Poster Category: Radiochemistry - ^{18}F

P-043 | Rhenium complexation-dissociation strategy for fluorine-18 labelling of bidentate PET ligands

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Objectives

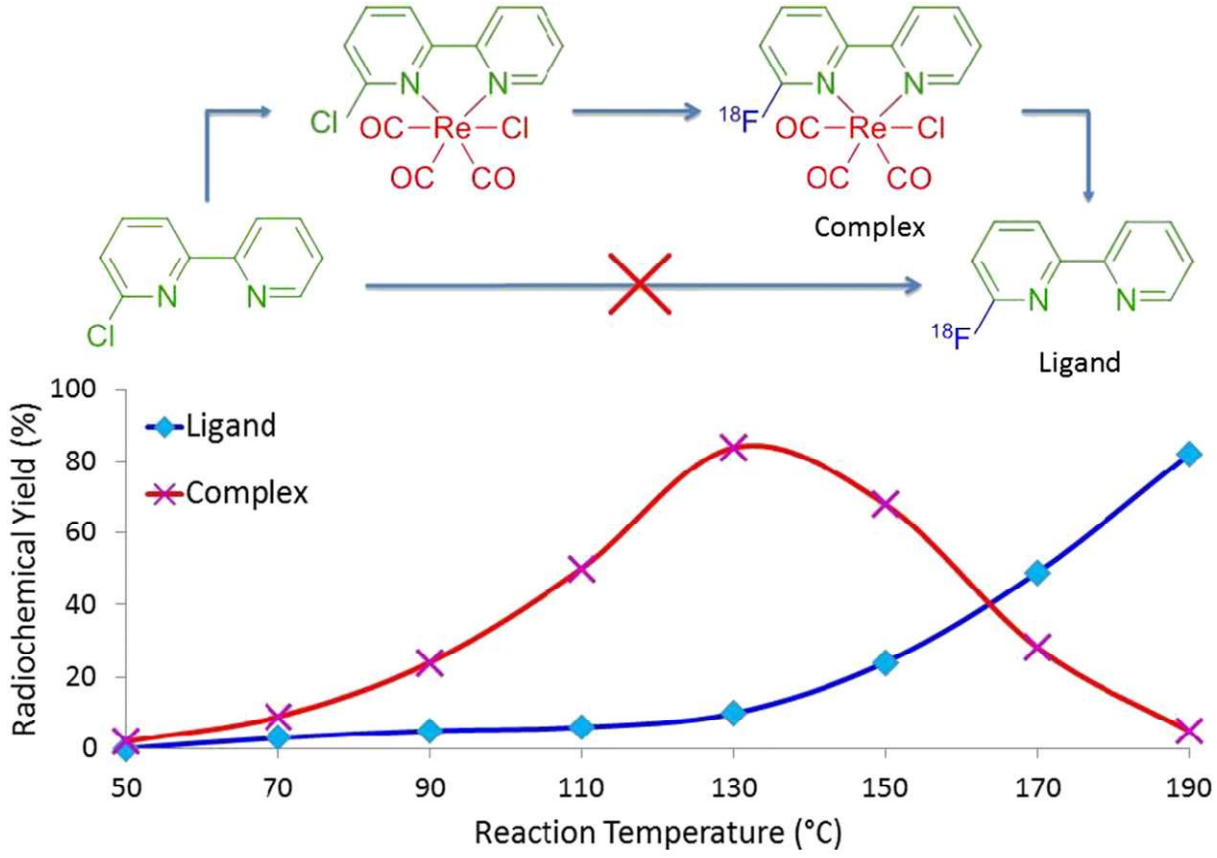
Pursuant to the discovery that rhenium complexation promotes fluorine-18 radiolabelling of 1,10-phenanthroline systems under low temperature, quasi-aqueous conditions, which circumvent the need for azeotropic drying,[1] we expanded our investigation towards thermal decomplexation strategies to improve the radiosynthesis of similar pyridinyl bidentate tracers.

Methods

Thirty-eight compounds were synthesised based upon chloro, bromo, nitro, and fluoro substitutions of 1,10-phenanthroline, 2,2'-bipyridine and 8-hydroxyquinoline structures and their respective rhenium tricarbonyl chloride complexes. Each of these compounds, save for the non-radioactive fluoro substituted standards, were reacted (>n = 8) under microfluidic conditions with tetraethyl ammonium [^{18}F]fluoride in anhydrous DMSO solvent with increasing reaction temperatures ranging from 50°C to 190°C in 20°C increments. All other parameters such as the precursor quantity, radioactivity, and flow rate/reaction time were kept constant (0.08 μmol, 29 ± 10 MBq, 20 μL·min^{-1}/47 s, respectively). Radiochemical yields (RCYs) for each reaction were then calculated from the Radio-HPLC peak integrations of the non-isolated products.

Results

High RCYs were observed for the [^{18}F]fluoride substitution of rhenium complexed 1,10-phenanthroline structures (up to 91%) at temperatures ≤90°C, which could prove useful as a novel method for producing PET-optical tracers given the optical emission properties of rhenium. Good RCYs were also observed for the 2,2'-bipyridine rhenium complexes, peaking at 84% at 130°C in one example, which then dissociated to form the radiolabelled ligand in 82% RCY at a higher temperature of 190°C, as shown in Figure 1. Radiolabelling of these ligands was unsuccessful under conventional conditions using dry [^{18}F]fluoride, thus establishing rhenium complexation-dissociation as a novel method for



radiolabelling. The fluorine-18 labelling of 8-hydroxyquinoline structures was also tested as a means of improving the radiosynthesis of Alzheimer's disease imaging PET tracers such as [^{18}F]CABS13.[2] While preliminary rhenium complexation-dissociation experiments have not yet improved on the radiosynthesis of [^{18}F]CABS13 (5% RCY of ligand & 18% RCY of rhenium complex vs 19±5% RCY of ligand in literature),[3] such experiments have enabled the radiosynthesis of related structures, which could not be radiolabelled under conventional conditions using dry [^{18}F]fluoride (eg, [^{18}F]5-fluoro-8-hydroxyquinoline).

Conclusions

We report a novel radiofluorination method utilising the rhenium complexation of pyridinyl bidentate structures. This method facilitates radiolabelling of certain analogues of 2,2'-bipyridine and 8-hydroxyquinoline structures, which do not radiolabel under conventional conditions. Investigations into monopyridine structures and the development of milder methods of decomplexation are currently ongoing.

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Poster Category: Radiochemistry - ^{18}F

P-044 | Drying free ^{18}F labeling of phosphate analogues with high stability in vivo

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Objectives

Phosphate analogues play important roles in both physiological processes and pharmaceutical development, which make themselves potential PET tracers. However, there has been no report that ^{18}F has been labeled on phosphate group so far, and the corresponding labeling method remains an open request.[1] Herein, to label phosphate group with ^{18}F and protect products from being hydrolyzed through feasible chemistry, precursors (2-thio-1,3,2-dithiaphospholane), and reference compounds were synthesized. To label and imitate phosphate analogues for tumor imaging, [^{18}F]O-(((2R,3S,4R,5R)-5-(6-amino-9H-purin-9-yl)-3,4-dihydroxytetrahydrofuran-2-yl) methyl)phosphorofluoridodithioate **4** was designed and labelled as an example to evaluation the accumulation in tumor.

Methods

Precursors were synthesized starting with 1,1-dichloro-N, N-diethylphosphanamine, followed by nucleophilic substitution using alcohol, finally sulfurization of P^{III} dithiaphospholane. The corresponding reference compounds were obtained by F^- nucleophilic substitution and purified by silica gel column chromatography. Precursors were labeled at different times to study the reaction kinetics. Precursors were labeled at different temperatures and reaction solvents for studying the optimum condition of the labeling strategy. Radiolabeling under each condition was repeated at least three times. The radiochemical yields were determined by semipreparative RP-HPLC. To study adenine nucleotide analogues accumulate in tumor, compound **4** was selected for evaluation in a xenograft tumor–bearing mouse with tumor implanted on the right shoulder.

Results

Precursor **1** and reference compound **2** were successfully synthesized with high yields and characterized by NMR spectrometry. ^{18}F labeling achieved high radiochemical yield (97%) by nucleophilic substitution in acetonitrile at room temperature with ultrafast reaction speed (in 30 s). Radiolabeling by nucleophilic substitution allowed good separation of the precursor and product, thereby ensuring high specific activity. The ultrahigh reaction efficiency is attributed to low free-energy barriers of F^- nucleophilic substitution. Furthermore, the labeling strategy exhibited excellent toleration for water, obtaining satisfactory radiochemical yields when the content of water was between 0% and 20%, which could skip multistep and complex processing procedures of $^{18}F^-$ containing azeotropic drying and trapped on QMA. The ^{18}F labeled phosphate analogue demonstrated the excellent stability in PBS, mice serum and healthy BALB/c mice during investigating the metabolic process. Whole-body PET image of a AR42J tumor–bearing mouse show that [^{18}F]**4** specifically accumulated in the tumor.

Conclusions

An efficient labeling strategy that allows to label phosphate group by ^{18}F with high radiochemical yields was introduced, providing a widely applicable strategy for ^{18}F labeling of phosphate analogues. ^{18}F labeled adenine nucleotide