NEW APPROACHES TO RADIOHALOGENATION USING SOLID-STATE BORONATED REAGENTS

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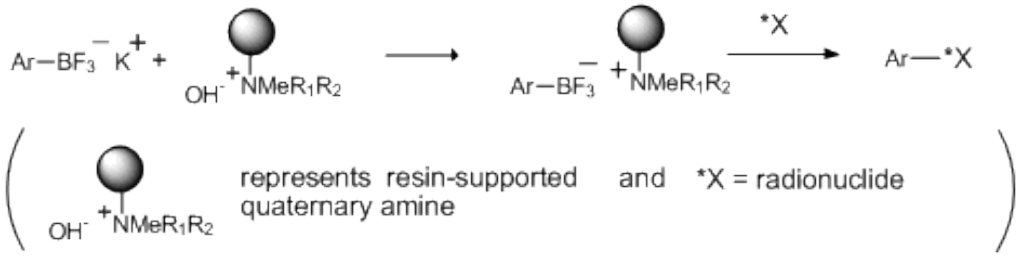
Objectives: The creation of solid-state, insoluble, reactive intermediates from which radiolabeled products can be readily "washed off" has been of interest to a number of research groups, including our own. These solid-state reagents, if stable to air and water, could be utilized in radiopharmaceutical "kits" in Nuclear Medicine departments. Our early investigations utilized polystyrene-supported organoborane reagents(J. Radiolabelled Compds. Radiopharm. 2001, 42, 5793). The methodology found few practical applications because of the air instability of the polymeric organoboron precursors. Recent studies involving the trifluoroborate derivatives have dramatically demonstrated how the boron reagents themselves tolerate a wide variety of chemical transformations, such as S_N2, epoxidation, Wittig, and Click chemistry. We also recently discovered that the radioiodination of trifluoroborate derivates proceed very effectively (J. Labelled Compl Radiopharm. 2005, 48, 359). Another point of importance is the fact that the air- and water-stable tetrabutylammonium trifluoroborate salts can be prepared and provide a novel bridge between polymer-supported chemistry, organotrifluoroborate chemistry, and radiolabeling. The objective of this study was to prepare a series of stable, polymeric organotrifluoroborate derivatives that could be used as precursors to radioiodinated and radiobrominated pharmaceuticals.

Methods: A Series of quaternary ammonium substituted resins were prepared and complexed with aromatic and vinyltrifluoroborate derivatives. The resultant complexes were radioiodinated under no-carrier-added conditions to produce the corresponding aryl and vinyl halide derivatives.

Results: The radioiodination of polymeric organotrifluoroborates proceeded efficiently at room temperature in less then 20 minutes. The radiochemical yields were quite high and were comparable to the yields obtained in earlier studies involving simple salts of the organotrifluoroborates.



Conclusions: The air and water-stable, polymeric tetrabutylammonium trifluoroborate salts can be prepared and provide a novel bridge between polymer-supported chemistry, organotrifluoroborate chemistry, and radiolabeling. The new reagents have potential use in radiopharmaceutical "kits" in Nuclear Medicine departments.

Research Support: This research was supported by the US Department of Energy

RADIOFLUORINATION OF UNSYMMETRICAL META-SUBSTITUTED DIARYLIODONIUM SALTS WITHIN A MICRO-REACTOR

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Objectives: The introduction of fluorine-18 ($t_{1/2}$ = 109.7 min) as no-carrier-added [^{18}F]fluoride ion into poorly activated arenes (e.g., aryl rings bearing only a meta substituent) is quite difficult to achieve with conventional aromatic nucleophilic substitution reactions [Cai et al., Eur. J. Org. Chem., 2008, 17, 2853]. Reactions of diaryliodonium salts with [^{18}F]fluoride ion are a potential means to circumvent this limitation [Pike and Aigbirhio, J. Chem. Soc., Chem. Commun., 1995, 2215]. Here we aimed to use a microfluidic device [Lu et al., Curr. Radiopharm., 2009, 2, 49] to study the radiofluorination of meta-substituted diaryliodonium salts, and in particular to establish optimal decay-corrected radiochemical yields (RCYs).

Methods: New meta-substituted diaryliodonium salts were prepared by treating appropriate aryltriakylstannanes [Pike et al., J. Chem. Soc., Perkin Trans. 1, 1999, 245] or arylboronic acids [Carroll et al., Tetrahedron Lett., 2000, 41, 5393] with [hydroxy(tosyloxy)iodo]arenes. Cyclotron-produced [^{18}F]fluoride ion in [^{18}O]H_2O was trapped on a QMA cartridge and then released into a solution of K_2CO_3-Kryptofix 2.2.2 complex in MeCN-H_2O (95: 5 v/v). Water was removed by two cycles of addition-evaporation of MeCN (450 μL) and the radioactive residue dissolved in MeCN. For each reaction, the [^{18}F]fluoride ion solution and a diaryliodonium tosylate solution (~ 10 mM) in MeCN were delivered simultaneously at a fixed equal flow rate into a 4-m silica glass micro-reactor (internal volume 31.41 μL; Advion) held at a preset temperature (nominally, between 130 and 190 °C). Residence times in the micro-reactor ranged from 236 to 471 s, depending on set flow rate. Exiting reaction mixtures were immediately quenched with MeCN-H_2O (1: 1 v/v) and analyzed by reversed phase radio-HPLC to determine the RCYs of [^{18}F] fluoroarenes.

Results: Under optimal reaction conditions, useful RCYs (25–87%) of meta-substituted [^{18}F]fluoroarenes (3-$RC_6H_4{}^{18}F$) were obtained selectively from the unsymmetrical diaryliodonium tosylates (3-$RC_6H_4I^+$Ar OTs^-; R = CN, Me, NO_2 or CF_3; Ar = 4-$MeOC_6H_4$, 2-thienyl, 5-Me-2-thienyl) versus Ar^{18}F product (Figure). For example, radiofluorination of 3-cyanophenyl(4'-methoxyphenyl) iodonium tosylate gave 87% RCY for a reaction conducted at 130 °C with a residence time of 291 s.

Conclusions: The use of the micro-reactor was efficient and fast for optimizing the [^{18}F]radiofluorination of diaryliodonium salts. Factors impacting on RCY, such as infusion rate (residence time), and temperature, were manipulated easily. Diaryliodonium salts proved effective and reliable precursors for the preparation of meta-substituted [^{18}F]fluoroarenes.

Research Support: Intramural Research Program of NIH, NIMH

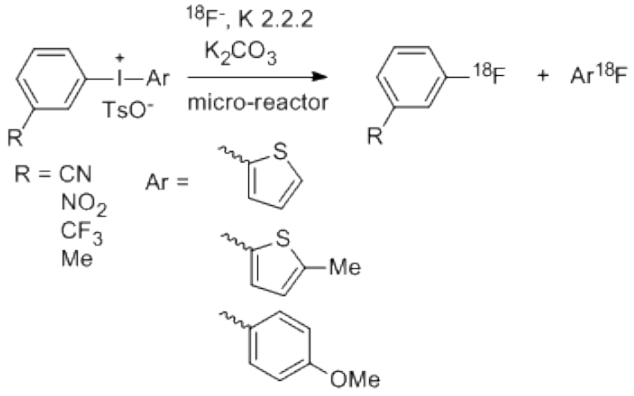

Figure Radiofluorination of *m*-substituted diaryliodonium salts in a micro-reactor.

APPROACHES TOWARDS RADIOLABELING OF TRIFLUORO-MISONIDAZOLE WITH 18F

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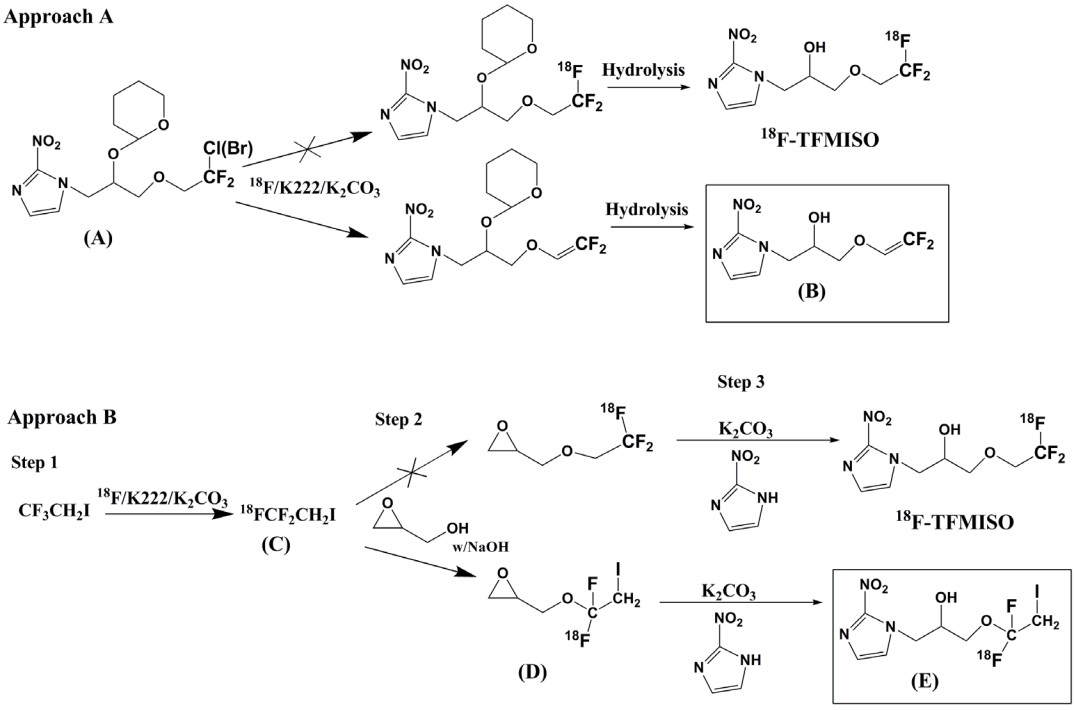
Objectives: The objective of this project is to label trifluoro-misonidazole (TFMISO), 2-nitro-α-[(2,2,2-trifluoroethoxy) methyl]-imidazole-1-ethanol, with ^{18}F so that the compound transforms into a bimodal tool for in vivo imaging of hypoxia not only by ^{19}F-MRI but also by ^{18}F-PET.

Methods: We have tested several approaches including the two outlined in the Figure below. Approach A was designed to label TFMISO via a 2-step procedure which involves substitution of the halogen (Cl/Br) in the 2-chloro(bromo)-2,2-difluoroethoxy analog of TFMISO (A) with ^{18}F followed by hydrolysis of the OH-protection group (Fig). Approach B was a 3-step procedure in which trifluoroethyl iodide was used as the starting material. The rationale behind this approach was that since the labeling efficiency of CF_3CH_2I with ^{18}F (Step 1) is approximately 90%, if the reaction of $[^{18}F]CF_3CH_2I$ (C) with glycidol proceeds well (Step 2) in parallel to the reaction with CH_3CH_2I, ^{18}F-labeling of TFMISO could be achieved with high efficiency via the intermediate 1,2-epoxy-3-(2,2,2-[^{18}F]trifluoroethoxy)-propane (Fig).

Results: Approach A: The 2 electron-withdrawing fluorine atoms in the CF_2X group (X: Cl or Br) of the precursor (A) rendered competitive elimination of the leaving group (Cl or Br) from the molecule more dominant than the desired substitution. As a result, after heating the chloro(bromo)-difluoro precursor (A) with ^{18}F in the presence of Kryptofix 222 and K_2CO_3 and removing the OH-protection group, the major product was the elimination product (Compound B in Figure). Approach B: In Step 2, the nucleophile derived from glycidol in the presence of a base attacked the electron-deficient carbon site of the CF_3-group replacing one of the fluorine atoms, instead of the iodine, yielding Compound D. In Step 3, Compound D was combined with 2-nitroimidazole in ethanol in the presence of K_2CO_3, which resulted in Compound E as the final product.

Conclusions: The results of these approaches illustrate the difficulties in labeling of TFMISO with ^{18}F. It is difficult to insert ^{18}F by replacing a halogen, such as Cl or Br, attached to the same carbon where 2 electron-withdrawing fluorine atoms are bound without inducing the elimination reaction. Model alkylation reactions with ethyl halide are not applicable to trfluoroethylation with trifluoroethyl halide. However, they have provided some interesting and important information based on which we can establish new strategies for labeling TFMISO with ^{18}F. The questions are a) how can the elimination reaction be controlled, b) is there a way to take advantage of the elimination reaction and insert ^{18}F such as by addition, and c) is there a strategy to convert trifluoroethyl halides to reactive electrophilic trifluoroethylating agents? We are currently addressing these issues.



SYNTHESIS OF AN MGLUR5 RADIOLIGAND, [^{18}F]SP203B, THROUGH RADIOFLUORINATION OF A DIARYLIODONIUM SALT PRECURSOR

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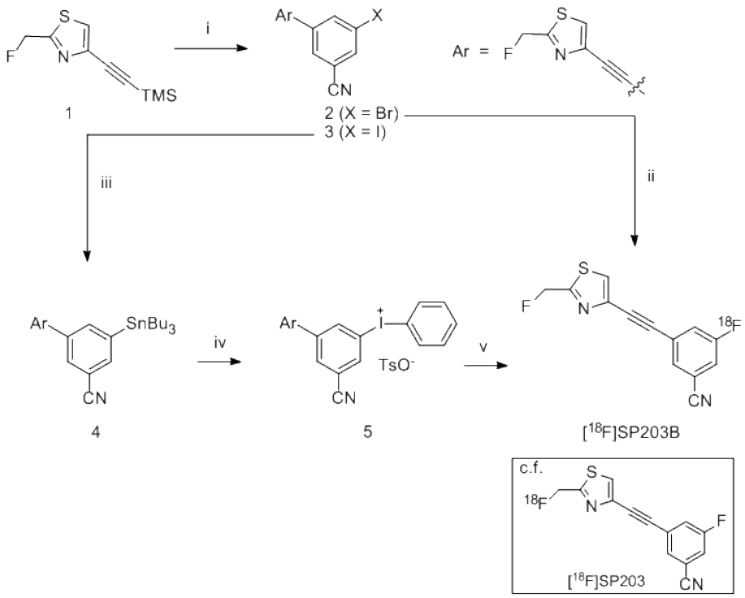
Objectives: SP203 (3-fluoro-5-[[2-(fluoromethyl)thiazol-4-yl]ethynyl]benzonitrile), when labeled in its 2-fluoromethyl position with fluorine-18 (Scheme) (Siméon et al., J. Med. Chem., 2007, 50, 3256), is an effective radioligand for imaging mGluR5 receptors in human subjects (Brown et al., J. Nucl. Med., 2008, 49, 2042). However, this radioligand is defluorinated in monkey in vivo giving rise to high radioactivity uptake into skull, which hampers analysis of radioligand binding in brain. We therefore aimed to label SP203 at its aryl fluoro position to avoid radiodefluorination in monkey. This position is not however well-activated towards aromatic nucleophilic substitution of halo leaving groups. Here we show that the targeted new radioligand, [^{18}F]SP203B (Scheme), can be prepared in usefully high radiochemical yield by treatment of a diaryliodonium salt precursor with [^{18}F]fluoride ion.

Methods: Pd(0)-catalyzed coupling of 1 with 3,5-dibromo- and 3,5-diiodo-benzonitrile gave 2 and 3, respectively. Compound 2 (3 mg, 9.3 μmol) was treated with no-carrier-added (NCA) [^{18}F]fluoride ion in DMSO (0.75 mL) containing K_2CO_3 (0.37 μmol) and K 2.2.2 (1.34 μmol) under microwave irradiation (10 min, ~ 150 °C). [^{18}F]SP203B was then separated on a semi-preparative size Luna C18 column eluted at 6.5 mL/min with a gradient of aq. 10 mM $HCOONH_4$ (A)-MeCN (B), with B increased from 40 to 50% over 20 min, and then to 100% over 10 min. The decay-corrected radiochemical yield (RCY) of [^{18}F]SP203B was calculated from the chromatogram. Pd(0)-catalyzed coupling of 3 with Bu_6Sn_2 gave the tri-n-butylstannane 4, which was converted into the iodonium salt 5 by treatment with Koser's reagent in CH_2Cl_2 (Pike et al., JCS, Perkin Trans. 1, 1999, 245). Compound 5 was recrystallized in high purity for use in NCA radiofluorination reactions within a microfluidic apparatus (Advion). This apparatus was loaded with a solution of [^{18}F]fluoride ion, K_2CO_3 (6 mM) and K 2.2.2 (12 mM) in DMF and a solution of the salt 5 (8 mM) in DMF in separate reservoirs. Reaction times were controlled by the flow rates (3–5 μL/min) set for simultaneous infusion of the solutions into the micro-reactor. Reactions were run at different set temperatures. To determine the RCY of [^{18}F]SP203B, reactor outputs were quenched with aq. MeCN and analyzed with radio-HPLC on a Luna C18 column (250 × 4.6 mm) eluted at 1.75 mL/min with a linear gradient of H_2O-MeCN with MeCN increased from 60% at 1 min to 90% over 7 min. Product identity was verified by LC-MS-MS of associated carrier.



Scheme. Synthesis of [^{18}F]SP203B; reaction conditions and yields: i) 3,5-dihalo-benzonitrile (halo = Br or I), $Pd(PPh_3)_4$, CuI, TEA, TBAF, DME, 80 °C, 56% (X = Br), 31% (X = I); ii) [^{18}F]fluoride ion, K$^+$-K 2.2.2, DMSO, 10 min, 150 °C, 4-6% RCY; iii) Bu_6Sn_2, $Pd(PPh_3)_4$, toluene, 80 °C, 16 h, 55%; iv) Koser's reagent, CH_2Cl_2, rt, 48 h, 24%; v) [^{18}F]fluoride ion, K$^+$-K 2.2.2, DMF, 470 s, 160 °C in micro-reactor, 31% RCY. The structure of [^{18}F]SP203 is shown for comparison.

Results: Nucleophilic substitution in the bromo compound 2 gave [^{18}F]SP203B in low RCYs (4–6%). Variation in reaction conditions gave no improvement in RCY. Reaction of [^{18}F]fluoride ion with the salt 5 gave [^{18}F]SP203B in 31% RCY from a reaction conducted at 160 °C for 470 s. The only radioactive byproduct was [^{18}F]fluorobenzene (1.2% RCY).

Conclusions: The use of the iodonium salt 5 allowed [^{18}F]SP203B to be prepared in five-fold higher RCY than the halo precursor 2. This route can be adapted to provide [^{18}F]SP203B in adequate activity for evaluation in monkeys.

COPPER COMPLEXES FOR IMPROVED [11C]CARBON MONOXIDE REACTIVITY

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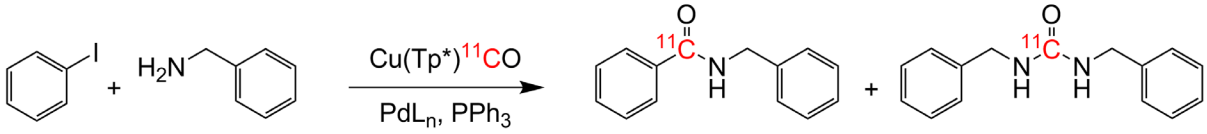
Objectives: The ubiquity of carbon in natural products and drug molecules makes ^{11}C an important positron-emitting radionuclide for incorporation into PET tracer molecules. [^{11}C]Carbon monoxide is a versatile ^{11}C-radiolabelling reagent as it can be incorporated into a range of biologically active functional groups. The use of this gas, however, has been hindered by its low solubility, high dilution and subsequent poor reactivity. To facilitate the use of ^{11}CO, we have been examining methods of improving its reactivity by enhancing solubility through a process of chemical complexation at room temperature and pressure. Following this trapping process, palladium-mediated [^{11}C]carbonylation reactions have been performed.

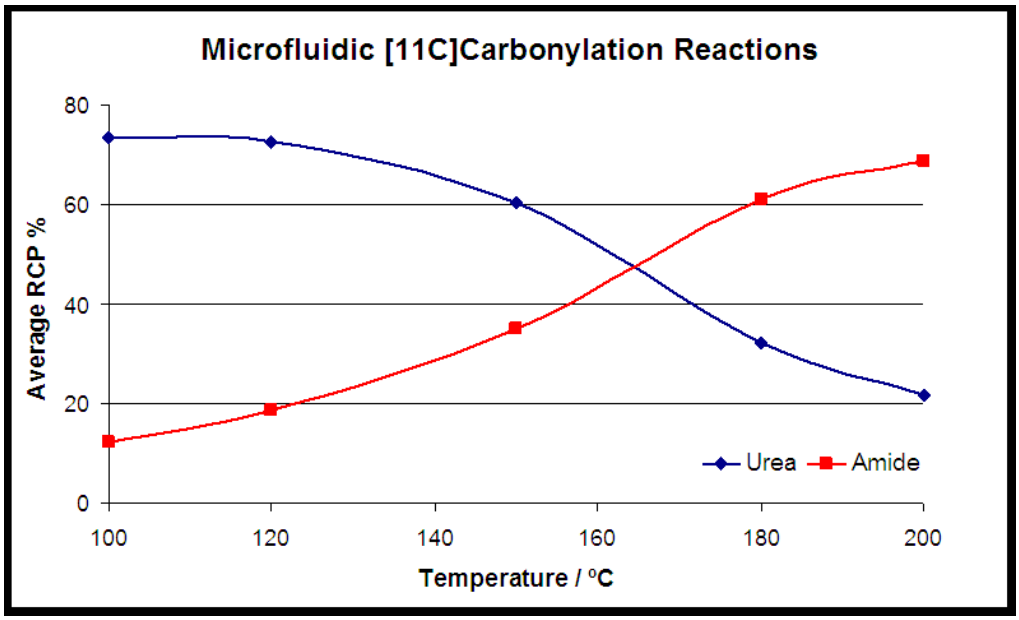
Methods: In a typical experiment, a ^{11}CO/helium gas stream was bubbled through a solution of copper(I) tris(3,5-dimethylpyrazolyl)borate in a glass vial with the waste gases being collected in a bag in a dose calibrator. Following these trapping reactions, palladium-mediated [^{11}C]carbonylation reactions were performed in situ by addition of a solution of palladium catalyst, aryl halide, amine nucleophile and triphenylphosphine and heating the sealed vial for 10 minutes.

Results: A saturated solution of CuTp* formed from potassium tris(3,5-dimethylpyrazolyl)borate (KTp*) and copper(I) chloride (CuCl) in THF (1 mL) is able to trap ^{11}CO in solution with trapping efficiencies of >90%. Following this trapping process, a DMF solution of benzylamine, iodobenzene, triphenylphosphine and the catalyst ($Pd_2(dba)_3$ and 1,3-bis(diphenylphosphino) propane), was added and the mixture heated at 120°C for 10 minutes. These reactions yielded [^{11}C-carbonyl]N-benzylbenzamide in 90% RCP and with a RCY of 40% (decay corrected to EOB). A palladium(II) catalyst, $Pd(dppp)Cl_2$, resulted in significant amounts of an unexpected side product, which was identified as [^{11}C-carbonyl]dibenzylurea. Removal of the iodobenzene from the reaction mixture and heating at 100°C for 10 minutes produced the urea in high purity (RCP >99%) and with a decay corrected RCY of 41%.



The effects of temperature on product distribution in the Pd(II)-catalysed [^{11}C]carbonylation reactions were examined using a microfluidic reactor (NanoTek LF). These reactions, involving iodobenzene, benzylamine and CuTp*(^{11}CO) showed that the amide:urea ratio increases as the temperature increases (from 100 to 200°C).

Conclusions: The use of the ^{11}CO for PET radiolabelling experiments has been facilitated by improving its solubility through temporary complexation to a copper(I) species in solution. Once trapped, ^{11}CO can be used to form amides in reasonable RCYs via palladium(0)-mediated carbonylation reactions. A new approach to [^{11}C-carbonyl]ureas is reported via palladium(II)-mediated oxidative carbonylation reactions.



NEW PHOSPHONIC ACID DERIVATIVES OF CROSS-BRIDGED CYCLAM AS 64Cu CHELATORS

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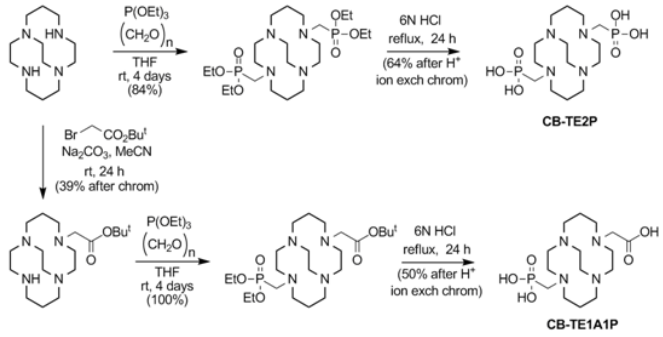
Objectives: ^{64}Cu is a promising radionuclide that is well suited for both PET imaging and therapy and can be produced in high yield and specific activity on a biomedical cyclotron. Azamacrocycles are chelators of choice for complexing ^{64}Cu. When conjugated to a targeting moiety and radiolabeled, these are potentially able to recognize specific targets, accumulate and allow for external, non-invasive detection. Widespread use of ^{64}Cu for imaging and radiotherapy depends on development of optimal chelators. Copper(II) binds to several endogenous proteins; therefore, in order to be of practical use, the macrocycles need to form complexes that are stable under physiological conditions. The cross-bridged macrocycle (CB-TE2A) forms Cu(II) complexes that are much more kinetically inert than the non-bridged DOTA and TETA analogs.[1] Unfortunately, Cu(II)-CB-TE2A has a slow rate of complexation requiring conditions that are harsher than desirable in order to achieve ^{64}Cu labeling in a reasonable time frame. In order to find chelators that complex Cu(II) with faster kinetics while retaining the high stability and the significant inertness observed with CB-TE2A, phosphonic acid (-CH_2-PO_3H_2) donor groups were investigated as pendant arms.[2,3] It has been shown previously that chelators with phosphonic acid pendant arms have higher selectivity as well as increased thermodynamic and kinetic stability compared to their acetic acid analogs.[4]

Methods: The newly synthesized compounds were radiolabeled and compared in vivo to other macrocycles commonly used to complex ^{64}Cu through biodistribution studies using healthy rats.

Results: CB-TE2P and CB-TE1A1P were synthesized, radiolabeled with ^{64}Cu and their in vivo behavior was investigated. While CB-TE2P labeling with ^{64}Cu was complete within 1 hour in buffer at higher temperatures, radiolabeling yields above 90% were observed even at 37° C. Remarkably, CB-TE1A1P had 100% radiolabeling yields at 37° C.



A biodistribution study showed rapid blood clearance and low liver accumulation at 24 h, suggesting that ^{64}Cu-CB-TE2P did not appreciably dissociate in vivo. A higher uptake was observed in the kidney while no significant uptake was detected in lung, spleen, heart or stomach. There was a relatively high uptake in the bone, however, this was not surprising as the methanephosphonic pendant arms are known to have high affinity for the hydroxyapatite in bone. An even better profile was observed for CB-TE1A1P, with lower uptake and faster clearance in kidney and bone.

Conclusions: The biodistribution of ^{64}Cu-CB-TE2P and ^{64}Cu-CB-TE1A1P compared favorably to CB-TE2A, NOTA and DiamSar, with better blood, liver and kidney clearance and lower accumulation in bone marrow than ^{64}Cu-labeled NOTA and DiamSar. The biodistribution of the two new compounds was comparable to ^{64}Cu-CB-TE2A at 24 h post-injection, with the added advantage of more rapid formation kinetics under milder conditions. Research is underway to investigate the conjugation of these chelators with biological targeting molecules.

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SYNTHESIS AND LABELING OF A NOVEL CAGED-LIKE BIFUNCTIONAL CHELATOR AMBASAR FOR PREPARATION OF Cu-64-RADIOPHARMACEUTICALS

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Objectives: Stable attachment of $^{64}Cu^{2+}$ to a targeting molecule requires the use of a bifunctional chelator (BFC). Sarcophagine (Sar) ligands rapidly coordinate $^{64}Cu^{2+}$ within the multiple macrocyclic rings comprising the cage structure under mild conditions, providing high stability in vivo.We designed a novel versatile Sar caged-like BFC named AmBaSar for ^{64}Cu-radiopharmaceuticals. Here we report the synthesis for preparing AmBaSar and its ^{64}Cu labeling.

Methods: The AmBaSar was synthesized in four steps starting from (1, 8-Diamine-Sar) cobalt (III) pentachloride (2, [Co(DiAmSar)]Cl_5) using a facile synthesis (Fig.1). The AmBaSar and its synthetic intermediates were characterized by MS and ^{1}H-NMR. The AmBaSar was labeled with ^{64}Cu in pH 5.0 ammonium acetate buffer solution, following analyzed and purified by HPLC.

Results: The chemical yield of the AmBaSar ranged from 6.6~8.3%. The ^{1}H-NMR results of the AmBaSarwere as following: ^{1}H-NMR (D_2O): δ 7.76-7.67 (m, 2H, aromatic); 7.45-7.37 (m, 2H, aromatic; 3.66 (s, 2H, NCH_2C) 3.26-3.04 (m, 12H, $NCCH_2N$); 2.99-2.84 (m, 12H, NCH_2CH_2N). The MS of AmBaSarcalculatedfor $C_{23}H_{41}N_8O_2$ $[M+1]^+$ m/z 449.34, found 449.70. Radiochemical yield of ^{64}Cu-AmBaSar was ≥ 95% after 30 min incubation at 25 °C. The ^{64}Cu-AmBaSar complex was analyzed and purified by HPLC (Fig.2), with retention time of ^{64}Cu-AmBaSar being 17.9 min.

Conclusions: The novel caged-like bifunctional chelator AmBaSar was readily synthesized in reasonable yield and characterized. Labeling with Cu-64 to form the new ^{64}Cu-AmBaSar complex occurred with high radiochemical yield (≥ 95%) under mild conditions.

References: (1)Smith, S. V. (2004) Molecular imaging with copper-64. J. Inorg. Biochem. 98, 1874-1901. (2)Smith, S. V. (2007) Sarar technology for the application of copper-64 in biology and materials science.Q. J. Nucl. Med. Mol. Imaging. 51, 1-10.

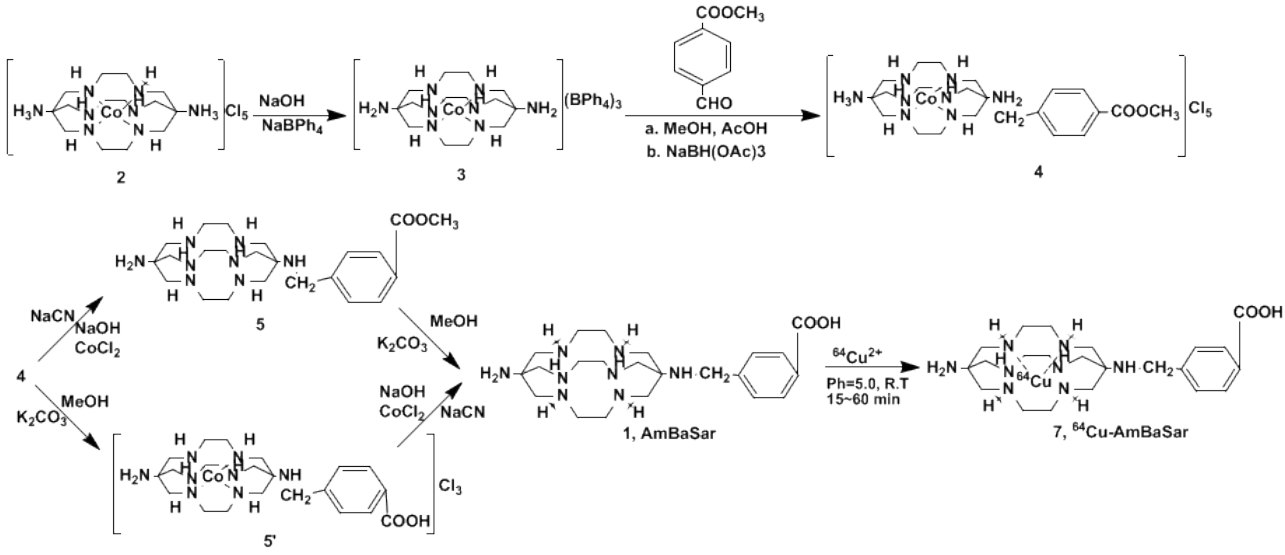

Fig.1 Synthesis of bifunctional chelator AmBaSar and ^{64}Cu labeling

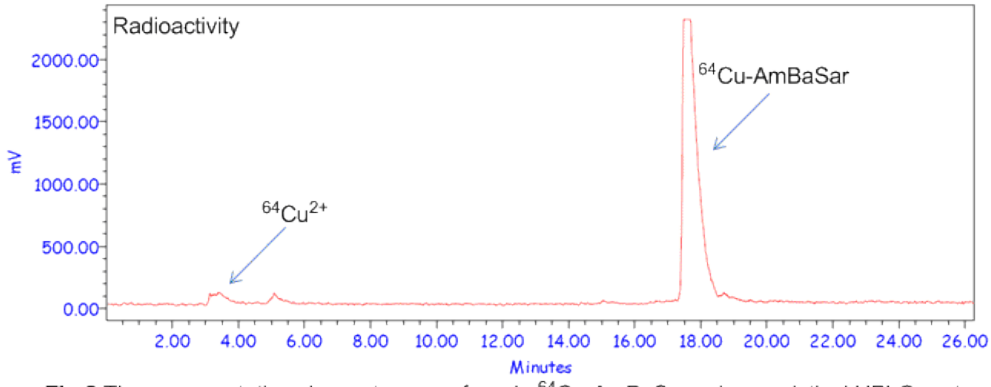

Fig.2 The representative chromatogram of crude ^{64}Cu-AmBaSar using analytical HPLC system.