Dalton Transactions

Accepted Manuscript

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ROYAL SOCIETY OF CHEMISTRY

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View Article Online
DOI: 10.1039/C8DT01583J

For submission to *Dalton Transactions*

ARTICLE

An innovative and efficient route to the synthesis of metal-based glycoconjugates: proof-of-concept and potential applications†

Received
Accepted

DOI: 10.1039/x0xx00000x

www.rsc.org/

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With a view to developing more efficient strategies to the functionalization of metallodrugs with carbohydrates, we here report on an innovative and efficient synthetic route to generate gold(III) glycoconjugates in high yields and purity. The method is based on the initial synthesis of the zinc(II)-dithiocarbamato intermediate [Zn^{II}(SSC-Inp-GlcN)$_2$] (Inp = isonipecotic moiety; GlcN = amino-glucose) followed by the transfer of the glucoseisonipecoticdithiocarbamato ligand to the gold(III) center *via* transmetallation reaction between the zinc(II) intermediate and K[$Au^{III}Br_4$] in 1:2 stoichiometric ratio, yielding the corresponding glucose-functionalized gold(III)-dithiocarbamato derivative [$Au^{III}Br_2$(SSC-Inp-GlcN)]. No protection/deprotection of the amino-glucose scaffold and no chromatographic purification were needed. The synthetic protocol was optimized for glucose precursors bearing the amino function at either the C^2 or the C^6 position, and works in the case of both α and β anomers. The application of the synthetic strategy was also successfully extended to other metal ions of biomedical interest, such as gold(I) and platinum(II), to obtain [Au^{I}(SSC-Inp-GlcN)(PPh_3)] and [Pt^{II}(SSC-Inp-GlcN)$_2$], respectively. All compounds were fully characterized by elemental analysis, mid- and far-IR, mono- and multidimensional NMR spectroscopy, and, where possible, X-ray crystallography. Results and potential applications are here discussed.

Introduction

Research aimed at designing novel synthetic carbohydrate derivatives has been steadily expanding over the last two decades owing to their potential biomedical applications.[1] Glycosylation (that is, the biochemical process by which a carbohydrate is covalently bound to the target biomolecule such as proteins and lipids) is involved in many metabolic events and affects a number of cellular processes, including cell proliferation and differentiation, intercellular communications, and carbohydrate-mediated recognition processes such as the immune response.[2] Therefore, given the crucial biological role played by carbohydrates, it is not surprising that research in glycoscience has strong implications for biotechnology and medicine in order to develop new therapeutic agents for the treatment of various diseases.

Glycoconjugation (that is, the functionalization of drugs with glucose or other carbohydrates) is currently under intense investigation, and applications include: carbohydrate-based drugs and vaccines, adjuvants, metabolic labelling of glyco-structures, and glycan arrays for diagnostic purposes.[3] To date, several carbohydrate-derived or -containing drugs are marketed, *e.g.* zanamivir (antiviral), acarbose (antidiabetic), heparin and fondaparinux (anticoagulant), doxorubicin (anticancer), epoetin alfa and darbepoetin alfa (anemia treatment), hiberix (haemophilus B conjugate vaccine), menjugate (meningitis C vaccine),[4] and many more are currently under pre-clinical and clinical trials.[5]

Within the field of chemotherapy, conjugation of anticancer drugs to biomolecules has been successfully achieved in recent years by developing, for example, antibody-drug[6] and folate-drug[7] conjugates which are currently in clinical use. Intriguingly, compared with peptides, synthetic carbohydrates proved challenging to be obtained, mainly due to the complexity of the traditional synthesis in solution. In particular, difficulties associated with stereoselective glycosidic bond formation and the extensive use of protecting groups (and subsequent selective deprotection),[8] resulted in lengthy multi-step syntheses requiring several purifications of the various intermediate products by column chromatography and, ultimately, affording poor overall yields.[9] The exploitation and optimization of alternative synthetic approaches, such as chemoenzymatic,[10] automated solid-phase,[11] and microwave-assisted[12] synthesis, have substantially boosted the field in terms of shorter reaction times and higher yields. On the other hand, such techniques are not always exploitable for all glycoconjugates, especially when the carbohydrate functionalization is applied to metal-containing substrates.

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† Electronic Supplementary Information (ESI) available: materials and methods, characterization of the starting isonipecotic and metal reagents, synthesis of isonipecotamidedithiocarbamate, synthesis of the amino-sugar precursors, synthesis of (PPh_4)[$Pt^{II}Cl_3(NH_3)$]. CCDC 1835869, 1835870, 1835871. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/x0xx00000x

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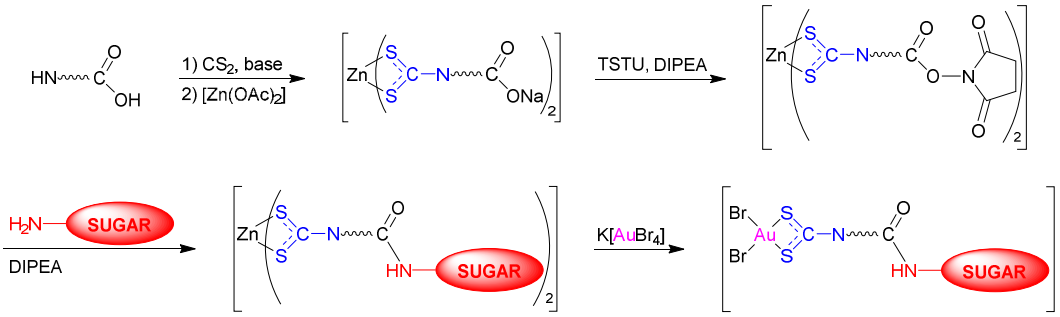

Scheme 1 General synthetic route to gold(III)-dithiocarbamato glycoconjugates.

Owing to the potentiality of metallodrugs, the latest approaches focus on the functionalization of metal-based scaffolds with biologically-active ligands having tumor targeting properties (*i.e.* carriers), thereby maximizing the therapeutic outcomes on cancer cells and minimizing the occurrence of side-effects.[13] A number of metal glycoconjugates have been reported to date,[14a,b] especially glucose derivatives in which conjugation occurs mainly at the anomeric C^1 position.[14c-f] Nevertheless, in most cases coordination of glucose-like substrates to metal centers proved somewhat demanding and involved several steps. For example, Lippard and co-workers have recently reported on the synthesis of all possible positional isomers ($C^{1\alpha}$, $C^{1\beta}$, C^2, C^3, C^4 and C^6) of a glucose-oxaliplatin conjugate.[15] Remarkably, each isomer required 4-12 steps with yields of 15-30% (considering only the final step leading to the corresponding platinum(II) glycoconjugate).

On the basis of the aforementioned considerations, given our well-established expertise in the development of gold(III)-dithiocarbamato complexes,[16] we here report on an innovative, facile and efficient synthetic route to the generation of gold(III)-dithiocarbamato glycoconjugates. Our strategy relies on the one-pot synthesis of a bis-dithiocarbamato-zinc(II) intermediate which can be subsequently functionalized with an amino-glucose moiety. The desired glucosedithiocarbamato ligand is then transferred to the gold(III) metal center *via* a zinc(II)-gold(III) transmetallation reaction yielding the corresponding high purity gold(III)-dithiocarbamato glycoconjugate in excellent yields (70-90%) (Scheme 1). Remarkably, neither protection/deprotection of the amino-glucose scaffold nor chromatographic purification were required, and the transmetallation reactions reached completion within a few hours.

In order to assess the potential of this synthetic protocol to other metal ions, we applied the same procedure also to gold(I) and platinum(II), and succeeded in generating the corresponding glycoconjugates.

Experimental details and results are here discussed and compared with the synthetic strategies currently available in the literature.

Results and Discussion

Rationale

In terms of medicinal applications, glycoconjugation can be exploited to achieve the specific targeting and treatment of cancer.[17] This strategy relies on the evidence that rapidly dividing tumor cells require higher amounts of nutrients and energy to sustain their fast proliferation, including especially glucose. In fact, glucose uptake proved to be 10 to 12-fold higher in tumors compared with healthy tissues, and glucose transporters (GLUTs), devoted to the recognition and cellular internalization of glucose, are largely overexpressed in tumor cells, thus indicating their strong dependence on such transporters for their survival and growth.[18] The fact that anaerobic glycolysis is the major glucose metabolism in tumors is a phenomenon called “the Warburg effect” (named after the German biochemist Otto Warburg who first observed it),[19] and it is acknowledged nowadays as one of the hallmarks of cancer.[20] Consequently, such increased demand of glucose by cancer cells makes it very attractive to selectively target tumor sites. In particular, tailored glucose-like substrates can be conjugated to chemotherapeutics to attain the site-specific delivery of drugs into the affected tissues (*i.e.* targeted anticancer chemotherapy and tumor imaging).[21] This approach was especially inspired by the evidence that the clinically-established positron emission tomography (PET) tracer [^{18}F]-fluorodeoxyglucose is preferentially taken up by cancer cells compared with normal tissues,[22] and has been recently extended to the design of carbohydrate-based nanocarriers.[23]

As previously pointed out, the complexity of carbohydrate chemistry may severely hamper glycoconjugation of drugs, in particular when metal-based scaffolds are involved. Therefore more efficient synthetic approaches to glyco-functionalization are required. As shown in Scheme 1, our suggested strategy relies on the pre-generation of a zinc(II)-dithiocarbamato glycoconjugate precursor followed by the transfer of the whole dithiocarbamato ligand to the desired metal center through a transmetallation reaction. Specifically, we developed a facile and reproducible protocol in which an amino acidic linker is functionalized with the dithiocarbamato moiety (–NCSS) at the amino terminus, whereas the carboxylate tail is first activated and then conjugated to an amino-sugar. The rationale of this strategy is based on the following considerations.

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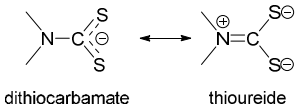
- Dithiocarbamates are versatile monoanionic ligands capable of stabilizing a wide range of metal ions by coordinating the metal center in either monodentate or chelating bidentate modes.[24] Although referred to as "soft" Lewis bases (and, thus, expected to coordinate mainly "soft" Lewis acids such as low-valent metal ions), they may be also regarded as "hard" ligands in the thioureide resonance form (Scheme 2), which favors the binding of metals in higher oxidation states (*i.e.* "hard" Lewis acids).[25]



Scheme 2 Resonance forms of the dithiocarbamato ligands.

Accordingly, dithiocarbamates can be used to coordinate a number of metal ions in different oxidation states affording stable complexes.[26]

- An added value of using dithiocarbamato ligands is that, once coordinated to a bioactive metal center, they may act as intrinsic chemoprotectants against the toxicity of metal-based drugs, thus reducing their side-effects.[27] Consequently, not only metal-dithiocarbamato derivatives have been largely explored in recent years as potential anticancer agents,[25] but the chemoprotective activity of the dithiocarbamato moiety has been confirmed *in vivo*, in particular for gold(III) derivatives.[28]
- Dithiocarbamates of primary and secondary amines are generally synthesized by reaction with carbon disulfide (CS_2) under basic conditions (*e.g.* NaOH, KOH, Et_3N) at low temperature, yielding the corresponding dithiocarbamato salts.[29] Dithiocarbamates generated from primary amines are often unstable and tend to decompose to give the corresponding isothiocyanates.[30] The secondary amine counterparts are generally more stable and a number of simple dithiocarbamates have been prepared and isolated as sodium or ammonium salts.[31] Nevertheless, isolation and storage of free dithiocarbamates is often challenging since, at room temperature, they may decompose back to the starting amine and CS_2, especially under acidic conditions.[32] For this reason, dithiocarbamates are best prepared *in situ*: once generated in solution they are reacted with the metal precursor in the appropriate stoichiometric ratio to obtain the corresponding metal-dithiocarbamato derivative.[25]
  In principle, direct functionalization of an amino-sugar could be achieved. To the best of our knowledge, only one of such example is reported in the literature. Zhang and co-workers synthesized and isolated 2-deoxy-2-dithiocarbamato-D-glucose as sodium salt by reacting D-glucosamine hydrochloride with CS_2 and NaOH, and used it to obtain the corresponding ^{99m}Tc-nitrido bis-dithiocarbamato complex.[33] Unfortunately, when following the same experimental procedure, we could not obtain the analogous gold(III) complex. Notwithstanding various attempts, the experimental conditions employed always led to the reduction of gold(III) to gold(I) and the simultaneous degradation of the carbohydrate scaffold resulting from the intramolecular attack of the –NCSS group located in the C^2 position of the glucose to the anomeric site (data not shown).[34]
- The use of an amino acidic linker between the dithiocarbamato function and the conjugated sugar has a two-fold purpose. From a practical synthetic point of view it allows the straightforward conversion of the amino terminus into an –NCSS group[35] without worrying about the possible side-reactions involving the carbohydrate scaffold, should the latter be present. On the other hand, the carboxylic function can be easily activated with *N*,*N*,*N*′,*N*′-tetramethyl-*O*-(*N*-succinimidyl)uronium (TSTU) and subsequently coupled to an amino-sugar to attain glycoconjugation through the formation of an amide bond.[36]
  Moreover, from a biological perspective, if the final goal is to target the GLUTs overexpressed in tumors to achieve selectivity, the anomeric position of the glucose-like unit should be sufficiently accessible to be recognized (and, thus, internalized inside the tumor cell) by such transporters.[21a] Therefore, the inclusion of a rigid linker (like the isonipecotic moiety used in this work) would reduce the steric hindrance around the anomeric site of the sugar, thus allowing, at least in principle, its recognition by GLUTs.

Model non-glycosylated gold(III)-dithiocarbamato complexes

Taking into account the aforementioned issues, we first evaluated the feasibility of our synthetic approach by generating non-glycosylated gold(III)-dithiocarbamato complexes *via* transmetallation from the corresponding zinc(II) intermediates (Scheme 3). Specifically, we focused on ethyl isonipecotate (Inp-OEt) and isonipecotamide (Inp-NH_2) dithiocarbamates as model ligands since their amino group is a symmetric secondary amine and, as such, can lead to very stable, symmetric compounds.[26]

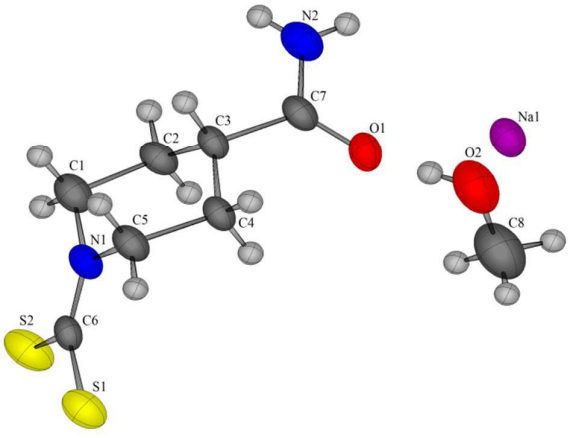


Figure 1 X-ray crystal structure with atom numbering scheme for Na(SSC-Inp-NH_2) (CCDC 1835869) (50% displacement ellipsoids).

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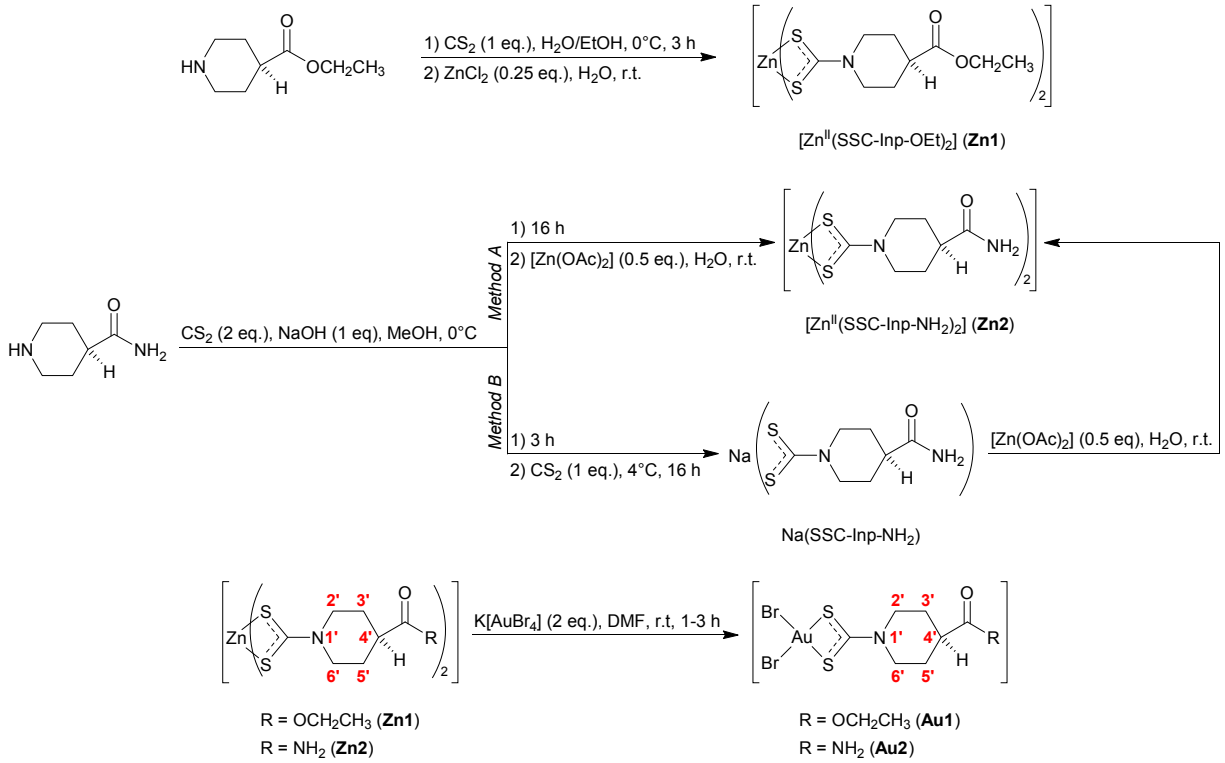

Scheme 3 Synthesis of the model (*i.e.* non-glycosylated) gold(III)-dithiocarbamato derivatives *via* transmetallation.

Amongst our numerous initial attempts to isolate free dithiocarbamates, we succeeded in obtaining only one, that is, isonipecotamidedithiocarbamate as sodium salt (Na(SSC-Inp-NH_2), Figure 1; see the ESI for details).

Both [Zn^{II}(SSC-Inp-$OEt)_2$] (**Zn1**) and [Zn^{II}(SSC-Inp-$NH_2)_2$] (**Zn2**) were obtained in a one-pot reaction. **Zn2** was obtained also by reacting the free ligand Na(SSC-Inp-NH_2) with [$Zn^{II}(OAc)_2$] in 2:1 ratio.

Zinc(II) is a "borderline" Lewis acid[37] and, although it forms stable covalent adducts with the "soft" dithiocarbamato ligands,[26] it is well-known to serve as a source of such ligands for a softer metal (possibly much more reliable and controllable than the commonly employed ionic sodium, potassium or ammonium dithiocarbamato salts).[38] Therefore, zinc(II) dithiocarbamates may undergo transmetallation reactions with many "soft" transition metals, including gold(III).[39] In this regard, the zinc(II)-gold(III) transmetallation reaction was optimized in DMF, yielding the gold(III) counterparts [$Au^{III}Br_2$(SSC-Inp-OEt)] (**Au1**) and [$Au^{III}Br_2$(SSC-Inp-NH_2)] (**Au2**) in high yields (>70%) and no need of further purification.

IR spectroscopy proved useful to identify the synthesized compounds. By comparison with the spectra recorded for the starting ethyl isonipecotate and isonipecotamide reagents (see the ESI for details), the appearance of a strong band at 1494 (**Zn1**)/1492 (**Zn2**) cm^{-1} in the zinc(II) derivatives (the so-called "thioureide" band, ν(N–CSS)) is consistent with a chelating dithiocarbamato ligand coordinated to a zinc(II) center.[40] When taking into account the gold(III) counterparts, the ν(N–CSS) is recorded at higher frequencies (1571 (**Au1**)/1565 (**Au2**) cm^{-1}) due to the increased electron-withdrawing effect upon moving from zinc(II) to the more positively charged gold(III) center, suggesting a greater contribution of the "thioureide" resonance form (Scheme 2).[41] Additionally, the detection of a single band at *ca.* 1000 cm^{-1} in all complexes (attributed to the ν_a(SCS)) clearly supports a symmetrical bidentate coordination of the –NCSS moiety to the metal centers, in agreement with the Bonati-Ugo criterion.[42]

In the far-IR spectra of a number of metal-dithiocarbamato complexes, bands recorded in the range 420-320 cm^{-1} are regarded as highly diagnostic since they are assigned to the metal-sulfur stretching vibrations. **Zn1** and **Zn2** show an intense absorption at *ca.* 395 cm^{-1} originating from the $\nu_a(ZnS_4)$,[43] whereas the corresponding symmetric stretching is absent as it is not IR-active in the tetrahedral bis-dithiocarbamato zinc derivatives.[44] On the contrary, both $\nu_{a,s}$(SAuS) are recorded for the square-planar **Au1** and **Au2** complexes (at 413/398 and 411/397 cm^{-1}, respectively), in agreement with those reported in the literature for similar gold(III)-dithiocarbamates.[45] Finally, other informative bands are observed at lower frequencies for the latter complexes at 249/228 (**Au1**) and 232/227 (**Au2**) cm^{-1}, attributed to the $\nu_{a,s}$(BrAuBr) for terminal *cis*-bromides.[46]

Mono- and multinuclear NMR spectroscopy provided further insights into the identification of the dithiocarbamato complexes. For example, compared with the starting ethyl isonipecotate reagent, a general downfield shift of the proton signals is observed for the zinc(II) intermediate **Zn1** and the

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corresponding transmetallation product **Au1** (Figure 2). This is consistent with the decreased electron density experienced by the hydrogen atoms of the isonipecotate scaffold upon introducing the dithiocarbamato moiety and the subsequent coordination to the metal centers, the gold(III) ion exerting greater deshielding than zinc(II) due to the higher oxidation state.[47] As expected, the larger shift involves the piperidine hydrogens, the only partial exception to this trend being the $C^{2',6'}\boldsymbol{H}$ equatorial protons which undergo a 0.7 ppm upfield shift in **Au1** with respect to **Zn1**. On moving away from the dithiocarbamato moiety, the magnitude of the chemical shift change decreases until being negligible for the farther ester group.

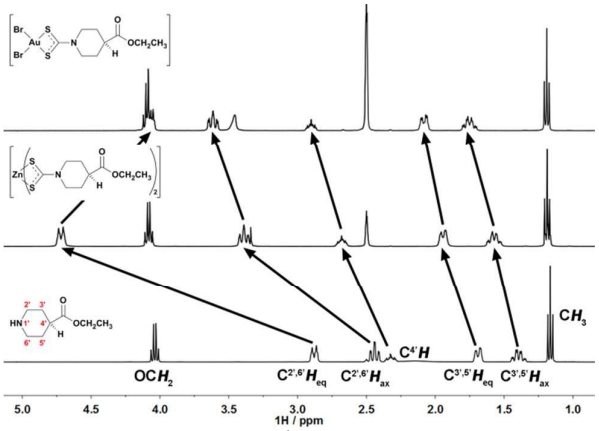

Figure 2 Comparison of the ^{1}H NMR spectra in DMSO-D_6 of ethyl isonipecotate, [Zn^{II}(SSC-Inp-OEt)$_2$] (**Zn1**) and [$Au^{III}Br_2$(SSC-Inp-OEt)] (**Au1**).

The most diagnostic peak recorded in the $^{13}C\{^{1}H\}$ NMR spectra is attributed to the dithiocarbamic carbon atom and is generally found in the range 180-220 ppm.[48] It is generally assumed that the ^{13}C chemical shifts of the –NCSS moiety are strongly dependent on both the type of metal-dithiocarbamate bonding and the oxidation state of the metal center. As to the dithiocarbamato complexes of transition metals owning a d^{10} electron configuration (such as zinc(II)), the $\delta(N^{13}CSS)$ peaks are recorded in the range 202-206 ppm,[49] whereas for derivatives of high oxidation state transition metals (such as gold(III)), the dithiocarbamic carbon signals appear upfield.[50] There is a strong empirical correlation between $\delta(N^{13}CSS)$ values and the N–CSS stretching vibrations in the infrared spectra: higher ν(N–CSS) values indicate an increased carbon–nitrogen double bond character, which well correlates with lower $\delta(N^{13}CSS)$ values because of a greater electron density on the –NCSS moiety, and the other way round.[48] All these considerations are fully consistent with the experimental ν(N–CSS) frequencies and the $N^{13}CSS$ carbon signals recorded for the object dithiocarbamato complexes (202.6 (**Zn1**), 202.3 (**Zn2**), 187.9 (**Au1**) and 186.9 (**Au2**) ppm).

Crystals suitable for X-ray diffraction crystallography were obtained for **Zn1** and **Au1** (Figure 3). Although crystal structures of monomeric bis-dithiocarbamato-zinc(II) complexes are known, which have highly strained structures with two four-membered rings,[51] a common arrangement for this class of compounds is dinuclear centrosymmetric,[52] and this was observed also for **Zn1**. Dimeric structures, in which one four-membered zinc(II)-dithiocarbamato ring is retained whereas the other has opened to form an eight-membered ring, were first reported for the bis-diethyldithiocarbamato-zinc(II) complex,[53] and have since been reported for several other analogous derivatives.[54] Relief of distortion is the most likely reason for the adoption of the dimeric structure, and the angle at the zinc(II) center in the four-membered ring is 75.79(4)°.

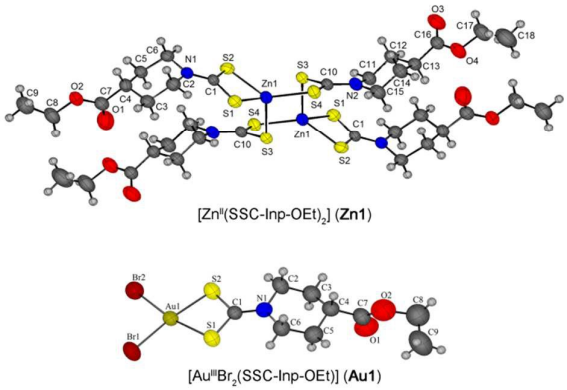

Figure 3 X-ray crystal structure with atom numbering scheme for **Zn1** (CCDC 1835870) and **Au1** (CCDC 1835871) (50% displacement ellipsoids).

As to the crystal structure of **Au1**, there is distortion from square-planar geometry due to the small bite angle of the dithiocarbamato ligand. However, there the maximum deviation from the least-squares plane defined by the gold(III) center and the ligating atoms of 0.008 Å is shown by S1 and S2. The bond distances are in the range previously reported and are close to those found in other dibromo-dithiocarbamato-gold(III) complexes.[55,56a] Interestingly, the zinc(II)-dithiocarbamato complex **Zn1** has Zn–S distances within the four-membered rings which differ by a near constant 0.1 Å, whereas in the gold(III) counterpart **Au1** the Au–S distances have differences which are ten times smaller. Further details of the structures are provided in the ESI.

Analogous gold(III)-dithiocarbamato complexes have been previously obtained through one-pot template reactions,[41,56] invariably resulting in a mixture of two forms (whose relative abundance varies depending on the synthetic conditions), that is, the expected gold(III) derivative and a dimeric form in which two bridging dithiocarbamato ligands are bound to both gold(III) centers whose coordination sphere is completed by two *trans*-bromide moieties.[57] Remarkably, our zinc(II)-gold(III) transmetallation strategy led to the generation of the expected monomeric form only.

Gold(III)-dithiocarbamato glycoconjugates

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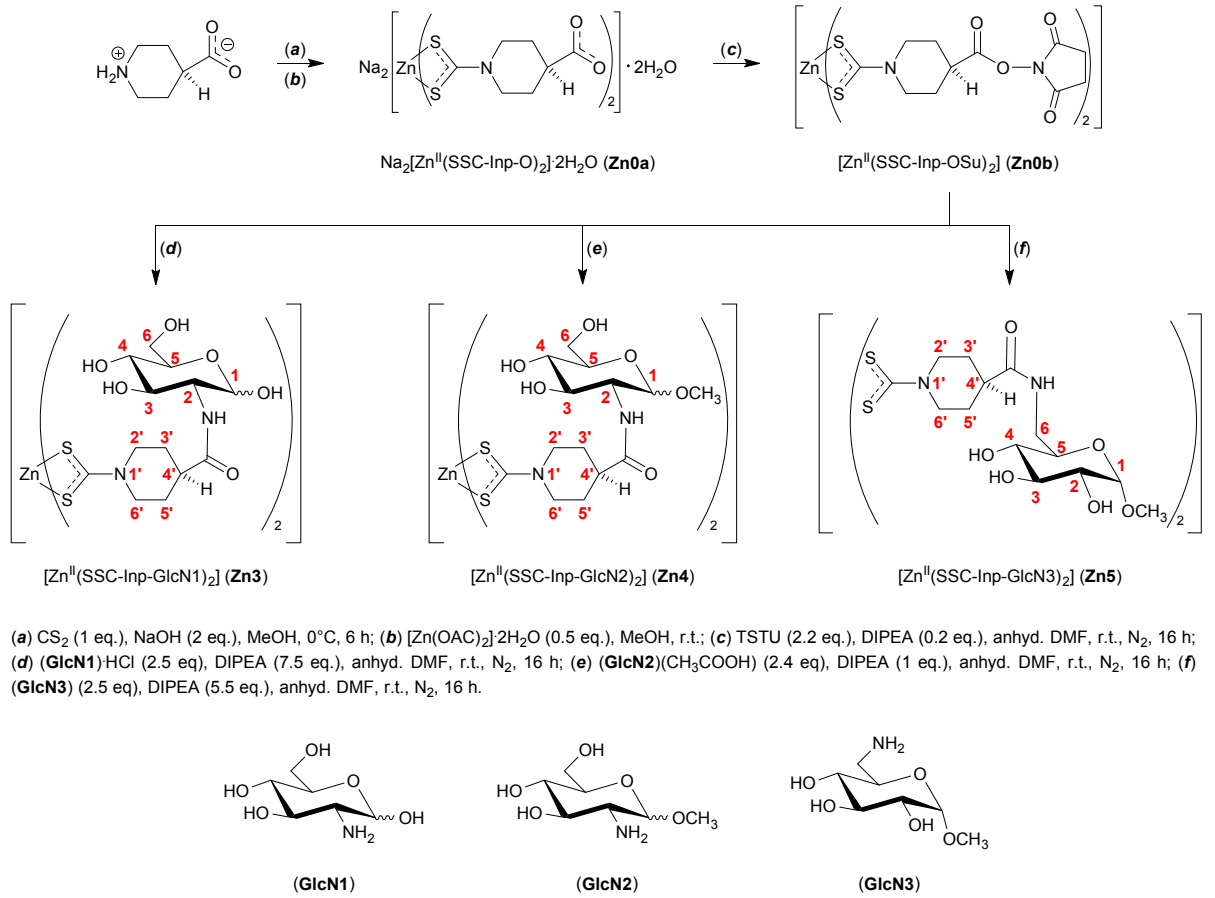

(***a***) CS_2 (1 eq.), NaOH (2 eq.), MeOH, 0°C, 6 h; (***b***) $[Zn(OAC)_2]\cdot 2H_2O$ (0.5 eq.), MeOH, r.t.; (***c***) TSTU (2.2 eq.), DIPEA (0.2 eq.), anhyd. DMF, r.t., N_2, 16 h; (***d***) (**GlcN1**)·HCl (2.5 eq), DIPEA (7.5 eq.), anhyd. DMF, r.t., N_2, 16 h; (***e***) (**GlcN2**)(CH_3COOH) (2.4 eq), DIPEA (1 eq.), anhyd. DMF, r.t., N_2, 16 h; (***f***) (**GlcN3**) (2.5 eq), DIPEA (5.5 eq.), anhyd. DMF, r.t., N_2, 16 h.

(**GlcN1**) (**GlcN2**) (**GlcN3**)

Scheme 4 Synthesis of the zinc(II)-dithiocarbamato glycoconjugate precursors.

Following the successful generation of the model non-glycosylated gold(III)-dithiocarbamato complexes, we applied the same synthetic strategy to obtain the corresponding glycoconjugate counterparts. With reference to Scheme 4, we first prepared the zinc(II)-dithiocarbamato derivative of isonipecotic acid, $Na_2[Zn^{II}(SSC\text{-}Inp\text{-}O)_2]\cdot 2H_2O$ (**Zn0a**), by optimizing a literature procedure.[58] In order to conjugate the amino-sugars to the isonipecotic linker, the carboxylic functions of **Zn0a** were subsequently activated by converting them into the corresponding succinimidyl ester, $[Zn^{II}(SSC\text{-}Inp\text{-}OSu)_2]$ (**Zn0b**). Although this is a well-known process, common synthetic routes involve the use of acidic media in which dithiocarbamates tend to decompose.[32] Therefore, we exploited the method reported by Suades and co-workers which makes use of the peptide coupling reagent *N*,*N*,*N*',*N*'-tetramethyl-*O*-(*N*-succinimidyl)uronium tetrafluoroborate (TSTU) in presence of *N*,*N*-diisopropylethylamine (DIPEA).[52] This procedure proved very efficient and straightforward also because **Zn0b** could be easily isolated from the DMF reaction medium by simple precipitation after addition of a 1:1 water/ethanol mixture. Both **Zn0a** and **Zn0b** were obtained in high yield (68% and 93%, respectively) and purity, and their spectroscopic characterization was fully consistent with literature data.[52]

As far as the amino-sugar substrates are concerned, we chose three different glucose-like scaffolds (see the ESI for details on syntheses and characterizations).

- 2-Amino-2-deoxy-(α,β)-D-glucose (aka (α,β)-D-glucosamine, **GlcN1**) hydrochloride, bearing the amino function in the C^2 position of the glucose, is commercially available and is sold as a mixture of α and β anomers (the former largely predominating). Glucosamine-appended ligands have been already used in some cases to obtain metal-glycoconjugates.[21b,c]
- 1-*O*-methyl-2-amino-2-deoxy-(α,β)-D-glucopyranoside (**GlcN2**) was prepared as ammonium acetate according to a literature procedure.[59] An α:β anomers ratio of approximately 5:1 was obtained. Methylation of the anomeric hydroxyl group (C^1 position) aimed at avoiding side-reactions involving the anomeric carbon in the subsequent steps, as well as at simplifying the NMR characterization of the final products.
- 1-*O*-methyl-6-amino-6-deoxy-α-D-glucopyranoside (**GlcN3**) was prepared according to a literature procedure[60] with the aim of investigating the feasibility of our synthetic method for amino-sugars bearing the amino function in positions other than the C^2 site of the glucose (*i.e.* C^6 position).

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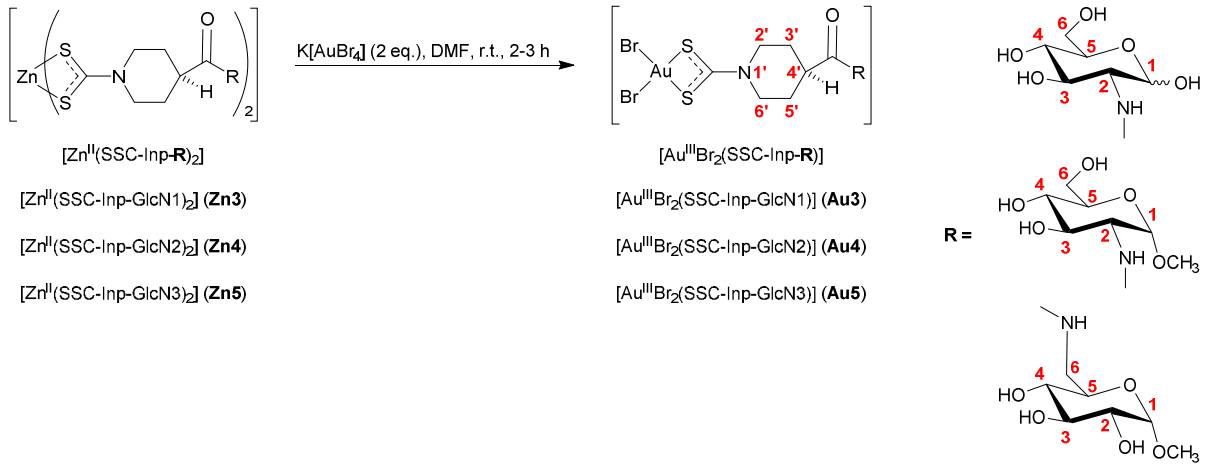

Scheme 5 Synthesis of the gold(III)-dithiocarbamato glycoconjugates *via* transmetallation.

An excess of each amino-sugar (2.4-2.5 eq.) was reacted with the activated zinc(II) precursor **Zn0b** in anhydrous DMF under basic conditions (DIPEA), leading to the coupling of the amino function of the glucose-like unit to the carboxylic group of the isonipecotic moiety, thus resulting in the formation an amide bond and the generation of the corresponding complexes [Zn^{II}(SSC-Inp-GlcN1)$_2$] (**Zn3**), [Zn^{II}(SSC-Inp-GlcN2)$_2$] (**Zn4**) and [Zn^{II}(SSC-Inp-GlcN3)$_2$] (**Zn5**) (Scheme 4).

By comparing the spectroscopic features of the starting reagents with those of the zinc(II)-dithiocarbamato glycoconjugates, the most affected signals were those related to the atoms in close proximity to the newly formed amide bond. In the IR spectra of **Zn3-Zn5** the absorption bands originating from both the succinimidyl fragment of **Zn0b** (ν_{ip}(C=O succinimidyl), ν_{oop}(C=O succinimidyl) and ν(C=O ester) at 1817, 1780 and 1737 cm^{-1})[52] and from the amino/ammonium group of the sugar substrates **GlcN1-GlcN3** ($\nu_a(NH_3^+)$, $\nu_s(NH_3^+)$, $\delta_a(NH_3^+)$, $\delta_s(NH_3^+)$, $\nu(NH_2)$ and $\delta(NH_2)$ at ~3090, 2840, 1620, 1580, 3260 and 1600 cm^{-1}, respectively)[61] disappeared. Instead, new intense bands at ~1640 (ν(C=O, amide I)) and ~1550 (δ_{ip}(CNH, amide II)) cm^{-1} were detected,[62] consistent with the replacement of the succinimidyl ester located in the same position by an amide group. On the contrary, ν(N–CSS), ν_a(SCS), ν_s(SCS) and $\nu_a(ZnS_4)$ remained substantially unchanged (at ~1490, 1000, 570 and 370 cm^{-1}, respectively) compared with **Zn0b**. Analogously, the ^{1}H and $^{13}C\{^1H\}$ NMR signals corresponding to the zinc(II)-dithiocarbamato isonipecotic fragment and the glucose moiety recorded for **Zn3-Zn5** were observed at chemical shifts similar to those found for the starting reagents, except the peaks associated with the $C^{4'}H$ group of the piperidine ring, and the C^2H group (for **Zn3** and **Zn4**) or the C^6H_2 group (for **Zn5**) of the glucose unit.

Eventually, zinc(II)-gold(III) transmetallation was achieved by reacting the zinc(II) precursors **Zn3-Zn5** with K[$Au^{III}Br_4$] in DMF, affording the final corresponding gold(III)-dithiocarbamato glycoconjugates [$Au^{III}Br_2$(SSC-Inp-GlcN1)] (**Au3**), [$Au^{III}Br_2$(SSC-Inp-GlcN2)] (**Au4**) and [$Au^{III}Br_2$(SSC-Inp-GlcN3)] (**Au5**) (Scheme 5) in high yields (>75%) and no need of further purification. The synthesized gold(III) complexes were characterized by the usual analytical and spectroscopic techniques. In the mid-IR spectra the ν(N–CSS) band shifted from ~1490 to ~1560 cm^{-1}, as a result of the increased electron-withdrawing effect in the gold(III) derivatives compared with the zinc(II) counterparts, whereas in the far-IR spectra the absorptions at ~370 cm^{-1} ($\nu_a(ZnS_4)$) disappeared and new bands at ~410/390 ($\nu_{a,s}$(SAuS)) and ~245/225 ($\nu_{a,s}$(BrAuBr)) cm^{-1} were recorded instead, consistent with the expected dibromide-gold(III)-dithiocarbamato scaffold.

In line with what is observed for the model non-glycosylated complexes (see above), when moving from the zinc(II) to the gold(III) glycoconjugates, major changes in the NMR spectra were detected for the signals associated with the isonipecoticdithiocarbamato fragments. A comparative example is given in Figure 4 for **Au5**. Remarkably, as a general trend, the ^{1}H signals recorded for the glucose hydroxyl groups are properly resolved only for the zinc(II) intermediates, whereas for both the starting amino-sugars and the corresponding gold(III) derivatives peaks tend to collapse into a single very broad band (Figure 5A).

In terms of the reactivity of the different anomers, the α to β ratio was substantially retained when using (α,β)-D-glucosamine (**GlcN1**). On the contrary, the percent of the α anomer dramatically increased by moving from *O*-methyl-2-amino-2-deoxy-D-glucopyranoside (**GlcN2**, α:$\beta \approx$ 5:1) to the corresponding zinc(II)-dithiocarbamato glycoconjugate (**Zn4**, α:$\beta \approx$ 25:1), the β anomer being completely absent in the gold(III) analogue (**Au4**). This was assessed by measuring the $^3J(C^1H,C^2H)$ coupling constants in the ^{1}H NMR spectra which were in the 1-4 Hz and 6-8 Hz for the α and β anomers, respectively.[63] Finally, 1-*O*-methyl-6-amino-6-deoxy-D-glucopyranoside (**GlcN3**) was obtained in its α anomeric form only and, as expected, no α to β anomerization processes occurred.

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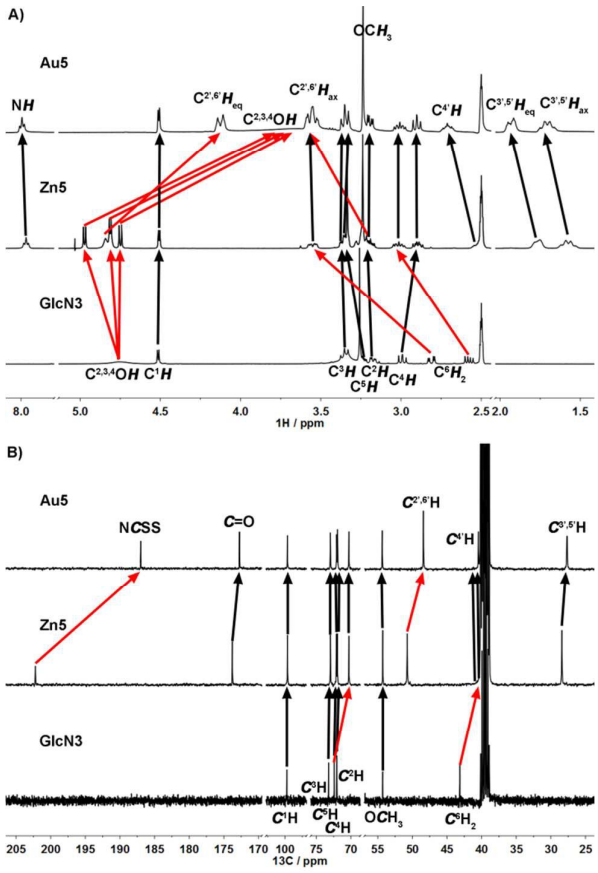
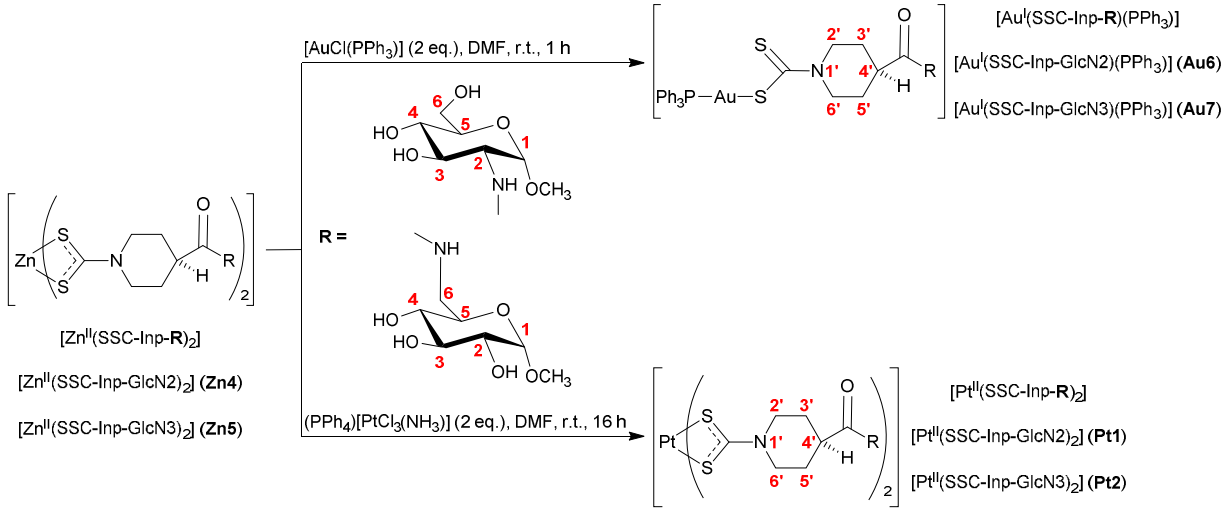


Figure 4 Comparison of the ^{1}H (**A**) and $^{13}C\{^{1}H\}$ (**B**) NMR spectra in DMSO-D_6 of 1-*O*-methyl-6-amino-6-deoxy-α-D-glucopyranoside (**GlcN3**), [Zn^{II}(SSC-Inp-GlcN3)$_2$] (**Zn5**) and [$Au^{III}Br_2$(SSC-Inp-GlcN3)] (**Au5**).

Gold(I)- and platinum(II)-dithiocarbamato glycoconjugates

The feasibility of the glycoconjugation strategy here proposed was assessed also towards metal centers other than gold(III). By reacting the zinc(II) precursors **Zn4** and **Zn5** with 2 eq. of [$Au^{I}Cl(PPh_3)$] in DMF, the corresponding gold(I)-dithiocarbamato derivatives [Au^{I}(SSC-Inp-GlcN2)(PPh_3)] (**Au6**) and [Au^{I}(SSC-Inp-GlcN3)(PPh_3)] (**Au7**) were obtained (Scheme 6) and characterized by elemental analysis, IR and NMR spectroscopy. Consistently with other triphenylphosphino-gold(I)-dithiocarbamato complexes reported in the literature,[64] those gold(I) compounds were expected to exhibit a near-linear geometry around the metal center with the dithiocarbamato scaffold acting as a monodentate ligand. Although attempts to grow crystals of **Au6** and **Au7** proved unsuccessful, the proposed molecular structure was confirmed by the presence in the mid-IR spectra of two bands at *ca.* 1000 and 914 cm^{-1} assignable to the stretching vibration of the S=C–S moiety. This is in agreement with the Bonati-Ugo criterion, according to which a split band in the 1050-900 cm^{-1} spectral region with a splitting larger than 20 cm^{-1} indicates monodentate bonding of the dithiocarbamato ligand.[65]
Compared with the gold(III) counterparts **Au4** and **Au5**, the ^{1}H and ^{13}C peaks of the glucosedithiocarbamato scaffold are recorded at similar chemical shifts with the exception of the atoms closer to the gold(I) core, which are more sensitive to the different metal center and coordination mode of the –NCSS group. In particular, a significant downfield shift is observed for the $C^{2',6'}H_{eq}$ (^{1}H: ~4.9 ppm (+0.7 ppm); ^{13}C: ~51 ppm (+2 ppm)) and the NCSS (^{13}C: ~203 ppm (+16 ppm)) moieties which, together with the detection of the ν(N–CSS) vibration at lower energy (~1485 cm^{-1} (-70 cm^{-1})), are consistent with a smaller electron-withdrawing effect upon moving from the gold(III) to the less positively charged gold(I) center.[41]
Glycoconjugation *via* transmetallation was achieved also in presence of platinum(II). Reaction of the zinc(II) precursors **Zn4** and **Zn5** with (PPh_4)[$Pt^{II}Cl_3(NH_3)$] led to the formation of the complexes [Pt^{II}(SSC-Inp-GlcN2)$_2$] (**Pt1**) and [Pt^{II}(SSC-Inp-GlcN3)$_2$] (**Pt2**) (Scheme 6), although the original plan was to synthesize the corresponding mono-dithiocarbamato



Scheme 6 Synthesis of the gold(I)- and platinum(II)-dithiocarbamato glycoconjugates *via* transmetallation.

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derivatives [$Pt^{II}Cl$(SSC-Inp-GlcN)(NH_3)]. In fact, notwithstanding various attempts and the exploitation of different experimental conditions, the replacement of all the chlorido and amino ligands with two dithiocarbamato ligands occurred, even when a large excess (5 eq.) of the starting platinum(II) reagent was used.

Although no crystals of the platinum(II) glycoconjugates were obtained, elemental analysis and spectroscopic results support the formation of the bis-dithiocarbamato adducts. In this regard, the N–CSS stretching vibrations observed at 1523 and 1554 cm^{-1} (compared with the same absorption recorded at ~1494 cm^{-1} for the zinc(II) precursors) are in agreement with data reported in the literature for analogous bis-dithiocarbamato-platinum(II) derivatives.[66] Moreover, the absence in the IR spectra of the bands associated with both the NH_3 ligand (at ~3200 ($\nu_{a,s}$), ~1640 (δ_a), ~1290 (δ_s), ~780 (ρ) cm^{-1}) and the chloride ligand (ν(Pt–Cl) at ~330 cm^{-1})[67] supports the hypothesis of a complete exchange of ligands in favor of the dithiocarbamato ligands.

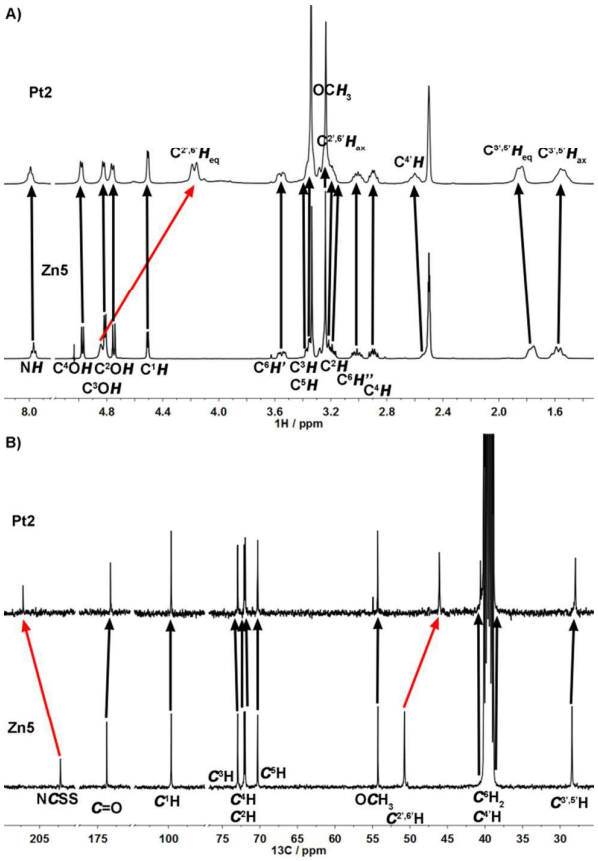

Figure 5 Comparison of the ^1H (**A**) and $^{13}C\{^1H\}$ (**B**) NMR spectra in DMSO-D_6 of [Zn^{II}(SSC-Inp-GlcN3)$_2$] (**Zn5**) and [Pt^{II}(SSC-Inp-GlcN3)$_2$] (**Pt2**)

As far as the NMR characterization is concerned, an illustrative example is given in Figure 5. The ^1H and $^{13}C\{^1H\}$ spectra of **Pt2** are very clean and clearly indicate the presence of only one species in solution. Although the majority of the signals resonate at chemical shifts almost identical to those of their counterparts in the zinc(II) precursor **Zn5**, **Pt2** is undoubtedly a different compound, as evidenced by the major upfield shift of the ^1H and ^{13}C peaks associated with the $C^{2',6'}H_{eq}$ group. Moreover, the ^{13}C peak at 207 ppm assigned to the dithiocarbamato carbon atom is fully consistent with those reported in the literature for other bis-dithiocarbamato-platinum(II) derivatives.[66a]

Remarkably, no signals attributable to the NH_3 ligand were observed in the ^1H NMR spectra. In this regard, we synthesized the ^{15}N-labeled analogues of **Pt1** and **Pt2** by reacting **Zn4** and **Zn5** with the platinum(II) precursor (PPh_4)[$Pt^{II}Cl_3$($^{15}NH_3$)], and both the IR and NMR spectra turned out to be identical to those of the unlabeled counterparts (data not shown). In particular, no ^{15}N peaks were recorded in the corresponding [^1H,^{15}N] HSQC spectra, thus confirming that the NH_3 ligand was replaced.

Notwithstanding the desired mono-dithiocarbamato-platinum(II) glycoconjugates were not obtained, the transmetallation reaction proved successful anyway. In perspective, this issue might be overcome by using organophosphino (instead of amino) platinum(II) precursors as recently reported.[68]

Conclusions

We have developed a relatively facile and efficient synthetic strategy to the functionalization of metal complexes with carbohydrates based on the initial synthesis of the zinc(II)-dithiocarbamato glycoconjugate intermediates followed by the transfer of the glucosedithiocarbamato ligand to other metal centers *via* transmetallation. Although transmetallation of dithiocarbamates has been known for decades, to the best of our knowledge, its systematic application to glycoconjugation has not been reported to date.

The main features of the proposed synthetic route are the following.

- It proved successful with different amino-glucose substrates, and no protection/deprotection of the glucose units nor chromatographic purification were required. We are now planning to extend this procedure to more complex amino-sugars, including oligosaccharides.
- Compared with the common dithiocarbamato sodium, potassium and ammonium salts, zinc(II)-dithiocarbamato glycoconjugate precursors are reasonably stable over time, can be synthesized in bulk in high yields and purity, and stored safely for subsequent transmetallation reactions.
- Transmetallation was achieved in high yields and purity for different metal ions, such as gold(III), gold(I) and platinum(II). We are now in the process of exploiting the same approach with organometallic-gold(III), carbene-gold(I) and carbonyl-manganese(I) precursors.

Given the potential biological applications of metal glycoconjugates, in particular for the targeted metal-based chemotherapy and diagnosis, the synthetic protocol here optimized and proposed may be applied to a number of different metal scaffolds, thus being of interest for scientists

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working in the field of medicinal inorganic and bioinorganic chemistry.

Experimental Section

Materials and general methods (including instrumentation used) are available in the ESI.

Amino-sugar precursors

2-Amino-2-deoxy-(α,β)-D-glucose (aka (α,β)-D-glucosamine, **GlcN1**) hydrochloride was commercially available, whereas 1-*O*-methyl-2-amino-2-deoxy-(α,β)-D-glucopyranoside (**GlcN2**)[59] and 1-*O*-methyl-6-amino-6-deoxy-α-D-glucopyranoside (**GlcN3**),[60] were synthesized according to literature procedures. Detailed syntheses and characterizations are reported in the ESI.

Zinc(II)-dithiocarbamato intermediates

$Na_2[Zn^{II}(SSC\text{-}Inp\text{-}O)_2]\cdot 2H_2O$ (Zn0a). This zinc(II) intermediate was synthesized according to a modified literature procedure.[58] NaOH (620.0 mg, 15.50 mmol) was dissolved in methanol (7 mL) and added under stirring to a methanol solution (10 mL) of isonipecotic acid (1.00 g, 7.74 mmol). The mixture was cooled down to 0°C, treated dropwise with CS_2 (480 µL, 7.94 mmol), and stirred for 6 h. The resulting solution was then added dropwise under stirring to a methanol solution (7 mL) of $[Zn(OAc)_2]\cdot 2H_2O$ (850.0 mg, 3.87 mmol), leading to the sudden precipitation of a white solid. The precipitate was centrifuged and the bulk of supernatant discarded. The residue was subsequently washed with methanol (3×20 mL) and then dried under vacuum over P_2O_5, yielding the title compound as a white solid (1.47 g, 68%). M.p. 295-297°C (dec.). Anal. (%) calcd. for $C_{14}H_{22}N_2Na_2O_6S_4Zn$ (MM = 553.94 g mol^{-1}): C, 30.36; H, 4.00; N, 5.06; found: C, 30.48; H, 4.08; N, 5.04. FT-IR (CsI disk; 298 K): $\tilde{\nu}_{max}$ 1555 (ν_a, COO^-), 1487 (ν, N–CSS), 1409 (ν_s, COO^-), 1002 (ν_a, SCS), 566 (ν_s, SCS), 397 (ν_a, ZnS_4) cm^{-1}. ^{1}H NMR (400 MHz; D_2O; 298 K): δ 4.93 (4 H, br dt, $C^{2',6'}\boldsymbol{H}_{eq}$), 3.31 (4 H, br td, $C^{2',6'}\boldsymbol{H}_{ax}$), 2.46 (2 H, tt, $C^{4'}\boldsymbol{H}$), 1.95 (4 H, dd, $C^{3',5'}\boldsymbol{H}_{eq}$), 1.66 (4 H, qd, $C^{3',5'}\boldsymbol{H}_{ax}$) ppm. $^{13}C\{^1H\}$ NMR (100 MHz; D_2O; 298 K): δ 201.6 (N***C***SS), 183.1 (***C***OO^-), 51.8 ($\boldsymbol{C}^{2',6'}H_2$), 42.8 ($\boldsymbol{C}^{4'}H$), 28.8 ($\boldsymbol{C}^{3',5'}H_2$) ppm.

$[Zn^{II}(SSC\text{-}Inp\text{-}OSu)_2]$ (Zn0b). This zinc(II) intermediate was synthesized according to a literature procedure.[52] *N*,*N*,*N*′,*N*′-tetramethyl-*O*-(*N*-succinimidyl)uronium tetrafluoroborate (TSTU, 3.07 g, 10.2 mmol) was added under stirring to an anhydrous DMF suspension (12 mL) of **Zn0a** (2.51 g, 4.53 mmol) and *N*,*N*-diisopropylethylamine (DIPEA, 160 µL, 0.92 mmol). The mixture was stirred at room temperature under inert atmosphere (N_2) for 16 h and then treated with a 1:1 water/ethanol solution (1.2 L), affording a white solid. The precipitate was filtered off, washed with ethanol (3×20 mL) and diethyl ether (3×20 mL), and then dried under vacuum over P_2O_5, yielding the title compound as a white solid (2.81 g, 93%). M.p. 220-222°C (dec.). Anal. (%) calcd. for $C_{22}H_{26}N_4O_8S_4Zn$ (MM = 668.09 g mol^{-1}): C, 39.55; H, 3.92; N, 8.39; found: C, 39.31; H, 3.98; N, 8.28. FT-IR (CsI disk; 298 K): $\tilde{\nu}_{max}$ 1817 (ν_{ip}, C=O succinimidyl), 1784 (ν_{oop}, C=O succinimidyl), 1737 (ν, C=O ester), 1496 (ν, N–CSS), 1206 (ν, C–OSu), 1001 (ν_a, SCS), 562 (ν_s, SCS), 397 (ν_a, ZnS_4) cm^{-1}. ^{1}H NMR (400 MHz; DMSO-D_6; 298 K): δ 4.72 (4 H, br d, $C^{2',6'}\boldsymbol{H}_{eq}$), 3.52 (4 H, br t, $C^{2',6'}\boldsymbol{H}_{ax}$), 3.26-3.19 (2 H, m, $C^{4'}\boldsymbol{H}$), 2.82 (8 H, s, $C\boldsymbol{H}_2$ succinimidyl), 2.10 (4 H, dd, $C^{3',5'}\boldsymbol{H}_{eq}$), 1.70 (4 H, qd, $C^{3',5'}\boldsymbol{H}_{ax}$) ppm. $^{13}C\{^1H\}$ NMR (100 MHz; DMSO-D_6; 298 K): δ 203.3 (N***C***SS), 170.2 (***C***=O succinimidyl), 169.9 (***C***=O ester), 49.9 ($\boldsymbol{C}^{2',6'}H_2$), 36.3 ($\boldsymbol{C}^{4'}H$), 27.6 ($\boldsymbol{C}^{3',5'}H_2$), 25.5 ($\boldsymbol{C}H_2$ succinimidyl) ppm.

$[Zn^{II}(SSC\text{-}Inp\text{-}OEt)_2]$ (Zn1). CS_2 (400 µL, 6.63 mmol) was added dropwise under stirring to a water/ethanol (7:3, 10 mL) solution of ethyl isonipecotate (1.03 g, 6.53 mmol) at 0°C. The mixture was stirred at 0°C for 3 h (pH turned from 12 to 6), and then added to an aqueous solution (3 mL) of $ZnCl_2$ (220.0 mg, 1.63 mmol), leading to the sudden precipitation of a white solid. The precipitate was centrifuged and the bulk of supernatant discarded. The residue was subsequently washed with water (2×10 mL), acetone (2×10 mL) and diethyl ether (2×10 mL), and then dried under vacuum over P_2O_5, yielding the title compound as a white solid (620.1 mg, 72%). Small colorless plate-shaped crystals suitable for X-ray crystallography were obtained upon slow evaporation of an acetonitrile/ethanol solution of the compound. M.p. 200-202°C. Anal. (%) calcd. for $C_{18}H_{28}N_2O_4S_4Zn$ (MM = 530.05 g mol^{-1}): C, 40.79; H, 5.32; N, 5.29; found: C, 40.57; H, 5.39; N, 5.10. FT-IR (CsI disk; 298 K): $\tilde{\nu}_{max}$ 1733 (ν, C=O), 1494 (ν, N–CSS), 1176 (ν, C–OEt), 1042 (ν, O–Et), 1007 (ν_a, SCS), 568 (ν_s, SCS), 398 (ν_a, ZnS_4) cm^{-1}. ^{1}H NMR (400 MHz; DMSO-D_6; 298 K): δ 4.72 (4 H, dt, $C^{2',6'}\boldsymbol{H}_{eq}$), 4.08 (4 H, q, $OC\boldsymbol{H}_2$), 3.39 (4 H, td, $C^{2',6'}\boldsymbol{H}_{ax}$), 2.72-2.60 (2 H, m, $C^{4'}\boldsymbol{H}$), 1.95 (4 H, dd, $C^{3',5'}\boldsymbol{H}_{eq}$), 1.57 (4 H, qd, $C^{3',5'}\boldsymbol{H}_{ax}$), 1.19 (6 H, t, $C\boldsymbol{H}_3$) ppm. $^{13}C\{^1H\}$ NMR (100 MHz; DMSO-D_6; 298 K): δ 202.6 (N***C***SS), 173.6 (***C***=O), 60.2 ($OC\boldsymbol{H}_2$), 50.4 ($\boldsymbol{C}^{2',6'}H_2$), 38.9 ($\boldsymbol{C}^{4'}H$), 27.8 ($\boldsymbol{C}^{3',5'}H_2$), 14.1 ($\boldsymbol{C}H_3$) ppm.

$[Zn^{II}(SSC\text{-}Inp\text{-}NH_2)_2]$ (Zn2). *Method A*: NaOH (310.0 mg, 7.80 mmol) was dissolved in methanol (10 mL) and added under stirring to a methanol solution (10 mL) of isonipecotamide (1.00 g, 7.80 mmol). The mixture was cooled down to 0°C, treated dropwise with CS_2 (470 µL, 7.80 mmol), stirred for 3 h (pH turned from 12 to 8), treated with further CS_2 (470 µL, 7.80 mmol), and stored at 4°C for 16 h. The mixture was then added to an aqueous solution (2 mL) of $[Zn(OAc)_2]\cdot 2H_2O$ (860.0 mg, 3.90 mmol) at room temperature, leading to the sudden precipitation of a white solid. The precipitate was centrifuged and the bulk of supernatant discarded. The residue was subsequently washed with water (2×15 mL) and then dried under vacuum over P_2O_5, yielding the title compound as a white solid (1.77 g, 96%).
Method B: An aqueous solution (18 mL) of Na(SSC-Inp-NH_2)·CH_3OH (900.0 mg, 3.48 mmol; see ESI for details on

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synthesis and characterization) was added under stirring to an aqueous solution (2 mL) of $[Zn(OAc)_2]\cdot 2H_2O$ (380.0 mg, 1.73 mmol) at room temperature, leading to the sudden precipitation of a white solid. The precipitate was centrifuged and the bulk of supernatant discarded. The residue was subsequently washed with water (2×15 mL) and then dried under vacuum over P_2O_5, yielding the title compound as a white solid (810.0 mg, 99%).
M.p. 293-294°C (dec.). Anal. (%) calcd. for $C_{14}H_{22}N_4O_2S_4Zn$ (MM = 471.98 g mol^{-1}): C, 35.63; H, 4.70; N, 11.87; found: C, 35.74; H, 4.89; N, 11.76. FT-IR (CsI disk; 298 K): $\tilde{\nu}_{max}$ 3439/3208 ($\nu_{a,s}$, NH_2), 1667 (ν, C=O (amide I)), 1649 (δ_{ip}, CNH_2 (amide II)), 1492 (ν, N–CSS), 1007 (ν_a, SCS), 561 (ν_s, SCS), 392 (ν_a, ZnS_4) cm^{-1}. ^{1}H NMR (400 MHz; DMSO-D_6; 298 K): δ 7.36 (2 H, s, N***H***$_{cis}$), 6.87 (2 H, s, N***H***$_{trans}$), 4.82 (4 H, br d, C$^{2',6'}$***H***$_{eq}$), 3.26 (4 H, td, C$^{2',6'}$***H***$_{ax}$), 2.40 (2 H, tt, C$^{4'}$***H***), 1.82 (4 H, dd, C$^{3',5'}$***H***$_{eq}$), 1.54 (4 H, qd, C$^{3',5'}$***H***$_{ax}$) ppm. ^{13}C{^{1}H} NMR (100 MHz; DMSO-D_6; 298 K): δ 202.3 (N***C***SS), 175.6 (***C***=O), 50.7 (***C***$^{2',6'}H_2$), 40.1 (***C***$^{4'}$H), 28.4 (***C***$^{3',5'}H_2$) ppm.

[Zn^{II}(SSC-Inp-GlcN1)$_2$] (Zn3). A mixture of (α,β)-D-glucosamine (**GlcN1**) hydrochloride (392.0 mg, 1.82 mmol) and *N*,*N*-diisopropylethylamine (DIPEA, 925 μL, 5.31 mmol) in anhydrous DMF (3 mL) was added under stirring to a suspension of **Zn0b** (473.3 mg, 0.71 mmol) in anhydrous DMF (2 mL). The mixture was stirred at room temperature under inert atmosphere (N_2) for 16 h and then treated with methanol (60 mL), leading to the sudden precipitation of a white solid. The precipitate was filtered off, washed with methanol (3×20 mL), and then dried under vacuum over P_2O_5, yielding the title compound as a white solid (341.6 mg, 61%). M.p. 200-203°C (dec.). Anal. (%) calcd. for $C_{26}H_{42}N_4O_{12}S_4Zn$ (MM = 796.26 g mol^{-1}): C, 39.22; H, 5.32; N, 7.04; found: C, 39.18; H, 5.19; N, 6.91. FT-IR (CsI disk; 298 K): $\tilde{\nu}_{max}$ 3293_{br} (ν, OH + NH overlapped), 1638 (ν, C=O (amide I)), 1547 (δ_{ip}, CNH (amide II)), 1487 (ν, N–CSS), $1071_{br}/1060_{br}$ (ν, C–OH), 1005 (ν_a, SCS), 570 (ν_s, SCS), 373 (ν_a, ZnS_4) cm^{-1}. ^{1}H NMR (400 MHz; DMSO-D_6; 298 K): δ 7.70 (0.5 H, d, N***H*** β), 7.67 (2 H, d, N***H*** α), 6.49 (0.5 H, d, C^{1}O***H*** β), 6.41 (2 H, d, C^{1}O***H*** α), 4.94-4.90 (4 H, m, C^{3}O***H*** + C^1***H*** α overlapped), 4.85-4.78 (5 H, br m, C$^{2',6'}$***H***$_{eq}$ α and β overlapped), 4.61 (2 H, d, C^{4}O***H*** α), 4.53 (0.5 H, dd, C^{6}O***H*** β), 4.45-4.42 (2.5 H, br m, C^{6}O***H*** α + C^1***H*** β overlapped), 3.69-3.39 (11.5 H , m, C^2***H*** α + C^4***H*** α and β + C^5***H*** α + C^6***H***$_2$ α and β overlapped), 3.31-3.22 (6 H, m, C$^{2',6'}$***H***$_{ax}$ α and β + C^2***H*** β + C^3***H*** β overlapped), 3.18-3.02 (2.5 H, m, C^3***H*** α + C^5***H*** β overlapped), 2.57-2.52 (2.5 H, m, C$^{4'}$***H*** α and β overlapped), 1.81-1.75 (5 H, m, C$^{3',5'}$***H***$_{eq}$ α and β overlapped), 1.62-1.56 (5 H, br qd, C$^{3',5'}$***H***$_{ax}$ α and β overlapped) ppm. C^{3}O***H*** β and C^{4}O***H*** β could not be undoubtedly assigned: those peaks are probably overlapped with other peaks in the 4.92-4.42 ppm range. ^{13}C{^{1}H} NMR (100 MHz; DMSO-D_6; 298 K): δ 202.2 (N***C***SS), 173.8 (***C***=O), 95.4 (***C***^{1}H β), 90.5 (***C***^{1}H α), 76.9 (***C***^{5}H β), 74.2 (***C***^{3}H β), 72.1 (***C***^{5}H α), 71.1 (***C***^{3}H α), 70.9 (***C***^{4}H β), 70.4 (***C***^{4}H α), 61.2 (***C***^{6}H$_2$ β), 61.1 (***C***^{6}H$_2$ α), 57.1 (***C***^{2}H β), 54.3 (***C***^{2}H α), 50.8 (***C***$^{2',6'}H_2$), 40.1 (***C***$^{4'}$H), 28.5 (***C***$^{3',5'}H_2$) ppm. No differentiation of the ^{13}C signals of the isonipecotic moiety due to the presence of both α and β anomers could be observed. Solution α:β anomers ratio ≈ 4:1 (based on the ^{1}H NMR spectrum).

[Zn^{II}(SSC-Inp-GlcN2)$_2$] (Zn4). A mixture of 1-*O*-methyl-2-amino-2-deoxy-(α,β)-D-glucopyranoside (**GlcN2**) (266.1 mg, 1.05 mmol) and *N*,*N*-diisopropylethylamine (DIPEA, 76 μL, 0.44 mmol) in anhydrous DMF (2 mL) was added under stirring to a suspension of **Zn0b** (292.8 mg, 0.44 mmol) in anhydrous DMF (2 mL). The mixture was stirred at room temperature under inert atmosphere (N_2) for 16 h and treated with methanol (30 mL), leading to the formation of a white precipitate that was filtered off and discarded. The resulting clear pale yellow solution was allowed to slowly concentrate under the fume hood at room temperature for two days. The resulting white solid was resuspended in methanol (20 mL), filtered off, washed with methanol (3×20 mL), and then dried under vacuum over P_2O_5, yielding the title compound as a white solid (464.6 mg, 35%). M.p. 268-272°C (dec.). Anal. (%) calcd. for $C_{28}H_{46}N_4O_{12}S_4Zn$ (MM = 824.31 g mol^{-1}): C, 40.80; H, 5.63; N, 6.80; found: C, 40.65; H, 5.74; N, 6.81. FT-IR (CsI disk; 298 K): $\tilde{\nu}_{max}$ 3319_{br} (ν, OH + NH overlapped), 1645 (ν, C=O (amide I)), 1557 (δ_{ip}, CNH (amide II)), 1494 (ν, N–CSS), $1062_{br}/1040_{br}$ (ν, C–OH + C^1–O–CH_3 overlapped), 1007 (ν_a, SCS), 576 (ν_s, SCS), 366 (ν_a, ZnS_4) cm^{-1}. ^{1}H NMR (400 MHz; DMSO-D_6; 298 K): δ 7.80 (2 H, d, N***H***), 5.00 (2 H, d, C^{4}O***H***), 4.82 (4 H, br d, C$^{2',6'}$***H***$_{eq}$), 4.73 (2 H, d, C^{3}O***H***), 4.56-4.52 (4 H, m, C^{6}O***H*** + C^1***H*** overlapped), 3.67-3.42 (8 H, m, C^2***H*** + C^3***H*** + C^6***H***$_2$ overlapped), 3.33-3.24 (6 H, m, C^5***H*** + C$^{2',6'}$***H***$_{ax}$ overlapped), 3.24 (6 H, s, OC***H***$_3$), 3.15-3.09 (2 H, m, C^4***H***), 2.59-2.52 (2 H, m, C$^{4'}$***H***), 1.81-1.76 (4 H, br m, C$^{3',5'}$***H***$_{eq}$), 1.57 (4 H, br qd, C$^{3',5'}$***H***$_{ax}$) ppm. The ^{1}H NMR signals refer to the α anomer. Signals related to the β anomer were hardly detectable, and only a very few were observed and could be undoubtedly assigned (such as δ(N***H***) = 7.68, δ(C^{3}O***H***) = 4.91, δ(C^1***H***) = 4.19 ($^3J_{1,2}$ = 8.4 Hz), δ(OC***H***$_3$) = 3.58 ppm). ^{13}C{^{1}H} NMR (100 MHz; DMSO-D_6; 298 K): δ 202.2 (N***C***SS), 173.9 (***C***=O), 97.9 (***C***^{1}H), 72.8 (***C***^{5}H), 70.8 (***C***^{3}H), 70.7 (***C***^{4}H), 60.9 (***C***^{6}H$_2$), 54.5 (O***C***H$_3$), 53.8 (***C***^{2}H), 50.8 (***C***$^{2',6'}H_2$), 40.0 (***C***$^{4'}$H), 28.5 (***C***$^{3',5'}H_2$) ppm. No ^{13}C signals assignable to the β anomer were detected. Solution α:β anomers ratio ≈ 25:1 (based on the ^{1}H NMR spectrum).

[Zn^{II}(SSC-Inp-GlcN3)$_2$] (Zn5). A mixture of 1-*O*-methyl-6-amino-6-deoxy-α-D-glucopyranoside (**GlcN3**, 760.0 mg, 3.93 mmol) and *N*,*N*-diisopropylethylamine (DIPEA, 1.50 mL, 8.64 mmol) in anhydrous DMF (4 mL) was added under stirring to a suspension of **Zn0b** (1.05 g, 1.57 mmol) in anhydrous DMF (4 mL). The mixture was stirred at room temperature under inert atmosphere (N_2) for 16 h and then treated with ethanol (80 mL), leading to the sudden precipitation of a white solid. The precipitate was filtered off, washed with methanol (3×15 mL), and then dried under vacuum over P_2O_5, yielding the title compound as a white solid (980.0 mg, 76%). M.p. 245-248°C (dec.). Anal. (%) calcd. for $C_{28}H_{46}N_4O_{12}S_4Zn$ (MM = 824.31 g mol^{-1}): C, 40.80; H, 5.63; N, 6.80; found: C, 40.91; H, 5.83; N, 6.76. FT-IR (CsI disk; 298 K): $\tilde{\nu}_{max}$ 3392_{br} (ν, OH + NH overlapped), 1637 (ν, C=O (amide I)), 1543 (δ_{ip}, CNH (amide II)), 1494 (ν, N–CSS), 1050_{br} (ν, C–OH + C^1–O–CH_3 overlapped), 1010 (ν_a, SCS), 564 (ν_s, SCS), 366

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(ν_a, ZnS_4) cm^{-1}. ^1H NMR (400 MHz; DMSO-D_6; 298 K): δ7.97 (2 H, dd, N***H***), 4.97 (2 H, d, C^4O***H***), 4.83 (4 H, br m, $C^{2',6'}$***H***$_{eq}$), 4.82 (2 H, d, C^3O***H***), 4.75 (2 H, d, C^2O***H***), 4.51 (2 H, d, C^1***H***, $^3J_{1,2}$ = 3.6 Hz), 3.58-3.52 (2 H, m, C^6***H'***), 3.40-3.35 (4 H, m, C^3***H*** + C^5***H*** overlapped), 3.24 (6 H, s, OC***H***$_3$), 3.28-3.19 (6 H, m, C^2***H*** + $C^{2',6'}$***H***$_{ax}$ overlapped), 3.08-2.98 (2 H, m, C^6***H''***), 2.92-2.88 (2 H, m, C^4***H***), 2.57-2.53 (2 H, m, $C^{4'}$***H***), 1.78-1.75 (4 H, m, $C^{3',5'}$***H***$_{eq}$), 1.57 (4 H, br qd, $C^{3',5'}$***H***$_{ax}$) ppm. $^{13}C\{^1H\}$ NMR (100 MHz; DMSO-D_6; 298 K): δ202.2 (N***C***SS), 173.8 (***C***=O), 99.6 (C^1H), 73.0 (C^3H), 72.1 (C^4H), 72.0 (C^2H), 70.3 (C^5H), 54.3 (O***C***H$_3$), 50.7 ($C^{2',6'}H_2$), 39.9 ($C^{4'}$H), 39.8 (C^6H_2), 28.4 ($C^{3',5'}H_2$) ppm.

Gold(III)-dithiocarbamato complexes

[Au^{III}Br$_2$(SSC-Inp-OEt)] (Au1). A DMF solution (2 mL) of **Zn1** (76.5 mg, 0.15 mmol) was added dropwise under stirring to a DMF solution (2 mL) of K[$AuBr_4$]·$2H_2O$ (170.5 mg, 0.30 mmol) at room temperature. The mixture was stirred for 3 h, after which the color of the solution turned from dark red to orange. Addition of a diethyl ether/*n*-hexane 2:1 solution (60 mL) resulted in the formation of a light orange precipitate. The precipitate was centrifuged and the bulk of supernatant discarded. The residue was subsequently washed with ethanol (15 mL) and a water/ethanol 1:1 solution (2×15 mL), and then dried under vacuum over P_2O_5, yielding the title compound as an orange solid (132.2 mg, 78%). Orange shiny plate-shaped crystals suitable for X-ray crystallography were obtained upon slow evaporation of an acetone solution of the compound. M.p. 243-246°C (dec.). Anal. (%) calcd. for $C_9H_{14}AuBr_2NO_2S_2$ (MM = 589.11 g mol^{-1}): C, 18.35; H, 2.40; N, 2.38; found: C, 18.27; H, 2.39; N, 2.25. FT-IR (CsI disk; 298 K): $\tilde{\nu}_{max}$ 1729 (ν, C=O), 1571 (ν, N–CSS), 1183 (ν, C–OEt), 1040 (ν, O–Et), 1002 (ν_a, SCS), 536 (ν_s, SCS), 413 (ν_a, SAuS), 398 (ν_s, SAuS), 249 (ν_a, BrAuBr), 228 (ν_s, BrAuBr) cm^{-1}. ^1H NMR (400 MHz; DMSO-D_6; 298 K): δ4.09 (2 H, q, OC***H***$_2$), 4.07-4.05 (2 H, m, $C^{2',6'}$***H***$_{eq}$), 3.61 (2 H, td, $C^{2',6'}$***H***$_{ax}$), 2.90 (1 H, tt, $C^{4'}$***H***), 2.08 (2 H, dd, $C^{3',5'}$***H***$_{eq}$), 1.75 (2 H, qd, $C^{3',5'}$***H***$_{ax}$), 1.19 (3 H, t, C***H***$_3$) ppm. $^{13}C\{^1H\}$ NMR (100 MHz; DMSO-D_6; 298 K): δ187.9 (N***C***SS), 173.2 (***C***=O), 60.9 (O***C***H$_2$), 48.6 ($C^{2',6'}H_2$), 39.0 ($C^{4'}$H), 27.3 ($C^{3',5'}H_2$), 14.6 (***C***H$_3$) ppm.

[Au^{III}Br$_2$(SSC-Inp-NH$_2$)] (Au2). A suspension of **Zn2** (42.0 mg, 0.09 mmol) in DMF (8 mL) was added dropwise under stirring to a DMF solution (2 mL) of K[$AuBr_4$]·$2H_2O$ (105.4 mg, 0.18 mmol) at room temperature. The mixture was stirred for 1.5 h, after which the suspension dissolved completely and the color of the solution turned from dark red to orange. Addition of diethyl ether (100 mL) led to the precipitation of an orange residue. The precipitate was centrifuged and the bulk of supernatant discarded. The residue was subsequently washed with methanol (3×15 mL) and then dried under vacuum over P_2O_5, yielding the title compound as an orange solid (69.3 mg, 70%). M.p. 268-272°C (dec.). Anal. (%) calcd. for $C_7H_{11}AuBr_2N_2OS_2$ (MM = 560.07 g mol^{-1}): C, 15.01; H, 1.98; N, 5.00; found: C, 15.06; H, 2.09; N, 4.96. FT-IR (CsI disk; 298 K): $\tilde{\nu}_{max}$ 3408/3176 ($\nu_{a,s}$, NH_2), 1660 (ν, C=O (amide I)), 1620 (δ_{ip}, CNH_2 (amide II)), 1565 (ν, N–CSS), 1007 (ν_a, SCS), 534 (ν_s, SCS), 411 (ν_a, SAuS), 397 (ν_s, SAuS), 232 (ν_a, BrAuBr), 227 (ν_s, BrAuBr) cm^{-1}. ^1H NMR (400 MHz; DMSO-D_6; 298 K): δ7.40 (2 H, s, N***H***$_{cis}$), 6.97 (2 H, s, N***H***$_{trans}$), 4.11 (2 H, dt, $C^{2',6'}$***H***$_{eq}$), 3.57 (2 H, td, $C^{2',6'}$***H***$_{ax}$), 2.62 (1 H, tt, $C^{4'}$***H***), 1.97 (2 H, dd, $C^{3',5'}$***H***$_{eq}$), 1.62 (2 H, qd, $C^{3',5'}$***H***$_{ax}$) ppm. $^{13}C\{^1H\}$ NMR (100 MHz; DMSO-D_6; 298 K): δ 186.9 (N***C***SS), 174.5 (***C***=O), 48.4 ($C^{2',6'}H_2$), 40.3 ($C^{4'}$H), 27.5 ($C^{3',5'}H_2$) ppm.

[Au^{III}Br$_2$(SSC-Inp-GlcN1)] (Au3). A DMF solution (2 mL) of **Zn3** (74.3 mg, 0.09 mmol) was added dropwise under stirring to a DMF solution (2 mL) of K[$AuBr_4$]·$2H_2O$ (110.5 mg, 0.19 mmol) at room temperature. The mixture was stirred for 3 h, after which the color of the solution turned from dark red to orange. Addition of diethyl ether (40 mL) resulted in the formation of an orange precipitate. The precipitate was centrifuged and the bulk of supernatant discarded. The residue was subsequently washed with methanol (3×10 mL) and then dried under vacuum over P_2O_5, yielding the title compound as an orange solid (100.9 mg, 75%). M.p. 210-211°C (dec.). Anal. (%) calcd. for $C_{13}H_{21}AuBr_2N_2O_6S_2$ (MM = 722.21 g mol^{-1}): C, 21.62; H, 2.93; N, 3.88; found: C, 21.78; H, 3.03; N, 3.78. FT-IR (CsI disk; 298 K): $\tilde{\nu}_{max}$ 3306_{br} (ν, OH + NH overlapped), 1636 (ν, C=O (amide I)), 1561 (ν, N–CSS + δ_{ip}, CNH (amide II) overlapped), 1060_{br} (ν, C–OH), 1008 (ν_a, SCS), 575 (ν_s, SCS), 412 (ν_a, SAuS), 392 (ν_s, SAuS), 244 (ν_a, BrAuBr), 227 (ν_s, BrAuBr) cm^{-1}. ^1H NMR (400 MHz; DMSO-D_6; 298 K): δ7.75 (0.4 H, d, N***H*** β), 7.73 (1 H, d, N***H*** α), 6.45 (1.4 H, br s, C^1O***H*** α and β overlapped), 4.91 (1 H, d, C^1***H*** α, $^3J_{1,2}$ = 3.1 Hz), 4.45 (0.4 H, d, C^1***H*** β, $^3J_{1,2}$ = 7.8 Hz), 4.12 (2.8 H, br dt, $C^{2',6'}$***H***$_{eq}$ α and β overlapped), ~4.0 (4.2 H, br s, C^3O***H*** + C^4O***H*** + C^6O***H*** α and β overlapped), 3.69-3.39 (9 H , m, C^2***H*** α + C^4***H*** α and β + C^5***H*** α + C^6H_2 α and β, $C^{2',6'}$***H***$_{ax}$ α and β overlapped), 3.37-3.23 (0.8 H, m, C^2***H*** β + C^3***H*** β overlapped), 3.11-3.04 (1.4 H, m, C^3***H*** α + C^5***H*** β overlapped), 2.75 (1 H, tt, $C^{4'}$***H*** α), 2.63 (0.4 H, tt, $C^{4'}$***H*** β), 1.98-1.91 (2.8 H, br m, $C^{3',5'}$***H***$_{eq}$ α and β overlapped), 1.75-1.67 (2.8 H, br m, $C^{3',5'}$***H***$_{ax}$ α and β overlapped) ppm. $^{13}C\{^1H\}$ NMR (100 MHz; DMSO-D_6; 298 K): δ186.9 (N***C***SS α; β not detected), 172.8 (***C***=O α), 172.7 (***C***=O β), 95.3 (C^1H β), 90.5 (C^1H α), 76.9 (C^5H β), 74.2 (C^3H β), 72.1 (C^5H α), 71.1 (C^3H α), 70.8 (C^4H β), 70.4 (C^4H α), 61.2 (C^6H_2 β), 61.1 (C^6H_2 α), 57.2 (C^2H β), 54.3 (C^2H α), 48.4 ($C^{2',6'}H_2$ α), 48.3 ($C^{2',6'}H_2$ β), 40.5 ($C^{4'}$H β), 40.1 ($C^{4'}$H α), 27.8 ($C^{3',5'}H_2$ α), 27.3 ($C^{3',5'}H_2$ β) ppm. Solution α:β anomers ratio ≈ 2.5:1 (based on the ^1H NMR spectrum).

[Au^{III}Br$_2$(SSC-Inp-GlcN2)] (Au4). A DMF solution (2 mL) of **Zn4** (88.6 mg, 0.11 mmol) was added dropwise under stirring to a DMF solution (3 mL) of K[$AuBr_4$]·$2H_2O$ (128.6 mg, 0.22 mmol) at room temperature. The mixture was stirred for 3 h, after which the color of the solution turned from dark red to orange. Addition of diethyl ether (50 mL) resulted in the formation of an orange precipitate. The precipitate was centrifuged and the bulk of supernatant discarded. The residue was subsequently washed with methanol (3×10 mL) and then dried under vacuum over P_2O_5, yielding the title

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DOI: 10.1039/C8DT01583J

compound as an orange solid (129.1 mg, 81%). M.p. 198-202°C (dec.). Anal. (%) calcd. for $C_{14}H_{23}AuBr_2N_2O_6S_2$ (MM = 736.24 g mol^{-1}): C, 22.84; H, 3.15; N, 3.81; found: C, 22.85; H, 2.98; N, 3.75. FT-IR (CsI disk; 298 K): $\tilde{\nu}_{max}$ 3400_{br}/3296_{br} (ν, OH + NH overlapped), 1649 (ν, C=O (amide I)), 1561 (ν, N–CSS + δ_{ip}, CNH (amide II) overlapped), 1059_{br}/1040_{br} (ν, C–OH + C^1–O–CH_3 overlapped), 1007 (ν_a, SCS), 577 (ν_s, SCS), 410 (ν_a, SAuS), 393 (ν_s, SAuS), 246 (ν_a, BrAuBr), 220 (ν_s, BrAuBr) cm^{-1}. ^{1}H NMR (400 MHz; DMSO-D_6; 298 K): δ 7.86 (1 H, d, N***H***), 4.97 (3 H, br s, C^3O***H*** + C^4O***H*** + C^6O***H*** overlapped), 4.52 (1 H, d, C^1***H***, $^3J_{1,2}$ = 3.5 Hz), 4.12 (2 H, br dt, $C^{2',6'}$***H***$_{eq}$), 3.68-3.27 (7 H, m, $C^{2',6'}$***H***$_{ax}$ + C^2***H*** + C^3***H*** + C^5***H*** + C^6***H***$_2$ overlapped), 3.24 (3 H, s, OC***H***$_3$), 3.12 (1 H, dd, C^4***H***), 2.75 (1 H, tt, $C^{4'}$***H***), 1.98-1.91 (2 H, m, $C^{3',5'}$***H***$_{eq}$), 1.76-1.66 (2 H, m, $C^{3',5'}$***H***$_{ax}$) ppm. ^{13}C{^{1}H} NMR (100 MHz; DMSO-D_6; 298 K): δ 186.9 (N***C***SS), 172.9 (***C***=O), 97.8 (***C***^{1}H), 72.8 (***C***^{5}H), 70.8 (***C***^{3}H), 70.7 (***C***^{4}H), 60.8 (***C***^{6}H$_2$), 54.4 (O***C***H$_3$), 53.7 (***C***^{2}H), 48.4 (***C***$^{2',6'}$H$_2$), 40.3 (***C***$^{4'}$H), 27.7 (***C***$^{3',5'}$H$_2$) ppm. No NMR signals assignable to the β anomer were detected.

[Au^{III}Br$_2$(SSC-Inp-GlcN3)] (Au5). A DMF solution (3 mL) of **Zn5** (101.7 mg, 0.12 mmol) was added dropwise under stirring to a DMF solution (3 mL) of K[$AuBr_4$]·$2H_2O$ (148.8 mg, 0.25 mmol) at room temperature. The mixture was stirred for 2 h, after which the color of the solution turned from dark red to orange. Addition of diethyl ether (60 mL) resulted in the formation of an orange precipitate. The precipitate was centrifuged and the bulk of supernatant discarded. The residue was subsequently washed with methanol (3×10 mL) and then dried under vacuum over P_2O_5, yielding the title compound as an orange solid (161.2 mg, 87%). M.p. 217-220°C (dec.). Anal. (%) calcd. for $C_{14}H_{23}AuBr_2N_2O_6S_2$ (MM = 736.24 g mol^{-1}): C, 22.84; H, 3.15; N, 3.81; found: C, 22.95; H, 3.07; N, 3.78. FT-IR (CsI disk; 298 K): $\tilde{\nu}_{max}$ 3400_{br} (ν, OH + NH overlapped), 1650 (ν, C=O (amide I)), 1555 (ν, N–CSS + δ_{ip}, CNH (amide II) overlapped), 1050_{br} (ν, C–OH + C^1–O–CH_3 overlapped), 1011 (ν_a, SCS), 570 (ν_s, SCS), 398_{br} ($\nu_{a,s}$, SAuS), 254 (ν_a, BrAuBr), 227 (ν_s, BrAuBr) cm^{-1}. ^{1}H NMR (400 MHz; DMSO-D_6; 298 K): δ 7.99 (1 H, dd, N***H***), 4.51 (1 H, d, C^1***H***, $^3J_{1,2}$ = 3.6 Hz), 4.13 (2 H, br d, $C^{2',6'}$***H***$_{eq}$), 3.60 (3 H, br s, C^2O***H*** + C^3O***H*** + C^4O***H*** overlapped), 3.59-3.53 (3 H, m, C^6***H***′ + $C^{2',6'}$***H***$_{ax}$ overlapped), 3.37-3.30 (2 H, m, C^3***H*** + C^5***H*** overlapped), 3.24 (3 H, s, OC***H***$_3$), 3.21-3.17 (1 H, m, C^2***H***), 3.05-2.94 (1 H, m, C^6***H***″), 2.90 (1 H, dd, C^4***H***), 2.71 (1 H, br tt, $C^{4'}$***H***), 1.93 (2 H, td, $C^{3',5'}$***H***$_{eq}$), 1.71 (2 H, qd, $C^{3',5'}$***H***$_{ax}$) ppm. ^{13}C{^{1}H} NMR (100 MHz; DMSO-D_6; 298 K): δ 187.0 (N***C***SS), 172.7 (***C***=O), 99.6 (***C***^{1}H), 73.0 (***C***^{3}H), 72.1 (***C***^{4}H), 71.9 (***C***^{2}H), 70.3 (***C***^{5}H), 54.4 (O***C***H$_3$), 48.4 (***C***$^{2',6'}$H$_2$), 40.5 (***C***$^{4'}$H), 40.1 (***C***^{6}H$_2$), 27.7 (***C***$^{3',5'}$H$_2$) ppm.

Gold(I)-dithiocarbamato complexes

[Au^I(SSC-Inp-GlcN2)(PPh$_3$)] (Au6). A DMF solution (2 mL) of **Zn4** (65.0 mg, 0.08 mmol) was added dropwise under stirring to a DMF solution (2 mL) of [AuCl(PPh_3)] (78.0 mg, 0.16 mmol) at room temperature, and the mixture was stirred for 1 h. Upon addition of diethyl ether (40 mL), the solution turned cloudy and a white solid residue formed. The precipitate was centrifuged and the bulk of supernatant discarded. The sticky residue was subsequently triturated with a 1:1 diethyl ether/dichloromethane mixture (3×10 mL), and then dried under vacuum over P_2O_5, yielding the title compound as a light yellow solid (80.2 mg, 60%). M.p. 188-190°C (dec.). Anal. (%) calcd. for $C_{32}H_{38}AuN_2O_6PS_2$ (MM = 838.72 g mol^{-1}): C, 45.83; H, 4.57; N, 3.34; found: C, 45.92; H, 4.63; N, 3.29. FT-IR (CsI disk; 298 K): $\tilde{\nu}_{max}$ 3424_{br} (ν, OH + NH overlapped), 1651 (ν, C=O (amide I)), 1545 (δ_{ip}, CNH (amide II)), 1490 (ν, N–CSS), 1100 ($\nu_{q\ vib}$, P–Ph_3), 1056_{br} (ν, C–OH + C^1–O–CH_3 overlapped), 1001/914 (ν, S=C–S), 710/694 ($\nu_{r\ vib}$, P–Ph_3), 578 (ν, C–S), 539/509/500 ($\delta_{y\ vib}$, P–Ph_3), 427 ($\nu_{t\ vib}$, P–Ph_3), 380 (ν, Au–S), 273/240 ($\delta_{x\ vib}$, P–Ph_3 + ν, Au–P) cm^{-1}. ^{1}H NMR (400 MHz; DMSO-D_6; 298 K): δ 7.80 (1 H, d, N***H***), 7.59-7.50 (15 H, m, C***H*** Ph), 5.01 (1 H, d, C^4O***H***), 4.90 (2 H, br dt, $C^{2',6'}$***H***$_{eq}$), 4.71 (1 H, d, C^3O***H***), 4.55 (1 H, d, C^6O***H***), 4.53 (1 H, d, C^1***H***, $^3J_{1,2}$ = 3.1 Hz), 3.68-3.61 (2 H, m, C^2***H*** + C^6***H***′ overlapped), 3.49-3.42 (2 H, m, C^3***H*** + C^6***H***″ overlapped), 3.33-3.26 (3 H, m, $C^{2',6'}$***H***$_{ax}$ + C^5***H*** overlapped), 3.24 (3 H, s, OC***H***$_3$), 3.15-3.09 (1 H, m, C^4***H***), 2.59-2.53 (1 H, br tt, $C^{4'}$***H***), 1.83-1.75 (2 H, m, $C^{3',5'}$***H***$_{eq}$), 1.65-1.55 (2 H, m, $C^{3',5'}$***H***$_{ax}$) ppm. ^{13}C{^{1}H} NMR (100 MHz; DMSO-D_6; 298 K): δ 202.2 (N***C***SS), 173.9 (***C***=O), 133.5 (d, *o*-***C***H, $^2J_{C,P}$ = 14.3 Hz), 131.9 (d, *p*-***C***H, $^4J_{C,P}$ = 2.0 Hz), 130.1 (d, ***C***P, $^1J_{C,P}$ = not detectable due to overlapping), 129.5 (d, *m*-***C***H, $^3J_{C,P}$ = 11.3 Hz), 97.9 (***C***^{1}H), 72.8 (***C***^{5}H), 70.8 (***C***^{3}H), 70.7 (***C***^{4}H), 60.8 (***C***^{6}H$_2$), 54.5 (O***C***H$_3$), 53.8 (***C***^{2}H), 50.8 (***C***$^{2',6'}$H$_2$), 40.3 (***C***$^{4'}$H), 28.4 (***C***$^{3',5'}$H$_2$) ppm. ^{31}P{^{1}H} NMR (162 MHz; DMSO-D_6; 298 K): δ 36.5 (Au***P***Ph_3) ppm.

[Au^I(SSC-Inp-GlcN3)(PPh$_3$)] (Au7). A DMF solution (2 mL) of **Zn5** (67.0 mg, 0.08 mmol) was added dropwise under stirring to a DMF solution (2 mL) of [AuCl(PPh_3)] (80.4 mg, 0.16 mmol) at room temperature, and the mixture was stirred for 1 h. Upon addition of diethyl ether (40 mL), the solution turned cloudy and a white solid residue formed. The precipitate was centrifuged and the bulk of supernatant discarded. The sticky residue was subsequently triturated with a 1:1 diethyl ether/dichloromethane mixture (3×10 mL), and then dried under vacuum over P_2O_5, yielding the title compound as a light yellow solid (95.2 mg, 70%). M.p. 162-166°C (dec.). Anal. (%) calcd. for $C_{32}H_{38}AuN_2O_6PS_2$ (MM = 838.72 g mol^{-1}): C, 45.83; H, 4.57; N, 3.34; found: C, 45.96; H, 4.56; N, 3.39. FT-IR (CsI disk; 298 K): $\tilde{\nu}_{max}$ 3429_{br} (ν, OH + NH overlapped), 1654 (ν, C=O (amide I)), 1544 (δ_{ip}, CNH (amide II)), 1483 (ν, N–CSS), 1101 ($\nu_{q\ vib}$, P–Ph_3), 1051_{br} (ν, C–OH + C^1–O–CH_3 overlapped), 1000/914 (ν, S=C–S), 711/694 ($\nu_{r\ vib}$, P–Ph_3), 577 (ν, C–S), 539/510/500 ($\delta_{y\ vib}$, P–Ph_3), 437 ($\nu_{t\ vib}$, P–Ph_3), 397 (ν, Au–S), 262/241 ($\delta_{x\ vib}$, P–Ph_3 + ν, Au–P) cm^{-1}. ^{1}H NMR (400 MHz; DMSO-D_6; 298 K): δ 7.98 (1 H, dd, N***H***), 7.60-7.52 (15 H, m, C***H*** Ph), 4.98 (1 H, d, C^4O***H***), 4.89 (2 H, br d, $C^{2',6'}$***H***$_{eq}$), 4.82 (1 H, d, C^3O***H***), 4.76 (1 H, d, C^2O***H***), 4.51 (1 H, d, C^1***H***, $^3J_{1,2}$ = 3.7 Hz), 3.55 (1 H, ddd, C^6***H***′), 3.38-3.33 (2 H, m, C^3***H*** + C^5***H*** overlapped), 3.24 (3 H, s, OC***H***$_3$), 3.24-3.17 (3 H, m, C^2***H*** + $C^{2',6'}$***H***$_{ax}$ overlapped), 3.01 (1 H, td, C^6***H***″), 2.93-2.87 (1 H, m, C^4***H***), 2.55 (1 H, br tt, $C^{4'}$***H***), 1.79-1.75 (2 H, m, $C^{3',5'}$***H***$_{eq}$), 1.65-1.56 (2 H, m, $C^{3',5'}$***H***$_{ax}$) ppm. ^{13}C{^{1}H} NMR (100 MHz; DMSO-D_6; 298 K): δ 203.6 (N***C***SS), 173.9 (***C***=O), 133.7 (d, *o*-***C***H, $^2J_{C,P}$ = 15.7 Hz), 131.9 (d, *p*-***C***H, $^4J_{C,P}$ = 2.8 Hz), 129.8 (d, ***C***P, $^1J_{C,P}$ = not detectable due to overlapping), 129.5 (d, *m*-***C***H, $^3J_{C,P}$ = 11.9 Hz), 99.6 (***C***^{1}H), 73.0 (***C***^{3}H), 72.1 (***C***^{4}H),

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DOI: 10.1039/C8DT01583J

72.0 (***C***^{2}H), 70.3 (***C***^{5}H), 54.3 (O***C***H$_3$), 51.2 (***C***$^{2',6'}$H$_2$), 40.5 (***C***$^{4'}$H), 40.1 (***C***^{6}H$_2$), 28.5 (***C***$^{3',5'}$H$_2$) ppm. ^{31}P{^{1}H} NMR (162 MHz; DMSO-D$_6$; 298 K): δ 36.5 (Au***P***Ph$_3$) ppm.

Platinum(II)-dithiocarbamato complexes

[Pt^{II}(SSC-Inp-GlcN2)$_2$] (Pt1). A DMF solution (2 mL) of **Zn4** (15.2 mg, 0.02 mmol) was added dropwise under stirring to a DMF solution (2 mL) of (PPh$_4$)[PtCl$_3$(NH$_3$)] (24.4 mg, 0.04 mmol) at room temperature. The mixture was stirred for 16 h and then treated with diethyl ether (40 mL). The resulting cloudy solution was stored at 4°C for 1 h, leading to the formation of a yellow precipitate. The precipitate was centrifuged and the bulk of supernatant discarded. The residue was subsequently washed with a 1:1 methanol/dichloromethane solution (3×10 mL) and then dried under vacuum over P_2O_5, yielding the title compound as a yellow solid (12.2 mg, 35%). M.p. 195-198°C (dec.). Anal. (%) calcd. for $C_{28}H_{46}N_4O_{12}PtS_4$ (MM = 954.02 g mol^{-1}): C, 35.25; H, 4.86; N, 5.87; found: C, 35.14; H, 4.95; N, 5.81. FT-IR (CsI disk; 298 K): $\tilde{\nu}_{max}$ 3401$_{br}$ (ν, OH + NH overlapped), 1650 (ν, C=O (amide I)), 1523 (ν, N–CSS + δ_{ip}, CNH (amide II) overlapped), 1055$_{br}$ (ν, C–OH + C^1–O–CH$_3$ overlapped), 1005 (ν_a, SCS), 577 (ν_s, SCS), 365 (ν_a, PtS$_4$) cm^{-1}. ^{1}H NMR (400 MHz; DMSO-D$_6$; 298 K): δ 7.84 (2 H, d, N***H***), 5.01 (2 H, d, C^{4}O***H***), 4.73 (2 H, d, C^{3}O***H***), 4.56-4.52 (4 H, m, C^{6}O***H*** + C^1***H*** overlapped), 4.20-4.16 (4 H, br d, C$^{2',6'}$***H***$_{eq}$), 3.67-3.62 (4 H, m, C^2***H*** + C^6***H***′ overlapped), 3.49-3.40 (4 H, m, C^3***H*** + C^6***H***″ overlapped), 3.33-3.24 (6 H, m, C^5***H*** + C$^{2',6'}$***H***$_{ax}$ overlapped), 3.24 (6 H, s, OC***H***$_3$), 3.15-3.09 (2 H, m, C^4***H***), 2.64 (2 H, tt, C$^{4'}$***H***), 1.90-1.83 (4 H, br m, C$^{3',5'}$***H***$_{eq}$), 1.60-1.51 (4 H, br m, C$^{3',5'}$***H***$_{ax}$) ppm. ^{13}C{^{1}H} NMR (100 MHz; DMSO-D$_6$; 298 K): δ 207.2 (N***C***SS), 173.4 (***C***=O), 97.8 (***C***^{1}H), 72.8 (***C***^{5}H), 70.8 (***C***^{3}H), 70.7 (***C***^{4}H), 60.8 (***C***^{6}H$_2$), 54.4 (O***C***H$_3$), 53.8 (***C***^{2}H), 46.1 (***C***$^{2',6'}$H$_2$), 40.4 (***C***$^{4'}$H), 27.9 (***C***$^{3',5'}$H$_2$) ppm. No NMR signals assignable to the β anomer were detected.

[Pt^{II}(SSC-Inp-GlcN3)$_2$] (Pt2). A DMF solution (2 mL) of **Zn5** (34.8 mg, 0.04 mmol) was added dropwise under stirring to a DMF solution (2 mL) of (PPh$_4$)[PtCl$_3$(NH$_3$)] (55.6 mg, 0.08 mmol) at room temperature. The mixture was stirred for 16 h and then treated with diethyl ether (40 mL). The resulting cloudy solution was stored at 4°C for 1 h, leading to the formation of an oily yellow residue. The residue was centrifuged and the bulk of supernatant discarded. The oily residue was subsequently triturated with dichloromethane (10 mL) to obtain a yellow solid which was filtered off, washed with dichloromethane (3×10 mL), and then dried under vacuum over P_2O_5, yielding the title compound as a yellow solid (40.0 mg, 49%). M.p. 217-220°C (dec.). Anal. (%) calcd. for $C_{28}H_{46}N_4O_{12}PtS_4$ (MM = 954.02 g mol^{-1}): C, 35.25; H, 4.86; N, 5.87; found: C, 35.34; H, 5.06; N, 5.84. FT-IR (CsI disk; 298 K): $\tilde{\nu}_{max}$ 3393$_{br}$/3324$_{br}$ (ν, OH + NH overlapped), 1647 (ν, C=O (amide I)), 1554 (ν, N–CSS + δ_{ip}, CNH (amide II) overlapped), 1048$_{br}$ (ν, C–OH + C^1–O–CH$_3$ overlapped), 1007 (ν_a, SCS), 566 (ν_s, SCS), 350 (ν_a, PtS$_4$) cm^{-1}. ^{1}H NMR (400 MHz; DMSO-D$_6$; 298 K): δ 7.99 (2 H, dd, N***H***), 4.98 (2 H, d, C^{4}O***H***), 4.83 (2 H, d, C^{3}O***H***), 4.76 (2 H, d, C^{2}O***H***), 4.51 (2 H, d, C^1***H***, $^3J_{1,2}$ = 3.3 Hz), 4.18 (4 H, br d, C$^{2',6'}$***H***$_{eq}$), 3.55 (2 H, br dd, C^6***H***′), 3.37-3.34 (4 H, m, C^3***H*** + C^5***H*** overlapped), 3.24 (6 H, s, OC***H***$_3$), 3.24-3.19 (6 H, m, C^2***H*** + C$^{2',6'}$***H***$_{ax}$ overlapped), 3.05-2.95 (2 H, m, C^6***H***″), 2.90 (2 H, br td, C^4***H***), 2.60 (2 H, br tt, C$^{4'}$***H***), 1.86-1.83 (4 H, m, C$^{3',5'}$***H***$_{eq}$), 1.57-1.52 (4 H, m, C$^{3',5'}$***H***$_{ax}$) ppm. ^{13}C{^{1}H} NMR (100 MHz; DMSO-D$_6$; 298 K): δ 207.2 (N***C***SS), 173.3 (***C***=O), 99.7 (***C***^{1}H), 73.0 (***C***^{3}H), 72.1 (***C***^{4}H), 72.0 (***C***^{2}H), 70.3 (***C***^{5}H), 54.3 (O***C***H$_3$), 46.1 (***C***$^{2',6'}$H$_2$), 40.7 (***C***$^{4'}$H), 40.1 (***C***^{6}H$_2$), 28.0 (***C***$^{3',5'}$H$_2$) ppm.

Conflicts of interest

To the best of our knowledge, there are no conflicts of interest to declare.

Acknowledgements

Financial support by NUI Galway (*College of Science Scholarship 2014* to AP; *Millennium Fund Minor Project 2013* to LR), Irish Research Council (*Postgraduate Scholarship GOIPG/2015/2961* to AP), and COST Action CM1105 "Functional metal complexes that bind to biomolecules" is gratefully acknowledged.

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DOI: 10.1039/C8DT01583J

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