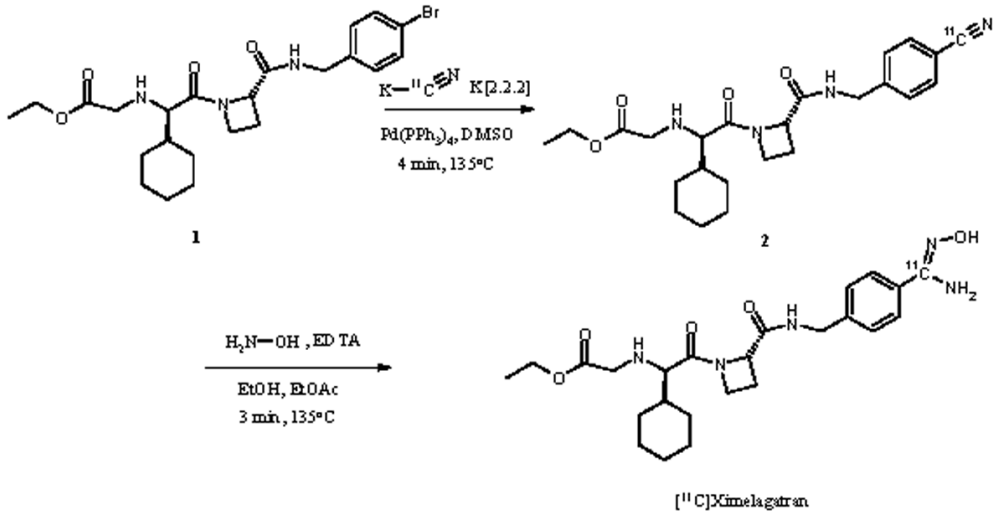
SYNTHESIS OF ([11]C)XIMELAGATRAN VIA PALLADIUM CATALYZED [11]C-CYANATION

A.J. AIRAKSINEN [1], J. ANDERSSON [1], P. TRUONG [1], O. KARLSSON [2] and C. HALLDIN [1]

[1]Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden; [2]Department of Medicinal Chemistry, Astrazeneca R&D, Mölndal, Sweden

Introduction: N-Hydroxyamidine functionalities (amidoximes) may be used in prodrug technology in improving oral bioavailability of drugs containing amidino functional groups. Amidines are very strong bases and are protonated under physiological conditions. In the body, the hydroxyamidine group is quickly reduced to its active amidino moiety by enzymes which are present in several organs. Positron emission tomography can be used in evaluating bioavailability of prodrugs *in vivo*. Our aim was to develop a fast and efficient labeling route for synthesis of ^{11}C labeled hydroxyamidine prodrugs with a label in a metabolically stable position. We used the oral direct thrombin inhibitor ximelagatran as a model compound.

Experimental: The ^{11}C labelled hydroxyamidine, [^{11}C]ximelagatran, was synthesized via a two step synthesis sequence, starting from its bromo-precursor, {2-[2-(4-bromo-benzylcarbamoyl)-azetidin-1-yl]-1-cyclohexyl-2-oxo-ethylamino}-acetic acid ethyl ester (**1**) (Scheme 1). The corresponding ^{11}CN-intermediate (**2**) was obtained from the bromo precursor by a palladium-catalyzed cyanation with H^{11}CN in 4 minutes at 135°C. [^{11}C]Hydroxyamidine function was synthesized via reaction between the ^{11}CN-intermediate and hydroxylamine in a mixture of EtOH and EtOAc in a presence of small amount of EDTA, in 3 minutes at 135°C. The synthesized [^{11}C]ximelagatran was purified with semi-preparative HPLC and evaporated to dryness under reduced pressure. The purified product was formulated to phosphate buffer solution (pH 7.4).



Results and Discussion: A fast and efficient method for synthesizing ^{11}C labelled hydroxyamidines via a two step synthesis sequence was developed. The model compound [^{11}C]ximelagatran was synthesized with good yield (27 ± 17%, total overall DCY), giving 1.75 ± 1.0 GBq of radiochemically pure compound (> 97%) with a total synthesis time of 45 minutes.

Keywords: Radiosynthesis, Palladium, Cyanation, Trombin Inhibitor

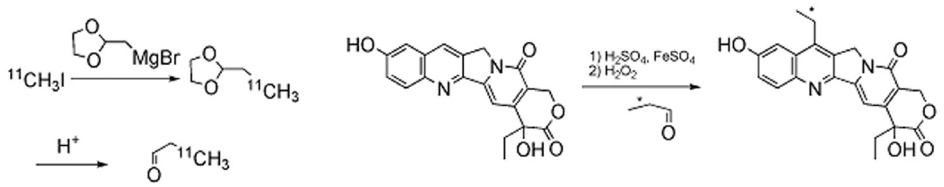
2-(^{11}C)PROPIONALDEHYDE AS A SYNTHETIC LABELING INTERMEDIATE

S.M. APANA [1] and M.S. BERRIDGE [1,2]

[1]3D Imaging, LLC, Cleveland, OH, USA; [2]Chemistry, Case Western Reserve University, Cleveland, OH, USA

Introduction: Camptothecin and derivatives are used in treatment of cancer, including ovarian, lung, and colon. Concentration of the compound in the tumor tissue is part of the mechanism of action, and non-responding patients are common. The ability to quantify drug accumulation in the tumor could provide an indication of expected therapeutic response before investing the time involved in treatment. One such derivative is 7-ethyl-10-hydroxycamptothecin (SN-38).

Experimental: SN-38 has been labeled using C-[13] propionaldehyde (Scheme) [1]. To label it with carbon-11, a synthesis of [^{11}C]propionaldehyde is required.



Propionaldehyde was synthesized by the reaction of methyl iodide with (1,3-dioxolan-2-yl) methyl magnesium bromide in the presence of dilithium tetrachlorocuprate. The approach followed previous methods of cuprate mediated carbon to carbon coupling reactions [2]. The 1,3-dioxolane was the Grignard of choice due to its availability, stability, and relative ease of deprotection in aqueous hydrochloric acid and methanol.

Results and Discussion: Propionaldehyde was obtained in 74 ± 3% yield in five minutes based on methyl iodide. Quantitative analysis was performed by gas chromatography. Synthesis of SN-38 under conditions similar to those used for C-11 labeling were reported to proceed in 25% yield, sufficient to allow use of this propionaldehyde preparation for synthesis of SN-38.

Other approaches that were examined included methylation of both 2(ethoxy)vinyl lithium and the acetaldehyde enolate. Neither approach proved successful, most likely due to the instability of the respective intermediates.

References: [1] Collins, J.M; Klecker, R.W. Jr; Anderson, L.W. Imaging of drug accumulation as a guide to antitumor therapy. Publication No. US2003/0198594 A1. [2] Kihlberg, T; Langstrom, B. Cuprate-mediated 11C-C coupling reactions using Grignard reagents and 11C-alkyl iodides. Acta Chemica Scandinavica, 1994; 48; 570-577.

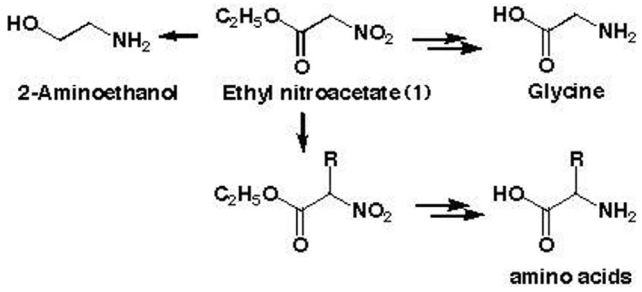
Keywords: Carbon-11, Propionaldehyde, Synthetic Intermediate, Camptothecin

SYNTHESIS OF (α-^{11}C)ETHYL NITROACETATE: A NEW LABELING INTERMEDIATE

K. KATO, M.-R. ZHANG and K. SUZUKI

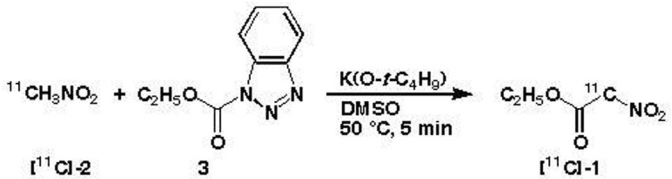
Department of Molecular Probes, National Institute of Radiological Sciences, 4-9-1 Anagawa, Inage-ku, Chiba, Japan

Introduction: Ethyl nitroacetate (**1**) is an important synthetic intermediate which can be utilized for the syntheses of glycine, other aminoacids and aminoethanol (Figure 1). The labeling synthesis of **1** by ^{11}C will provide versatile small molecules significantly utilized for PET ligand. We will report the synthesis of [α-^{11}C]-**1** from [^{11}C]nitromethane (**2**).



Experimental: [^{11}C]-**2** was prepared in accordance with the literature.[1] [^{11}C]-**2** was trapped in DMSO (300 μL) in the presence of K(O-*t*-C_4H_9) (1.5 μg, 13 μmol) and a DMSO (100 μL) solution of **3** (5 μg, 17 μmol) was added. After 5 min at 50°C an acetonitrile solution containing 30% acetic acid (v/v) was added and the mixture was analyzed by HPLC.

Results and Discussion: The ethoxy carbonylation of [^{11}C]-**2** was chosen for the synthesis of [^{11}C]-**1** since [^{11}C]-**2** was already available from [^{11}C]CH_3I. *N*-Ethoxycarbonylbenzotriazol (**3**) was easily prepared by the condensation of ethyl chloroformate and 1*H*-benzotriazol and was utilized for the *C*-carboxylation of nitroalkanes.[2] The metal, such as lithium and potassium, dianion of alkylnitronate undergo the *C*-acylation of nitroalkanes to give α-nitroketones,[3,4] therefore we used the excess amount of K(O-*t*-C_4H_9) in DMSO for trapping of [^{11}C]-**2** to produce dianion of methylnitronate. The condensation of trapping solution and **3** for 5 min at 50°C gave *C*-carboxylated compound [α-^{11}C]-**1** in approximately 30% yield (Figure 2).



Conclusion: We synthesized the [α-^{11}C]-**1** which could be a useful intermediate for the syntheses of PET tracers. Further progress will be presented.

Acknowledgement: This work was supported by a Grant-in-Aid for Molecular Imaging Program (Research Base for PET Diagnosis) from the Ministry of Education, Science and Culture, Japan.

References: [1] Schoeps, K.-F.; Stone-Elander, S.; Halldin, C. *Appl. Radiat. Isot.* **1989**, *40*, 261. [2] Proštenik, M.V.; Butula, I. *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 139. [3] Seebach, D.; Lehr, F *Angew. Chem. Int. Ed. Engl.* **1976**, *15*, 505. [4] Katritzky A.R. Abdel-Fattah, A.A.A.; Gromova, A.V.; Witek, R.; Steel, P.J. *J. Org. Chem.* **2005**, *70*, 9211.

Keywords: [^{11}C]Niromethane, [alpha-11C]Ethyl Nitroacetate, C-Carboxylation

SYNTHESIS AND BIODISTRIBUTION OF RADIOLABELED HIGH-AFFINITY CHOLINE UPTAKE INHIBITORS (^{11}C)HEMICHOLINIUM-3 AND (^{18}F)HEMICHOLINIUM-3

Q.-H. ZHENG [1], M. GAO [1], B.H. MOCK [1], S. WANG [1], M.A. MILLER [1], T.J. RECEVEUR [1], R. NAZIH [1], J.C. LOPSHIRE [2], W.J. GROH [2], D.P. ZIPES [2], G.D. HUTCHINS [1] and T.R. DEGRADO [1]

[1]Department of Radiology, Indiana University, Indianapolis, IN, USA; [2]Krannert Institute of Cardiology, Indiana University, Indianapolis, IN, USA

Introduction: The high-affinity choline uptake (HACU) system is an attractive target for the development of PET biomarkers to probe cardiac and cancer diseases. Hemicholinium-3 (HC-3), the most potent synthetic inhibitor, is a golden standard for studying the HACU system *in vitro*. ^{11}C- and ^{18}F-labeled HC-3 analogues, [^{11}C]hemicholinium-3 ([^{11}C]HC-3) and [^{18}F]hemicholinium-3 ([^{18}F]HC-3), may serve as *in vivo* PET agents for HACU. We present here our initial investigation on synthesis and biodistribution of [^{11}C]HC-3 and [^{18}F]HC-3.

Experimental: The bis-tertiary amine precursor 4,4'-bis-(1-methyl-3-hydroxy-morpholinyl-(3))-biphenyl and reference standard HC-3 were synthesized from 4,4'-bis-bromoacetyl-biphenyl with 2-(methylamino)ethanol and 2-(dimethylamino)ethanol in 80% and 92% yields, respectively. The precursor was labeled by [^{11}C]CH_3OTf through the primary *N*-[^{11}C]methylation and trapped on a cation-exchange CM Sep-Pak cartridge to release the non-reacted precursor with ethanol and to retain the pure ^{11}C-methylated single-side quaternary amine intermediate on the same cartridge. The intermediate underwent the secondary ^{12}C-methylation by addition of CH_3I/EtOH to the cartridge. Non-reacted CH_3I was removed from the cartridge by rinsing with ethanol, and the final bis-quaternary amine carbon-11 labeled product [^{11}C]HC-3 was then eluted from the cartridge with saline. Using similar methodology, fluorine-18 labeled target tracer [^{18}F]HC-3 was prepared by *N*-[^{18}F]fluoromethylation of the precursor using [^{18}F]FCH_2OTf followed by *N*-methylation using CH_3I and purified by the CM Sep-Pak method. The biodistribution of both compounds was determined in a subcutaneous 9L-glioma rat model.

Results and Discussion: The radiochemical yields of [^{11}C]HC-3 were 50-60% decay corrected to EOB, and specific activity was in a range of 4.0-6.0 Ci/μmol at EOB. The radiochemical yields of [^{18}F]HC-3 were 5-10%. Biodistribution data of [^{11}C]HC-3 at 5 and 20 min and [^{18}F]HC-3 at 5 and 30 min in 9L-glioma rats (n=3) showed the major organs of uptake were urine and kidney, and there was heart uptake observed. Tumor uptake was moderate, and tumor/muscle ratios were 3.0-5.1 for both [^{11}C]HC-3 and [^{18}F]HC-3 at 5-30 min post injection.

Conclusion: An efficient and convenient synthesis of [^{11}C]HC-3 and [^{18}F]HC-3 has been well-developed, and preliminary biodistribution has been performed. Further study will be to determine the specificity of binding to the HACU system of HC-3 tracers.

Acknowledgement: Supported in part by the Donald W. Reynolds Foundation and INGEN of Indiana University.

Keywords: Biodistribution, [^{11}C]Hemicholinium-3, [^{18}F]Hemicholinium-3, PET, High-Affinity Choline Uptake (HACU)

SYNTHESIS OF ^{18}F-LABELED STILBENES FROM 4-(^{18}F)FLUOROBENZALDEHYDE USING THE HORNER-WADSWORTH-EMMONS REACTION

F. WÜST, S. GESTER and J. PIETZSCH

Institut für Radiopharmazie, Forschungszentrum Dresden-Rossendorf, Dresden, Germany

Introduction: The coupling of phosphonic acid esters with carbonyl compounds, also referred to as the Horner-Wadsworth-Emmons reaction, represents a powerful carbonyl olefination reaction to form C-C double bonds, exhibiting E-configuration exclusively.

This work describes the application of the Horner-Wadsworth-Emmons reaction as novel labeling technique in 18F-chemistry. Various 18F-labeled E-configured stilbenes could be synthesized through the coupling of benzylic phosphonic acid esters with readily available 4-[^{18}F]fluorobenzaldehyde 1 as labeling precursor (Fig. 1).

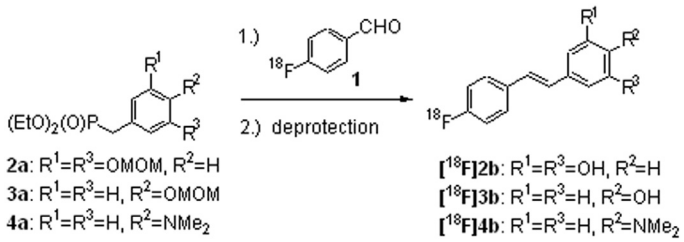


Fig. 1. Synthesis of ^{18}F-labeled E-stilbenes via Horner-Wadsworth-Emmons reaction.

Experimental: The carbonyl-olefination reaction was performed via a "multi-step/one-pot" reaction by the coupling of benzylic phosphonic acid esters (3,5-bis-methoxymethoxybenzyl)-phosphonic acid diethyl ester 2a, (4-methoxymethoxybenzyl)-phosphonic acid diethyl ester 3a and (4-dimethyl-aminobenzyl)phosphonic acid diethyl ester 4a) with 4-[^{18}F]fluorobenzaldehyde to give the corresponding 18F-labeled stilbenes [^{18}F]2b, [^{18}F]3b and [^{18}F]4b exclusively as the expected E-isomers after deprotection. The radiochemical yields ranged from 9 to 22% (based upon [^{18}F]fluoride, including HPLC purification). The specific activity reached up to 90 GBq/μmol.

Results and Discussion: The reaction can be applied for the synthesis of polyphenolic compounds and aromatic amines bearing an E-configured stilbene backbone as pharmaceutically interesting compounds. Several E-configured stilbene-based polyphenols are known to be potential anticancer compounds. In the case of amine group-containing stilbene compound [^{18}F]4b, structural comparable stilbenes have been reported as potential ligands to bind to Aβ-plaques found in the brain of patients with the neurodegenerative Alzheimer's disease. Preliminary radiopharmacological studies including small animal PET of compound [^{18}F]4b in normal rats showed promising brain uptake. Results on the radiopharmacological characterization of compound [^{18}F]4b will be presented.

Conclusion: The described method opens a convenient access to a large number of 18F-labeled compounds bearing an E-configured stilbene backbone.

Acknowledgement: The authors wish to thank S. Preusche for radioisotope production and T. Krauss for technical assistance.

Keywords: Stilbenes, [^{18}F]Fluorobenzaldehyde, Horner-Wadsworth-Emmons Reaction

RADIOLABELLED CUBANES. NEW SYNTHONS IN THE DEVELOPMENT OF RADIOPHARMACEUTICALS

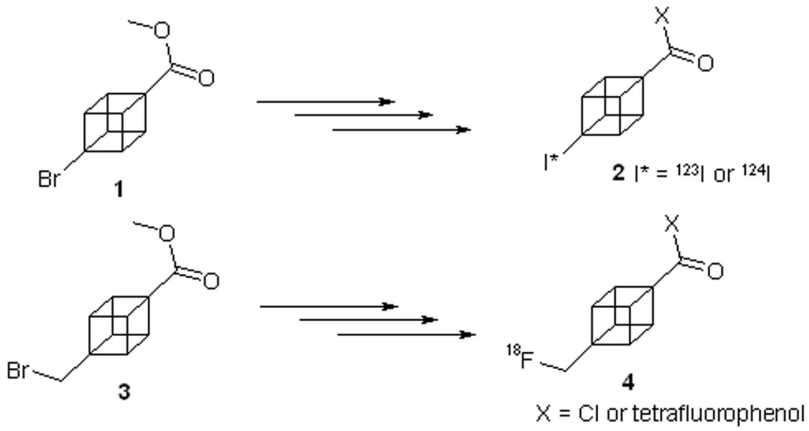
J.D.M. HERSCHEID and J. VERBEEK

Nuclear Medicine & PET Research, VU University Medical Centre, Amsterdam, Netherlands

Introduction: A major problem in the application of radiopharmaceuticals is dehalogenation. Especially aliphatic iodinated compounds are very instable *in vivo*, since they are easily susceptible to nucleophilic substitution. But also deiodination and even defluorination of aromatic compounds is not an uncommon issue.

These problems can be solved just by putting the radiolabel on a cubyl moiety.

Experimental: Reaction of **1** with water-free radioiodide in acetonitrile for 40 minutes at 130°C using Cu(II)triflate as a catalyst gave the corresponding labelled iodocubyl ester in 80-85% yield. Saponification and formation of the acid chloride or another active ester (**2**) was almost quantitative.



The radiofluorination of **3** was even more effective. Under standard fluorination conditions incorporation of ^{18}F was over 95% within 10 minutes.

Both **3** and **4** have been used for the coupling with amines, e.g. WAY-100634 to give radiolabelled cubyl-WAY derivatives, but also for the labelling of antibodies.

Results and Discussion: Its was found that in the radioiodination a small amount of a co-catalyst like dimethylpiperazine is essential and that the presence of water dramatically reduce the labelling yield.

Instead of the above multistep approach it is also possible to perform these reactions on an in advance prepared precursor. For instance, conversion of bromocubyl-WAY also proceeds in nearly 80%, autocatalyzed by its internal piperazine moiety (for $^{18}FCH_2$-cubyl-WAY see another abstract). Incubation of this ^{123}I-labelled cubyl-WAY with human hepatocytes revealed that the hydrolysis rate is lowered compared to e.g. MPPF. But more important, the only radioactive metabolite found was iodocubane carboxylic acid. No free radioiodide was formed, indicating an extremely stable carbon-iodine bond. Also the fluoromethylcubanes were found to be extremely stable *in vitro* and are expected to be so *in vivo*, since HF-elimination is impossible.

MAb's labelled with **2** showed better localizing characteristics than the directly iodinated ones. This is especially important with regard to ^{124}I-PET imaging in oncology.

Work is now in progress whether labelling on the 2- or 3-position of cubane would have additional advantages.

Conclusion: Radiolabelled cubanes are easily accessible and have the advantage of a more stable carbon-radioisotope bond than many other halogenated radiopharmaceuticals. In addition, due to steric hindrance the hydrolysis rate of cubyl-amides is reduced. Both aspects are important factors for *in vivo* application.

Keywords: Cubane, Radiofluorination, Radioiodination

(^{76}Br)BMK-152: A PET LIGAND FOR CORTICOTROPIN-RELEASING HORMONE (CRH) TYPE 1 RECEPTOR

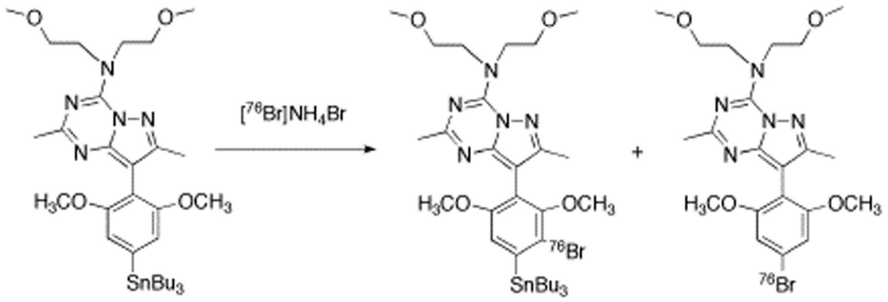
L. LANG [1], Y. MA [1], E.M. JAGODA [1], B.M. KIM [3], K.C. RICE [2], L.P. SZAJEK [4], C. CONTOREGGI [2], W.C. ECKELMAN [5] and D.O. KIESEWETTER [1]

[1]NIBIB, NIH; [2]NIDA; [3]CC; [4]NIDDK, NIH, Bethesda, MD, USA; [5]Molecular Tracer, LLC, Bethesda, MD, USA

Introduction: CRH receptors have been implicated in anxiety and depression. A CRH PET ligand could be used to study CRH receptor density in normal and abnormal states and evaluate the effect of treatment on disorders involving the CRH system. BMK-152 ([8-(4-bromo-2,6-dimethoxyphenyl)-2,7-dimethylpyrazolo[1,5-α][1,3,5]triazin-4-yl]-N,N-bis-(2-methoxyethyl)amine] is a non-peptide ligand that displays lower lipophilicity and increased brain uptake compared to the previously reported ligand MJL 1-109-2 (Jagoda et al. J. Med. Chem. 2003). Initial radiobromination procedures provided low yields of the desired product and one major side product. Optimization procedures led to a satisfactory yield of the desired product.

Experimental: Radiobrominations were carried out using peracetic acid and various solvents and temperatures in order to optimize radiochemical yield. Waters Q-TOF MS coupled with a Waters UPLC Acquity system was used to analyze and identify radioactive products. Affinity was determined using competition studies with I-125 CRH as the standard and regional money or rat brain localization was determined using in vitro autoradiography.

Results and Discussion: The 4-bromo isomer exhibited 10 times stronger affinity than 3-bromo isomer. Initial bromination conditions, using ACN as solvent and the 4-tributyltin precursor, yielded two radiochemical products. The product co-eluting with authentic BMK-152 was minor (~1%); the major product was highly retained. LC-MS analysis of this product was consistent with addition of bromine and retention of the tributylstannyl group. The product was treated with trifluoroacetic acid to give the 3-bromo isomer. The yield of BMK-152 was increased to 10% at higher temperature (120°C, ACN) and to 30% in DMF at 150°C. However, the product also contained the 3-bromo isomer that was resolved from the 4-bromo only by UPLC. Finally, conducting the radiobromination after removing sources of water provided the pure 4-bromo product in 50% radiochemical yield.



Conclusion: We demonstrated that by controlling the reaction conditions, either pure 3 or 4 [^{76}Br]BMK-152 can be prepared from the same tributyl tin precursor. 4-bromo has higher affinity than 3-bromo compound and 4-bromo has potential as a suitable PET ligand for imaging CRHR1 in vivo.

Acknowledgement: The funding was provided by NIH intramural research program.

Keywords: Bromine-76, CRH Receptors, Radiosynthesis