OP11

A novel versatile precursor efficient for F-18 radiolabelling via click-chemistry

B. Lugatoa[1], S. Stucchia[1], E.A. Turollaa[1], L. Giulianoa[1], S.Toddea[1], P. Ferraboschib[2]
[1]Department of Medicine and Surgery, Tecnomed Foundation, University of Milano-Bicocca, Milan, Italy; [2]Dipartimento di Biotecnologie Mediche e Medicina Traslazionale, Università degli Studi di Milano, Milan, Italy
Correspondence: B. Lugatoa – Department of Medicine and Surgery, Tecnomed Foundation, University of Milano-Bicocca, Milan, Italy
EJNMMI Radiopharmacy and Chemistry 2016, **1(Suppl 1):**OP11

Introduction In the last years, the Cu(I)-catalyzed Huisgen [3+2] cycloaddition between terminal alkynes and azides emerged as a powerful tool in F-18 radiolabelling of biomolecules such as peptides, because of its regioselectivity, mild aqueous organic conditions, reduced reaction times, and high yields.(1).A weak point of the method is the lack of suitable commercially available, stable precursors.(2) In this paper we report the synthesis and F-18 radiolabelling of a new, versatile, easy to handle, and stable azido precursor useful for *click-chemistry*.
Materials and methods: Reagents and solvents were purchased from Sigma-Aldrich. [^{18}F]Fluoride was produced with an IBA Cyclone 18/9 cyclotron. Radioactive synthesis were carried out on a fully automated radiosynthesis module (GE TracerLab FX-FN Pro), and analyzed by analytical RP-HPLC with UV and radiochemical detectors. Non-radioactive compounds were fully characterized by NMR, ESI-MS and IR.
Results: A series of bifunctional precursors, bearing the azido moiety and different leaving groups (e.g. tosylate, mesylate, iodo), coupled to a short polyetyleneglycol chain (to improve their stability and hydrophilicity) were designed and successfully prepared following a ten-step synthetic pathway. A protection-deprotection strategy of functional groups achieved the precursors and the fluorinated reference with good yield and purity. Precursors were radiolabelled with F-18 and then coupled to propargylglycine as alkyne counterpart. [^{18}F]Fluoride was purified following standard procedure, and nucleophilic displacement of the iodo leaving group took place at 100° C, in 20 min. The resulting labelled azide was successfully purified using a Sep-Pak tC18 cartridge (51% radiochemical yield not decay corrected, 93% radiochemical purity). The purified azide was then conjugated to propargylglycine, showing 52% conversion within 30 min at room temperature. Purification and formulation have still to be optimized.
Discussion/conclusion: A new optimized precursor useful for F-18 radiolabelling and *click-chemistry* was prepared. It demonstrated to be effective in radiolabelling non-protected alkynyl-modified aminoacids, by a fully automated synthetic procedure. Good results, in terms of radiochemical yield and purity, were obtained from the iodo-derivative precursor. Purification and formulation of the final cycloaddition product are in progress.

OP12

A general applicable method to quantify unidentified UV impurities in radiopharmaceuticals

R.P. Klok[1], M.P.J. Mooijer[1], N.H. Hendrikse[1,2], A.D. Windhorst[1]
[1]Department of Radiology & Nuclear Medicine, VU University Medical Center, Amsterdam, The Netherlands; [2]Department of Clinical Pharmacology & Pharmacy, VU University Medical Center, Amsterdam, The Netherlands
EJNMMI Radiopharmacy and Chemistry 2016, **1(Suppl 1):**OP12

Introduction: Radiopharmaceuticals are released for administration by a quality control procedure against pre-set specifications. One of these release specifications is the chemical purity of the drug product, determined with High Pressure Liquid Chromatography (HPLC) and UV detection. In the European Pharmacopeia (EP) hardly any specifications are given for the chemical purity of a radiopharmaceutical. When unknown impurities are present in the chromatogram, the decision if the radiopharmaceutical can be released, is very frequently based on unclear parameters like 'no unidentified UV signals present'. There is a need for an objective specification in order to have a save and reliable release.
Aim: The purpose of the presented work is to define a generally applicable method to define tolerances for unidentified impurities in radiopharmaceuticals.
Materials and methods: A retrospective analysis was performed on HPLC analysis results of [11C]Flumazenil, [11C]PIB, [11C]Erlotinib, [11C]DPA713, [18F]PK209 and [18F]FES. Quantification of the carrier signal in the UV chromatogram was determined by use of calibration curves, utilizing Chromeleon® 6.8. Unidentified impurities were semi-quantified utilizing the surface area in the UV chromatogram relative to the quantified carrier signal. Based on the EP. monography of [11C]Flumazenil and [18F]FET, the specification for unidentified UV impurities was determined to be 0.22 pmol/injection volume for a single unidentified impurity and 0.88 pmol/injection volume for the total of unidentified impurities. This specification was tested for over 500 batches of the radiopharmaceuticals and compared to the less specific parameter 'no unidentified UV signals present'.
Results: In a pilot assessment we encountered in 5-10% cases unidentified UV impurities leading to rejection of the batch, based on the specification 'no unidentified UV signals present'. Of these rejected batches 25% was also rejected with the new defined specification. Reason for this reduced number of rejections is that with the new specification the presence of unidentified impurities is evaluated objectively. The analysis of the full database is currently on-going.
Discussion/conclusion: With this method the amount of unidentified impurities can be estimated in an optimal and objective way, utilizing EP limits of [11C]Flumazenil and [18F]FET, without operator variability.

OP13

Development of [^{18}F]Fluoro-*C*-glycosides to radiolabel peptides

Collet C.[1,2], Petry N.[1,3], Chrétien F.[1,3], Karcher G.[1,2,4], Pellegrini-Moïse N.[1,3], Lamandé-Langle S.[1,3]
[1]Université de Lorraine, F-54500 Vandoeuvre les Nancy – France; [2]NancycloTEP, Plateforme d'imagerie expérimentale, 54500 Vandoeuvre les Nancy – France; [3]CNRS, UMR 7565 SRSMC, F-54506 Vandoeuvre les Nancy – France; [4]CHU de Nancy-Brabois, F-54511 Vandoeuvre les Nancy – France
Correspondence: Collet C. – Université de Lorraine, F-54500 Vandoeuvre les Nancy – France
EJNMMI Radiopharmacy and Chemistry 2016, **1(Suppl 1):**OP13

Introduction: The ^{18}F-labeling of peptides for PET applications has been used for many years.[1] However, the sensitivity of these peptides does not allow their direct radiolabelling under harsh conditions, except few recent examples. A solution is to use a prosthetic group, an easily radiolabeled small molecule, subsequently coupled in mild condition to the peptide. In continuation of our previous work,[2] we therefore propose to develop and use new *C*-glycoside-based prosthetic groups. The use of sugar derivatives as prosthetic group would improve bioavailability and pharmacokinetic properties of peptides.
Materials and methods: These *C*-glycoside derivatives should have a good leaving group thus allowing easy substitution by fluorine-18, *i.e.* triflate. A copper catalyzed azide alkyne cycloaddition (CuAAC) was then used for coupling these carbohydrates with a peptide. Some model peptides containing a cysteine residue as RGDC and c(RGDfC) are used. The high nucleophilicity of the thiol function can thus be exploited to prepare *S*-propargylated derivatives. The fully automated radiosynthesis of these [^{18}F]fluoro-glycopeptides was performed on an AllInOne® (Trasis) synthesizer.
Results: Triflated precursors of these *C*-glucosides prosthetic groups and the non-radioactive references were synthesized in alpha and beta configuration. Fluoride-18 radiolabeling was optimized and the automated radiosynthesis of [^{18}F]fluoro-glycopeptides with some model peptides (RGDC, c(RGDfC)) was presented.