvard Apparatus).

Results and Discussion: [^{18}F]Fluoride trapping efficiencies of 80-97% were achieved using resin volumes of 6-13 μL. At a flowrate of 1000 μL/min, 1mL of cyclotron produced [^{18}F]fluoride solution was extracted from the resin in 60s. [^{18}F]Fluoride elution efficiencies of up to 90% were achieved at a flowrate of 250 μL/min. When the extracted [^{18}F]fluoride solution was passed directly onto the subsequent microfluidic 'T'- mixer and reacted with mannose triflate, TA-[^{18}F]FDG was synthesised in 6 min with rcp of 83%. The deprotection reaction was performed in >80% yield to give 2-[^{18}F]FDG.

Conclusion: This work demonstrates an elegant solution for conducting [^{18}F]fluoride phase transfer which is also suitable for incorporation onto an inexpensive disposable microchip. Through optimisation of the reaction parameters, we have been able to eliminate the azeotropic drying process whilst retaining the capability to process a typical 1mL volume of cyclotron produced [^{18}F]fluoride.

Comparison of the subsequent radiolabelling yield with results obtained using conventional phase transfer techniques demonstrate that our microscale method is suitable for the radiosynthesis of 2-[^{18}F]FDG. The method presented here is equally applicable to other nucleophilic fluoridation reactions.

Keywords: Microfluidic Radiosynthesis, 2-[F-18]FDG, Simplification, Elimination of Azeotropic Drying

P124 ONE-POT SYNTHESIS OF ^{18}F-FLUOROMETHYL ETHERS AND SULFIDES

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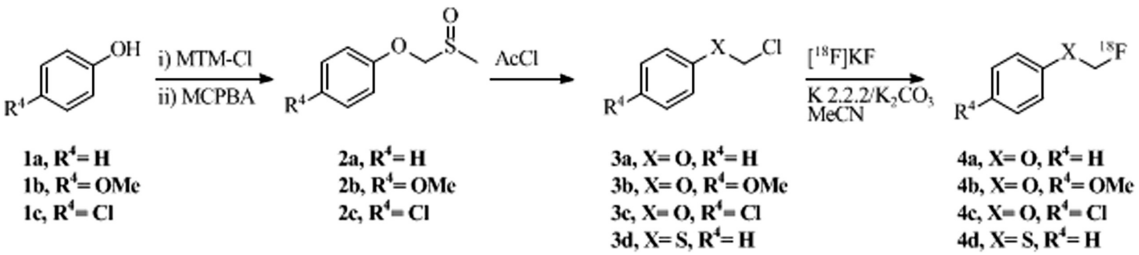
Introduction: Fluorine-18 labeling of aryl fluoromethyl ethers and sulfides has mainly been performed by alkylation of *desfluoromethyl*- phenolic or sulfide precursors with ^{18}F-labeled electrophiles. In all cases, purification of the electrophile has been deemed necessary for the subsequent fluoroalkylation step. Typical radiochemical yields (RCYs) for compounds obtained with this chemistry are around 15-25%. Here we investigated an alternative labeling method by direct substitution with [^{18}F]fluoride ion. Due to its commercial availability, chloromethyl phenyl sulfide (**3d**, Scheme 1) was chosen as a model substrate for reaction. In addition, three aryl chloromethyl ethers and their sulfone precursors (**2a-c**) were investigated, namely *p*-chloro, *p*-methoxy and phenyl chloromethyl ether (**3a-c**).



Scheme 1. Preparation of [^{18}F]fluoromethyl aryl ethers and sulfides (MTM-C = $ClCH_2SCH_3$; MCPBA = *m*-choroperbenzoic acid).

Experimental: Aqueous ^{18}F-fluoride ion (~1 mCi, 0.1 mL) was dried azeotropically with acetonitrile. Precursors and standards were prepared according to literature procedures. RCYs were estimated using radio-thin layer chromatography. Cesium and potassium carbonate were used as metal salts alone or together with either K 2.2.2 or 18-crown-6 as kryptands in dry acetonitrile, DMF or DMSO under thermal or microwave-aided heating.

Results and Discussion: The highest radiochemical yield for [^{18}F]**4d** (75%) was observed after heating a mixture of chloromethyl phenyl sulfide, K_2CO_3 and K 2.2.2 in MeCN at 130°C for 40 min. The reaction time could be decreased to 10 min with marginally reduced yield (74%) when using microwave-aided heating instead of thermal heating. Higher temperatures (in DMF and DMSO) and prolonged microwave heating had either negative or no effect on the yield. Under the above conditions, [^{18}F]**4b** was obtained in 67% RCY from [^{18}F]fluoride ion and **3b**. An even higher yield was observed when generating **3b** in the radiofluoridation mixture *in situ* from **2b** and acetyl chloride (76%). When further applying these conditions, the rank order for the radiochemical yield with regards to the different substituents on the phenyl ring was: *p*-methoxy (76%) > H (44%) >*p*-chloro (22%).

Conclusion: A one-pot procedure was established for the ^{18}F-labeling of aryl fluoromethyl ethers from their corresponding sulfones. Moderate to high radiochemical yields were obtained. Further experiments are required on more complex structures, such as receptor ligands, to verify the true utility of the method.

Acknowledgement: The authors thank the IRP at the NIH (NIMH) and the NIH-KI GPP.

Keywords: Fluorine-18, Fluoromethyl Ether

P125 ROBUST METHODS FOR THE PREPARATION OF ([11]C)PK 11195 INCLUDING CAPTIVE SOVENT RADIOSYNTHESIS

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Introduction: Imaging peripheral-type benzodiazepine receptors (PBR) with appropriate PET radioligands is potentially a powerful approach for *in vivo* assessment of various inflammatory pathologies, with the most widely used PET radioligand being [^{11}C]PK11195 [1]. However its radiosynthesis by carbon-11 methylation using highly basic conditions has been found to be highlysensitive to various aspects of its reaction conditions, leading to significant unreliability for regular productions. We have also shown that the use of solid potassium hydroxide as a base, combined with heating, can lead to significant dechloroination of product during radiosynthesis [2]. Therefore, there is a need for more robust methods for the regular radiosynthesis of this radiotracer, especially to undertake clinical imaging studies. In particular we wished to consider the use of a captive solvent method, which has significant advantages of milder reaction conditions, combined with simplicity for automated radiosynthesis.

Results and Discussion: *Solution Method:* To a solution of des-methyl-PK11195 (1 mg) in dimethylsuphoxide (500 μl) was added 5M sodium hydroxide (3 μl). The solution was allowed to stand for 20 min at room temperature then [^{11}C]iodomethane, transferred in a stream of helium, was collected. The reaction solution was then heated at 85°C for 2.5 min then subjected to preparative radio-HPLC (μ-Bondapak, C18 10μm, 300 x 7.8 mm, ethanol/water 60/40 v/v, 3.0 ml/min.) Radiochemical yield (decay corrected) based on [^{11}C]iodomethane was determined to be 21-29% (n > 10). Collection of the product's HPLC fraction followed by its formulation resulted in a radiochemical product of 1.5-2.3 GBq at end-of-synthesis.

Captive solvent Method: To a solution of des-methyl-PK11195 (1 mg) in dimethylsuphoxide (200 μl) was added 5M sodium hydroxide (3 μl). The solution was allowed to stand for 10 min at room temperature then loaded onto HPLC injector sample loop (1 ml). A stream of helium is briefly passed through the loop (30 sec) to create the internal coating of the precursor solution, then [^{11}C]iodomethane, in a stream of helium is passed through the loop over a period of 3 min. The loop contents were then injected onto the HPLC column for radio-HPLC analysis (Phenomenex Luna, C18 3μm, 20 x 2 mm, acetonitrile/water 28/72 v/v, 1.7 ml/min). This showed the showed the radiochemical yield (decay corrected) based on [^{11}C]iodomethane to be 25-35% (n = 4). The radiochemical activity trapped by the loop represented 25-40% of the delivered [^{11}C]iodomethane.

Conclusion: The solution method we have found to be high reproducible for the regular synthesis of [^{11}C]PK11195 with no detectable evidence of dechlorination occurring. This method is now being used for undertaking our clinical imaging studies. Our preliminary results have shown, for the first time that [^{11}C]PK11195 can be produced by a captive solvent method on a loop. Now on-going is optimisation of this method to increase the efficiency of [^{11}C]iodomethane trapping, as well as increasing the radiochemical yield.

References: [1] Shah F, Hume S, Pike V, Ashworth S McDermott J Nucl. Med. Biol. 1994, 21, 573-581. [2] Cleij MC, Aigbirhio FI, Baron JC, Clark JC. J. Labelled Compd. Radiopharm., 2003, 46 (S), S88.

P126 SYNTHESIS OF SUCCINIMIDYL 4-(^{18}F)-FLUOROBENZOATE USING THE TRACERLAB MX_{FDG} SYNTHESIZER

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Introduction: The objective of our work is to develop radioligands for vascular peptide receptor systems and we have for this purpose established the synthesis of succinimidyl 4-[^{18}F]-fluorobenzoate ([^{18}F]-SFB). The aim of this work was to investigate if the TRACERlab MX_{FDG} synthesizer could be modified to allow the synthesis of [^{18}F]-SFB and if the obtained product could be used to label big endothelin-1 (big ET-1) and urotensin II (UII) with ^{18}F to enable imaging of the endothelin and the urotensin receptor system.

Experimental: The TRACERlab MX_{FDG} synthesizer including an add-on HPLC unit was used. The program sequence was re-written and the FDG cassette was modified to enable the radiosynthesis of [^{18}F]-SFB. The synthetic sequence includes: ^{18}F-fluorination of the trimethylamonium triflate precursor; hydrolysis and SPE isolation of the formed [^{18}F]-fluorobenzoic acid ([^{18}F]-FBA); cleaning of the reaction vial; re-transfer of [^{18}F]-FBA back to the reaction vial; evaporation of solvent; formation of [^{18}F]-SFB and HPLC purification. The collected [^{18}F]-SFB fraction was isolated using SPE and eluted out in a small volume of CH_3CN (0.5 ml). Aliquots of this solution were used for peptide labelling. Peptides were conjugated with [^{18}F]-SFB at pH 8.5 (borate buffer) at room temperature. UII have to sites available for conjugation (*N*-terminal and Lys^8) thus we also investigated the effect of pH on the preferred position of conjugation.

Results and Discussion: The TRACERlab MX_{FDG} synthesizer could be adapted to allow the synthesis of [^{18}F]-SFB. A total radiochemical yield of 45.5± 3.4% from [^{18}F]-fluoride (n=12, decay corrected) and specific activities of 250-350 GBq/mmol was obtained. Using this procedure we have produced 8-12 GBq [^{18}F]-SFB in 98 min. Radiochemical conversion of [^{18}F]-SFB to [^{18}F]-big ET-1 was 15%. The preferred site for conjugation of UII at the pH tested was Lys^8 (Table 1).

Table 1

pH	Site of conjugation as a function of pH	
	N-terminal	Lys^8
8.5	5.8	50.2
7.5	10.6	41.0
7.2	13.0	40.0

Conclusion: [^{18}F]-SFB was produced in an automated process using the TRACERlab MX_{FDG} synthesizer in good radiochemical yield and to high specific activities in 98 min. We have used [^{18}F]-SFB for the labelling of big ET-1 and UII. *In vitro* binding characterisation and microPET evaluation of these peptides are currently in progress.

Acknowledgement: We thank P. Burke, O. Golovko and R. Smith for helpful discussion and technical support. This work was supported by grants from the British Heart Foundation and the Medical Research Council Technology Foresight (UK Government).

Keywords: succinimidyl 4-[^{18}F]-fluorobenzoate, endothelin receptors, urotensin receptors, peptide labelling, microPET

P127 DEVELOPMENT OF NEW DIRECT METHODS FOR ^{18}F-LABELING OF PEPTIDES

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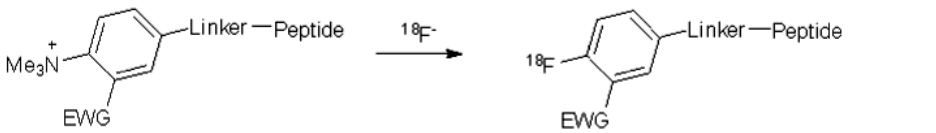
Introduction: Positron emission tomography (PET) is a medical imaging method, which uses positron-emitting radioisotope-labeled compounds to trace biochemical transformations and the movement of drugs in living system. An adequate method for labeling of a molecule with fluorine-18 requires rapid, convenient and efficient incorporation of the radionuclide into the molecule of interest. A large number of ^{18}F-labeled prosthetic groups have been developed which can be attached to biomolecule by different research groups [1–4]. Up to now, all the methods are based on multi-step reactions. Therefore, new direct radiolabeling methods were developed by coupling building blocks to the target peptides followed by a one step nucleophilic substitution with fluoride-18. One approach for example is the trimethylammonium-fluoride exchange reaction as shown in Scheme I. To find the best building block for coupling to peptides, a series of model phenyltrimethylammonium compounds with different linkers and different electron withdrawing groups were synthesized and labeled with ^{18}F. The influence of the radiolabeling temperature, amount of precursor, solvent and fluorination reagent was investigated. With the optimized building block and radiolabeling conditions (50-90°C, 15-30 min), good ^{18}F incorporation ranging from 10% to 92% was achieved for target peptides. *In vivo* PET imaging of the ^{18}F-labeled peptides is currently ongoing.



Scheme I

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