P-230 - Aryliodonium ylides as efficient precursors for astatine-211 labeling

Clémence Maingueneau, Marion Berdal, Romain Eychenne, Joëlle Gaschet, Michel Chérel, Jean-Francois Gestin, Francois Guérard

(43.0±1.2 % at EOS, decay collected; n=3). Radiochemical purity of [^{211}At]**1** was >99% at EOS (n=3).

Summary: We radiosynthesized [^{211}At]**1** with sufficient amounts of radioactivity for application in TAT reagent of mGluR1 for melanoma therapy.

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P-229
Quantitation of a CB1R tracer [^{18}F]FPATPP with radioLC/MS/MS

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Objectives: The cannabinoid receptor subtype 1 (CB1R) is an interesting target in PET as CB1Rs control various physiological and pathological conditions. [^{18}F]FPATPP ((3*R*,5*R*)-5-(3-[^{18}F]Fluorophenyl)-3-(((*R*)-1-phenylethyl)amino)-1-(4-(trifluoromethyl)phenyl)pyrrolidin-2-one) is a new CB1R tracer.[1]

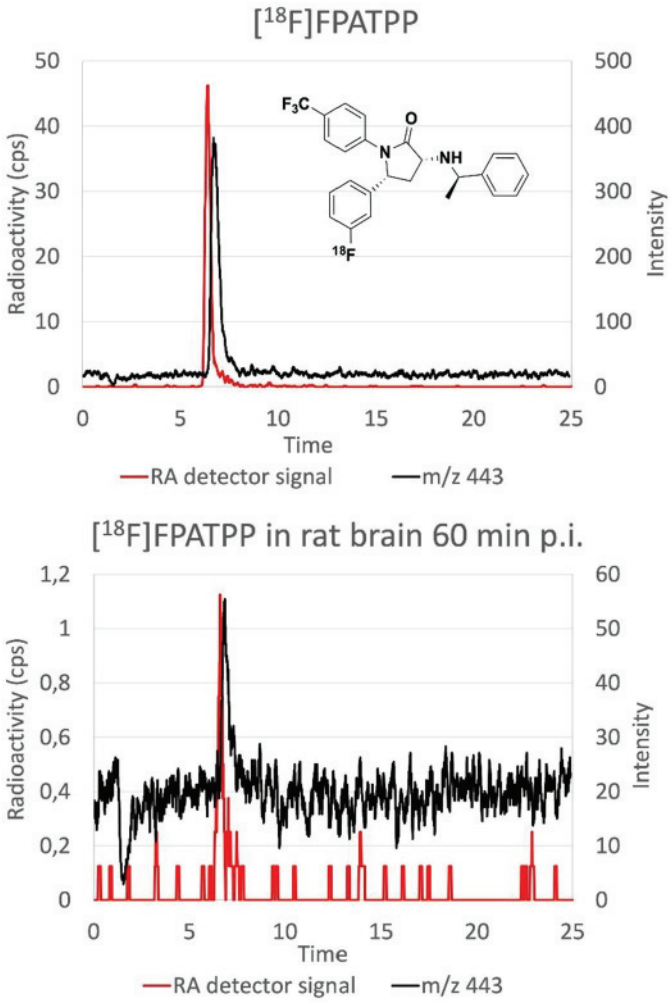

Fig. 1. Radiochromatograms from the positron detector and targeted mass traces from the MS with purified [^{18}F]FPATPP sample and rat brain sample 60 min after [^{18}F]FPATPP injection.

LC/MS/MS is an increasingly used analytical technique in radiochemical and radiopharmaceutical research. The combination of a radioactivity detector and LC/MS/MS allows the quantitation of radiopharmaceuticals. In this study, we introduce a highly sensitive radioLC/MS/MS method for [^{18}F]FPATPP quantitation and for determination of molar activity of [^{18}F]FPATPP.

Methods: The radioLC/MS/MS system consisted of a HPLC pump, a 0.6 µL Rheodyne injector, a HPLC column, an online positron detector[2] and a linear ion trap quadrupole mass spectrometer equipped with a turbo ion spray source. The positron detector was located between the HPLC column outlet and MS inlet. The positron detector was calibrated using fluorine-18 samples with known radioactivity concentration. An LC/MRM method was developed for detection of FPATPP (m/z 443) with high specificity and sensitivity.

[^{18}F]FPATPP was synthetized using Ru-mediated ^{18}F-fluorination.[1] The purified product was injected to the radioLC/MS/MS system in EtOH/H_2O formulation. The animal experiment was conducted in healthy Fischer rat. A brain sample was collected at 60 min post injection. The brain sample was homogenized in MeOH/H_2O (90:10 v/v). The supernatant was concentrated and injected to the radioLC/MS/MS.

Results: Molar activity of [^{18}F]FPATPP at the end of synthesis was determined to be 140 ± 30 GBq/µmol (n=3). As a comparison, using analytical HPLC with UV-detection the molar activity of [^{18}F]FPATPP was determined to be > 95 GBq/µmol.[1] The concentration of FPATPP in rat brain sample was determined to be 20 ng/mL. Figure 1 shows system performance with [^{18}F]FPATPP and [^{18}F]FPATPP in a rat brain sample at 60 min p.i.

Conclusions: We developed a successful radioLC/MS/MS method for direct molar activity determination. As a proof-of-concept of the sensitivity, we were able to determine the low concentration of FPATPP in rat brain sample.

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P-230
Aryliodonium ylides as efficient precursors for astatine-211 labeling

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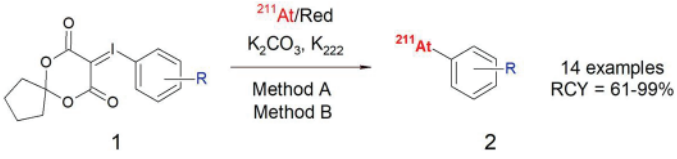
Introduction: Targeted alpha therapy (TAT) is a promising modality to treat micrometastases, blood cancers or residual disease. Among available alpha-emitting radionuclides, astatine-211 is a center of a growing attention. Even if studies on physical and chemical properties of astatine have multiplied over recent years, shadow areas still remain, limiting the number of available radiosynthetic methods.[1] The historic astatination reaction consists in electrophilic astatodemetallation of arylstannanes.[2] However the reaction suffers from lack of robustness due to the use of At^+ difficult to control because of its narrow Eh/pH domain of existence. On the contrary, At^- exhibit a broader domain of existence under reducing conditions which can simplify the development of robust labeling methods.[3] For this reason, we have recently started the investigation of new nucleophilic labeling approaches with At^- and demonstrated the high potential of aryliodonium salts to label proteins.[4] Although this class of precursors can afford high RCYs, they are limited to electron rich

compounds and can produce side products. Then, the copper catalyzed halodeboronation of arylboronic acids and esters was reported for astatination of small compounds[5] or proteins.[6] Despite these new reactions, the need of new ^{211}At-labeling methods is important to face the growing demand in novel astatinated molecules.

Objectives: The aim of the study was to investigate a novel class of precursors, aryliodonium ylides, recently reported for the ^{18}F-labeling of (hetero)arylcompounds. Based on their similarity with aryliodonium salts, we expected a high reactivity without the need of catalyst, unlike arylboronic chemistry, and without chemoselectivity issue observed with aryliodonium salts.

Results and discussion: Initial conditions set up provided RCY>95% at room temperature in 30 min (Method A) with the most activated electron deficient precursors. For deactivated compounds, heating up to 90°C and addition of the radical scavenger TEMPO was necessary (Method B) leading to high RCY up to >99%. The reaction was applied successfully on a set of 14 compounds, including prosthetic groups. This methodology was then applied to the preparation of a relevant molecule for TAT, 4-astato-L-phenylalanine (4-APA) an amino acid derivative for targeting LAT1 transporter overexpressed in various tumor cells. The procedure outperformed the standard approach for 4-APA preparation (halogen exchange), providing improved activity yield and molar activity. Furthermore, in vitro assay indicated full preservation of cellular uptake in comparison with the same labeled compounds prepared by the standard method, validating the potential of application of this class of precursors.



Conclusion: The reaction reported herein appears as a valuable complement to already existing methods and should be considered as a valuable addition to the growing list of astatination reactions.

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P-231
Copper catalyzed radiobromination of boronic pinacol esters: utility in PARP inhibitor synthesis

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Objectives: Theranostics radiopharmaceuticals utilize a pair of matched radionuclides having both imaging and therapeutic properties. Bromine-76 ($t_{1/2}$ = 16 h, 55% ß$^+$) and bromine-77 ($t_{1/2}$ = 57 h, 6 – 7 Auger electrons per decay) is one such pair that can be incorporated into small molecule targeting vectors such as inhibitors of the DNA damage response protein poly-ADP ribose polymerase (PARP).[1,2] With recent advances in the cyclotron production of $^{76/77}$Br there is a need for efficient and reproducible methods for the radiobromination of small molecule targets. This work represents a systematic investigation of the copper-catalyzed coupling of boronic pinacol esters and ^{77}Br for the production of theranostic PARP inhibitors (PARPi) derived from clinical therapeutics olaparib and rucaparib.

Methods: Bromine-77 was produced on a GE PET trace cyclotron via ^{77}Se(p,n)^{77}Br (12.5 MeV protons) and isolated via dry distillation.[1] Bromine-77 was trapped on a pre-equilibrated (10 mL - EtOH, 0.5 M Na_2SO_4 or $NaHCO_3$, and H_2O) QMA cartridge and eluted with 0.1 M base (Figure 1A). Dried ^{77}Br (6 – 370 MBq) was added to [Cu(py)$_4$OTf$_2$] / 3,4,7,8-tetramethyl-1,10-phenanthroline (50 mol%) and corresponding boronic pinacol ester (1 µmol) in MeOH/H_2O (9:1, 100 µL) and reacted at 23°C for 30 minutes. Radiochemical conversion (RCC) was determined using C18 solid-phase extraction and radio-HPLC. Inhibitor studies were conducted similarly with the addition of the corresponding inhibitor (1 µmol).

Results: While ^{77}Br was nearly quantitatively recovered from Na_2SO_4-prepped, NH_4OH-eluted QMA cartridges, variability in the subsequent Cu-catalyzed bromodeborylation chemistry (5 – 90%) is observed,[1] potentially due to residual sulfate ion deactivating the catalyst. Transitioning to $NaHCO_3$ QMA preparation required stronger bases (Figure 1A) to recover high levels of ^{77}Br, similar to that observed for ^{18}F QMA elution behavior.[3] This product led to reproducible Cu-catalyzed bromodeborylation reaction RCCs (vide infra). To obviate late-stage radiolabeling failures due to substructure incompatibility, we undertook a competitive labeling study using 4-formylphenylboronic acid, pinacol ester. RCCs of 4-[^{77}Br]bromobenzaldehyde were measured in the presence of substructures found in PARP inhibitors and other targeting vectors (e.g. amines and thiols). Radiobromination tolerates various functional groups, with RCCs matching that without inhibitor, although in rare cases lower RCCs were observed (e.g. thiosalicylic acid). Radiobromination yielded high RCCs (87 – 99%) (Figure 1b) and late-stage bromination of olaparib and rucaparib derivatives were isolated in 84 and 75% radiochemical yields respectively.

Conclusions: This work represents a detailed investigation into the radiobromination of PARPi from boronic pinacol ester precursors. QMA trap/release, substructure analysis, and radiobromination were systematically studied to determine optimal conditions for the late-stage bromination of olaparib and rucaparib derivatives.

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P-232
EGSnrc Monte Carlo calculated dose distribution around brachytherapy sources

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Brachytherapy is a treatment technique that uses homogenous radiation to apply to the location where it needs treatment. The effectiveness of treatment depends on the exact calculation of the dose distribution in the patient's body. Calculating dose distribution results depend in an essential part on assessing the accuracy of the strength of the radiation source. In this study, we will use the EGSnrc program, specifically DOSRZnrc code, to survey the dose distribution, as well as the effect of the source to directional (DF) shell of dose