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A Click procedure with heterogeneous copper to tether technetium-99m chelating agents and rhenium complexes. Evaluation of the chelating properties and biodistribution of the new radiolabelled glucose conjugates

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ABSTRACT

An efficient protocol was developed to tether chelating agents and rhenium complexes onto a glucoside scaffold with a heterogeneous copper catalyst via click chemistry. The supported catalyst avoids the formation of unwanted copper complexes during the cyclisation step. The possibility to graft a pre-chelated $M(CO)_3$ core by click chemistry onto a biomolecule was highlighted for the first time. $^{99m}Tc(CO)_3$-gluco-conjugates displayed excellent in vitro stability, a fast in vivo blood clearance and a low specific organ uptake or long-term retention in spleen and stomach.

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1. Introduction

Carbohydrates play a pivotal role in a host of biological events including molecular recognition, inflammation, tumour metastasis and viral or bacterial adhesion.[1] In particular, they provide a major energy source for life forms through the processing of glucose inside the cells. The energy requirement in many tumour types is significantly higher than in normal cells due to a rapid growing and altered metabolism. This feature has been extensively explored for the development of glucose conjugates as selective radiotracer for tumours in oncology. FDG (2-deoxy-2-[^{18}F]fluoro-D-glucose) has become an important radiopharmaceutical approved by the Food and Drug Administration to detect melanoma, lymphoma, breast and lung cancers by positron emission tomography (PET) scans.[2] FDG is internalized into the cells by the GLUT1 transporter and phosphorylated by hexokinase to a very polar product that cannot diffuse out of the cell. Applications are however limited by the short half life of the positron emitting fluorine-18 ($T_{1/2}$ = 109.8 min), which should be produced on site by expensive cyclotrons.

In this regard, the development of more readily available FDG analogues would be of high interest. The technetium-99 m radionuclide (^{99m}Tc) is extensively used in nuclear imaging with single photon emission computed tomography (SPECT), due to ideal imaging characteristics (140 keV γ emitter, relatively short half life of 6 h) combined with a convenient availability at low cost from the commercial ^{99}Mo/^{99m}Tc generator. A wide range of chelators is now available to efficiently coordinate diverse technetium species like TcO^{3+} and $Tc(CO)_3^+$ cores, and to form stable complexes under physiological conditions.[3] Numerous chemical strategies have been developed to graft such compounds onto biologically relevant carriers such as peptides,[4] antibodies[5] and carbohydrates.[6,7] In particular, several groups recently reported the synthesis of glucose derivatives containing ^{99m}Tc-chelating systems to substitute the expensive FDG in the localization of tumours.[8] These complexes were chemically grafted onto the different hydroxyl groups of the glucose scaffolds by glycosylation (C-1),[9] nucleophilic substitutions and reductive aminations (C-2, 3, 6),[10] or peptidic coupling when starting from glucose amine.[11] Despite the numerous attempts, a ^{99m}Tc based radiopharmaceutical that fulfils the criteria of a potent [^{18}F]-FDG surrogate has not been

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designed yet. It seems that the major drawback of this strategy is the presence of the technetium complex, which is too hindered to allow the glycoconjugate internalization into cells via the GLUT1 transporter.[12]

Nevertheless, carbohydrates attract much attention, as hydrophilic and biocompatible scaffolds for the development of molecular imaging agents,[13] or as vectors able to target carbohydrate binding proteins (lectins).[14] In this regard, the development of simple and efficient protocols to graft chelating agents or metal complexes onto carbohydrate scaffolds are of particular interest. In the present work we described a simple and efficient protocol to synthesize C-1 functionalized glucose derivatives-containing tridentate chelating systems via a copper catalysed azide–alkyne cyclization reaction (click reaction). We demonstrated for the first time the possibility to graft a pre-chelated $M(CO)_3$ core directly onto a biomolecule by click chemistry. The preparation and spectroscopic analysis of both cold $Re(CO)_3$ and radioactive $^{99m}Tc(CO)_3$ glycoconjugates are reported. In vitro histidine challenge experiments and first biodistributions of technetium glucoconjugates are also investigated.

2. Results and discussion

2.1. Synthesis of glucoconjugates and their corresponding metallic complexes (*M* = ^{99m}Tc, Re)

An ideal bifunctional chelating agent should (i) coordinate a metal ion with a high yield, (ii) form metal complexes with both high thermodynamic stability and in vivo kinetic inertness to minimize metal toxicity, (iii) be produced quickly, in a gram-scale and with an excellent overall yield. For the complexation of the $M(CO_3)^+$ core, recent in vitro and in vivo investigations showed that tridentate chelating systems are more appropriate.[15] A Tc- or Re-tricarbonyl complex with a tridentate ligand is less prone to cross-metallation due to its coordinative saturation and thermodynamic stability. Among these ligands, iminodiacetic acid (IDA) and di-(2-picolyl)amine (DPA) derivatives react avidly with the *fac*-$[M(CO)_3]^+$ core to form complexes with a stable octahedral coordination sphere. We first designed a set of alkynyl-armed chelating systems **1**–**4** based on DPA, IDA or analogous derivatives (Chart 1). Building blocks **1–3** could be considered as bifunctional chelating agents where the acetylenic arm allows conjugation to the glucopyranosyl azide by click chemistry. Recently, Schibli and co-workers reported that a 1,2,3-triazole ring formed during the cyclisation step is an effective binder for $M(CO_3)^+$ core.[16] Following their so-called 'click to chelate' approach, we synthesized pre-chelator **4**[17] that will potentially bind the metallic core through both nitrogen atoms and the formed triazole.

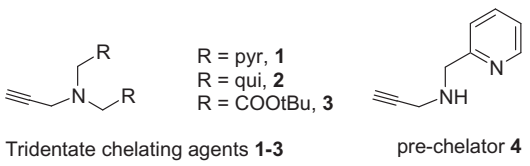


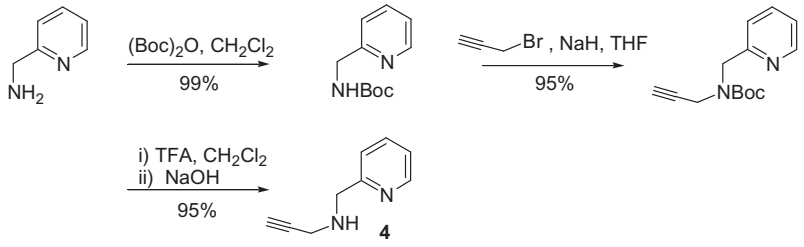
Chart 1. Design features of Tc-chelating agents.

The chelate systems **1** and **3** were prepared in excellent yields (near 90%) by refluxing commercial di-(2-picolyl)amine or *tert*-butyl iminodiacetate with propargyl bromide in the presence of potassium carbonate in acetonitrile as previously described.[18] In a similar way, the reaction of propargyl amine with the chlorohydrate of 2-chloroquinoline gave the desired compound **2** in a fair yield of 62%. Particular interest arises in developing a fast access to such chelating systems, which can be either used to design radioimaging or fluorescent probes with technetium or rhenium, respectively. *N*-Propargyl-di-(2-picolyl)amine **4** was recently prepared by reductive amination with a moderate yield of 57%.[19] Consequently, we developed a more suitable synthetic pathway to prepare this compound in gram-scale starting from 2-(aminomethyl)pyridine, as outlined in Scheme 1. Following a three-step sequence already described for analogous derivatives,[20] the amine was first protected as a *tert*-Boc carbamate to avoid the formation of *N,N*-dipropargyl derivatives during the alkylation step. Subsequent treatment with an excess of sodium hydride in the presence of propargyl bromide, followed by amine deprotection with TFA, provided **4** with an overall yield of 89%.

As proof of concept, two tricarbonylrhenium complexes were readily obtained by reacting equivalent amounts of ligands **1** or **2** and $Re(CO)_5Br$ in refluxing methanol. The co-ordination reactions were quantitative in 6 h and after purification led to mononuclear complexes isolated as bromine salts of general formula $[Re(CO)_3(L)][Br]$.

The glucopyranosyl azide[21] scaffold was easily obtained in two steps from glucose pentaacetate[22] (Scheme 2). Displacement of the anomeric acetate group with $TMSN_3$ in the presence of tin chloride followed by deprotection under Zemplén conditions (NaOMe in MeOH) led to **5** in 70% yield. The first copper(I)-catalysed cycloaddition with alkynyl-armed chelating agent **1** was performed in the presence of copper sulfate and sodium ascorbate in a mixture of *tert*-butanol and water to ensure the solubility of reagents. The reaction proceeded smoothly, leading to the expected cycloadduct **6** polluted by its copper complex, which was identified by ESI-MS during the experiment.

It was previously reported that treatment by a chelating resin (QuadraPure-IDA) allows the regeneration of the desired cycloadducts by transchelation of copper.[16i] However, this procedure will be ineffective for chelators possessing high kinetic inertness or stronger binding constants than the iminodiacetic groups attached to the resin. Performing the cyclization step with a supported or heterogenous source of copper(I) would be more appealing with this regard. Lipshutz and Taft have developed an efficient catalyst for the Huisgen [3+2] cyclization based on copper impregnated wood charcoal.[23] Interestingly, the authors claimed that the reaction takes place heterogeneously without any leaching of copper



Scheme 1. Synthetic pathway for the preparation of **4**.

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