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### ► To cite this version:

Mauro Safir-Filho, Thomas Scattolin, Pascal Dao, Nikolaos V Tzouras, Rachid Benhida, et al.. Straightforward synthetic route to gold(I)-thiolato glycoconjugate complexes bearing NHC ligands (NHC = N-heterocyclic carbene) and their promising anticancer activity. *New Journal of Chemistry*, inPress, 10.1039/D1NJ02117F . hal-03225368

**HAL Id: hal-03225368**

**<https://hal.science/hal-03225368>**

Submitted on 12 May 2021

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## ARTICLE

# Straightforward synthetic route to gold(I)-thiolato glycoconjugate complexes bearing NHC ligands (NHC = N-heterocyclic carbene) and their promising anticancer activity

Received 00th January 20xx,  
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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A simple and eco-friendly route to gold-NHC complexes bearing different thiosugars is reported. The reaction between [Au(NHC)Cl] precursors, the thiosugars and a weak base proceeds under air using technical grade acetone under mild conditions (60 °C, 1h). The one-pot synthesis of the same complexes starting from the corresponding imidazolium salts was also investigated. The obtained complexes showed strong cytotoxic activities against selected cancer cell lines with IC<sub>50</sub> values in the submicromolar to low micromolar concentration range.

## Introduction

Since the serendipitous discovery of cisplatin, many researchers in the field of coordination and organometallic chemistry of middle and late-transition metals have contributed to the development of new promising anticancer agents.<sup>1</sup> Although the research conducted on platinum complexes has led to the commercialization of the well-known second- and third-generation platinum-based antineoplastic drugs (*e.g.* carboplatin and oxaliplatin),<sup>2</sup> their ineffectiveness against different types of tumours or the development of drug resistance observed in many patients<sup>3</sup> has prompted numerous scientists to explore the anticancer properties of complexes containing metals other than platinum.

In this context, the remarkable *in-vitro*, *ex-vivo* and *in-vivo* anticancer activity exhibited by some categories of mono- and poly-nuclear gold,<sup>4</sup> ruthenium<sup>5</sup> and palladium<sup>6</sup> complexes has proven particularly encouraging. Many of these compounds are considered attractive as they display a completely different mechanism of action compared to classical platinated agents and therefore are often effective toward cisplatin-resistant cancer cells.<sup>7</sup>

Among the various metal derivatives mentioned above, a place of absolute importance in medicinal chemistry is covered

by gold(I) complexes, which are currently used as therapeutic drugs for the treatment of rheumatoid arthritis.<sup>8</sup> Results addressing their activity as antibiotics and chemotherapeutic agents are so encouraging that a number of most promising compounds are currently under clinical trials.<sup>1,4</sup> In-depth studies carried out in recent decades have shown that anticancer gold complexes have a wide range of cellular targets such as mitochondria and proteins playing relevant functional roles (*e.g.* thioredoxin reductase, poly (ADP-ribose) polymerase (PARP-1), cathepsins, proteasome and protein tyrosine phosphatase).<sup>4</sup>

In this respect, the pioneering studies carried out by Mirabelli *et al.* on the 1-thio-β-D-glucopyranose-2,3,4,6-tetraacetato-S(triethylphosphine) gold(I) complex, which is commonly known as auranofin, has played a crucial role in the explosion of gold anticancer agents.<sup>9</sup> This compound, which was introduced on the market in the 1980s as an anti-arthritis drug, has recently received approval by FDA for clinical phase II for cancer therapy.<sup>10</sup>

Although the mechanism of action of auranofin is still being debated, it appears to involve the inhibition of thioredoxin reductase (Trx), a key protein overexpressed by tumor cells, in which the metal center selectively and covalently bind the selenium atom present in this category of selenocysteine enzymes.<sup>11</sup> From a composition perspective, auranofin presents triethylphosphine as an ancillary ligand and the thio-β-D-glucopyranose-2,3,4,6-tetraacetate actor ligand. The presence of a glycosidic unit is an important factor in the design of new chemotherapeutic agents since the ability of carbohydrates to act as active sites for molecular recognition, their high water-solubility and above all the more efficient uptake in tumor cells with respect to the healthy ones (Warburg's effect) are well-known characteristics of these moieties.<sup>12</sup>

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† Electronic Supplementary Information (ESI) available: Synthetic procedure, characterisation and biological data. For ESI See DOI: 10.1039/x0xx00000x

However, recent studies have demonstrated that the interaction between auranofin and some model proteins containing free thiol groups leads to the release of the thio- $\beta$ -D-glucopyranose-2,3,4,6-tetraacetate ligand and the formation of a covalent bond between the protein and the  $[\text{Au-PEt}_3]^+$  residue.<sup>13</sup>

With the aim of improving the performance of auranofin, many research groups have focused on the synthesis of new gold(I) derivatives by varying the two ligands present in the parent compound. Casini and co-workers reported in 2011 the preparation of Au(I)-thiolato glycoconjugate complexes bearing water-soluble phosphines such as 1,3,5-triaza-7-phosphaadamantane (PTA) and 3,7-diacetyl-1,3,7-triaza-5-phosphabicyclo[3.3.1]nonane (DAPTA).<sup>14</sup> These complexes proved to be less active than auranofin towards A2780 and A2780cis cell lines. More recently, Messori and colleagues have examined the antitumor activity of gold(I) complexes in which the thiosugar unit was replaced by halides (Cl and I), maintaining the original triethylphosphine ligand.<sup>15</sup>  $[(\text{PEt}_3)\text{AuCl}]$  and  $[(\text{PEt}_3)\text{AuI}]$ , despite being very reactive toward oligo- and polynucleotides, they showed cytotoxicity and a DNA-independent mechanism of action analogous to auranofin. Inspired by these interesting previous studies, herein we report the synthesis and anticancer activity of gold(I)-NHC (NHC = N-heterocyclic carbene) complexes bearing different thiosugars.

Although few complexes of this potentially huge family have already been synthesized,<sup>16</sup> and only a very limited number have been tested *in vitro*,<sup>16c-f</sup> we believe that a systematic study examining several thiosugars and various NHCs can provide valuable information on their anticancer properties.

It should be noted that NHC ligands represent an attractive alternative to phosphines as they possess a heightened ability to form strong bonds with most transition metals, rendering them promising ligands for metallodrug design.<sup>17</sup> The particular stability of gold-NHC complexes, even in a physiological environment, has been exploited for the design of promising anticancer agents.<sup>4</sup> Moreover, in the last decade numerous efforts have been devoted to the development of simple and sustainable synthetic strategies to metal-NHC complexes.<sup>18</sup> More specifically, we have demonstrated the possibility of transforming classical azolium salts into the carbene complexes of interest, using weak bases (e.g.  $\text{K}_2\text{CO}_3$ , NaOAc and  $\text{NEt}_3$ ), operating under aerobic conditions and with eco-friendly solvents (e.g. acetone, ethanol and ethyl acetate).<sup>19</sup> This approach, which we have coined the *weak base route*, has recently prove surprisingly effective also for the activation of C-H, N-H and S-H bonds under mild conditions.<sup>19b-i</sup>

Based on this background, we propose here the synthesis of the target complexes taking advantage of this simple methodology.

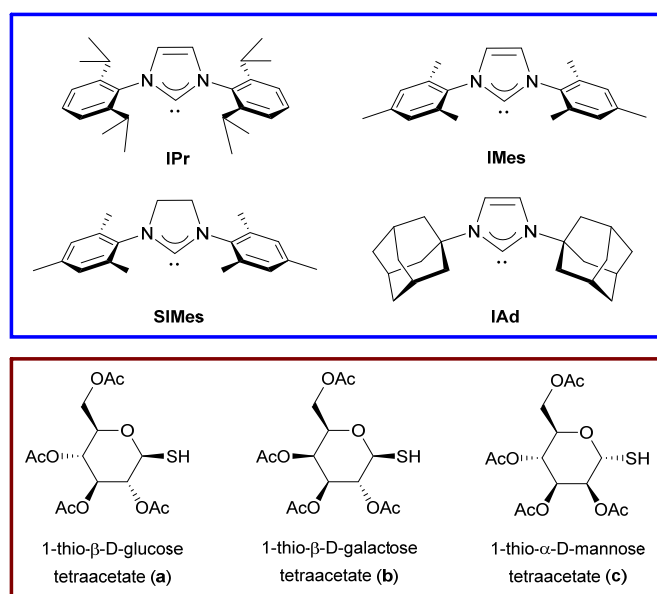
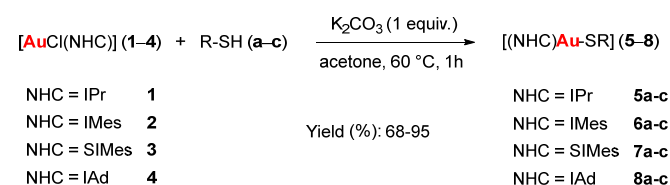
## Results and Discussion

### Synthesis of $[\text{Au}(\text{NHC})(\text{S-R})]$ complexes

In order to carry out our desired systematic study, we have chosen to synthesize gold(I)-thiolate complexes using 4

different NHC ligands (IPr, IMes, SIMes and IAd) and 3 different thiosugars (1-thio- $\beta$ -D-glucose tetraacetate, 1-thio- $\beta$ -D-galactose tetraacetate and 1-thio- $\alpha$ -D-mannose tetraacetate). The reaction conditions yielding complexes **5a-c**, **6a-c**, **7a-c** and **8a-c** in high yields and purity were developed using complex **5a** as the model target. This compound had previously been synthesized by Nolan and co-workers using two different approaches: a)  $[\text{AuCl}(\text{IPr})]$  in the presence of 1-thio- $\beta$ -D-glucose tetraacetate using NaH as base; b)  $[\text{Au}(\text{OH})(\text{IPr})]$  reacted with 1-thio- $\beta$ -D-glucose tetraacetate.<sup>16b-c</sup> Both methods required strictly inert conditions and the use of deleterious solvents such as  $\text{CH}_2\text{Cl}_2$ .

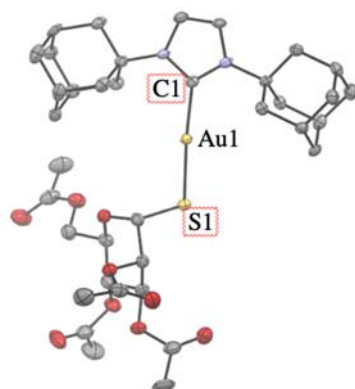
Inspired by recent work on the *weak base route*, we found that complex **5a** can be easily synthesized by reaction between  $[\text{AuCl}(\text{NHC})]$  (**1**) and 1-thio- $\beta$ -D-glucose tetraacetate (**a**) in the presence of 1 equiv. of  $\text{K}_2\text{CO}_3$  (weak base) and using technical grade acetone (green acetone) as solvent. Operating at 60 °C, under air, it is possible to completely convert the starting reagents in the desired complex **5a** within 1 hour. The same reaction conditions were used for the synthesis of all 12 complexes examined herein, with yields in the range 68-95 % (Scheme 1). The very mild reaction conditions and operations being carried out in air render the synthesis of such a library a very simple and time-, resource-efficient endeavour.



**Scheme 1.** Synthesis of gold-NHC thiolato complexes **5-8**

Complexes **5-8** were fully characterized by NMR ( $^1\text{H}$  and  $^{13}\text{C}$ ) and elemental analysis. The  $^1\text{H}$  NMR spectra highlight the diagnostic shifts of the final complexes signals with respect to the starting

reagents and the disappearance of the indicative signal attributable to the S-H group at 2.28-2.35 ppm. Furthermore, for complex **8c**, X-ray diffraction study of single crystals grown from tetrahydrofuran and pentane, permit the unambiguous atom connectivity to be established.



**Figure 1.** X-ray molecular structure of **8c**, showing thermal displacement ellipsoids at the 50% probability level with hydrogen and solvent atoms omitted for clarity. Selected bond lengths (Å) and angles (°): (C<sub>1</sub>-Au<sub>1</sub> = 2.024(6), Au<sub>1</sub>-S<sub>1</sub> = 2.2826(16), C<sub>1</sub>-Au<sub>1</sub>-S<sub>1</sub> = 174.44(16)). CCDC: 2072449

With the aim of further simplifying the synthetic procedure to gold-NHC thiolates, we tested the direct conversion of the azolium salts (NHC-HCl), which are the classical precursors of NHC ligands, into the desired complexes. Gratifyingly, by first reacting the azolium salt with the [AuCl(DMS)] precursor in the presence of K<sub>2</sub>CO<sub>3</sub> (1 equiv.) for 1h in acetone at 60 °C and subsequently adding 1-thio- $\alpha$ -D-mannose tetraacetate (**c**) as a representative thiosugar and an additional equivalent of base, it was possible to obtain the final complexes in yields comparable to the two-step process (Scheme 2).



**Scheme 2.** One-pot synthesis of gold-NHC thiolato complexes

### Cytotoxicity

Three cancer cell lines representing highly relevant human malignancies, namely A549 lung carcinoma, HT-29 colon adenocarcinoma, and MDA-MB-231 breast carcinoma, were selected to evaluate the anticancer potential of complexes **5-8**. All complexes showed strong antiproliferative effects with IC<sub>50</sub> values in the sub-micromolar to low micromolar range (see Table 1). With IC<sub>50</sub> values in the range of 0.7 to 2.4  $\mu$ M, MDA-

MB-231 cells were most sensitive towards the compounds (IC<sub>50</sub> values in the range of 1.3 to 3.9  $\mu$ M for HT-29 cells and 2.3 to 6.7  $\mu$ M for A-549 cells). The experimental assay conditions required a 96 h incubation period with MDA-MB-231 cells, while for A-549 and HT-29 cells the exposure period was 72 h. The results therefore indicate that the biological activity of the compounds increases over time.

Comparing the results obtained with the individual complexes, a slight preference for glucose as thiosugar ligand was noted. Comparison with results obtained for other gold(I)-NHC complexes in previous reports using similar experimental conditions,<sup>4g,20</sup> confirms the overall improvement of cytotoxic activity exhibited by complexes **5-8**.

**Table 1** Cytotoxic activity of NHC-Au-thiolato glycoconjugate complexes **5-8**

Complex	IC <sub>50</sub> ( $\mu$ M) <sup>a</sup>		
	A-549	HT-29	MDA-MB-231
<b>5a</b>	3.0±0.2	1.6±0.1	0.8±0.1
<b>5b</b>	3.7±0.5	1.3±0.2	0.8±0.2
<b>5c</b>	4.5±0.9	2.3±0.6	1.5±0.0
<b>6a</b>	2.2±0.7	1.0±0.3	0.7±0.2
<b>6b</b>	2.9±0.9	1.9±0.7	1.2±0.6
<b>6c</b>	3.4±0.7	1.8±0.5	1.3±0.5
<b>7a</b>	2.3±0.8	1.2±0.6	1.0±0.4
<b>7b</b>	3.7±0.4	2.0±0.3	1.5±0.3
<b>7c</b>	3.4±0.9	1.6±0.5	1.3±0.6
<b>8a</b>	5.8±0.3	3.4±0.1	2.2±0.5
<b>8b</b>	6.7±0.5	3.9±0.4	2.4±0.5
<b>8c</b>	5.7±1.0	3.6±0.3	2.1±0.2

IC<sub>50</sub> values were obtained from 3 independent experiments. Experimental errors were calculated as standard deviations.

It should be remembered that in a previous study conducted by Riches and Nolan on a panel of cancer cell lines (LNCaP and P21PZ prostate carcinoma, MDA MB231 and B42-Cl16 breast carcinoma, MGH-U1 bladder carcinoma) and normal cells (SUV-HUC-1 and P21TZ), a good cytotoxicity of both **5a** and its chloride precursor **1a** was already observed in all examined cancer cell lines.<sup>16c</sup> More in detail, **5a** was generally more active than **1a** and Au(I) neutral derivatives bearing other biocompatible units.

Although **5a** and **1a** have proved to be cytotoxic also towards normal cells, it is widely recognized that an *in vivo* study is essential to clarify the real toxicity of the compounds and their effectiveness in reducing tumor mass.

Trx inhibition and the mechanism of action of an NHC-Au-thioglyucose complex (NHC = 1,3-dibenzyl-4,5-diphenyl-imidazolylidene)<sup>19g-h</sup> and other non-glycosidic NHC-Au-thiolates<sup>20</sup> have recently been explored by some research groups.

These studies examined the ability of gold-thiolate complexes to inhibit the mammalian thioredoxin reductase enzyme, showing IC<sub>50</sub> values in the low micromolar range and thus indicating that apoptosis induction through elevated oxidative stress could be their main mechanism of action.

## Conclusions

In summary, we have reported a simple and eco-friendly procedure for the synthesis of 12 gold-NHC thiolate complexes (5-8). In particular, these derivatives can be obtained in high yields and purity by reaction of a [Au(NHC)Cl] precursor with a thiosugar in the presence of a weak base such as K<sub>2</sub>CO<sub>3</sub>. All reactions proceed, under air, in technical grade acetone under mild conditions (60 °C, 1h). Interestingly, we have shown that these compounds can be obtained directly from the corresponding azolium salts in a one-pot procedure.

Complexes 5-8 showed strong cytotoxic activities against a panel of selected highly relevant cancers from different tissues (lung, colon, breast). Further evaluation of the anticancer potential of this class of gold organometallics is warranted and is the subject of ongoing studies in our laboratories.

In particular, based on the promising *in vivo* results obtained by Zhu and Tacke with an NHC-Au-thioglyucose complex (NHC = 1,3-dibenzyl-4,5-diphenyl-imidazolylidene)<sup>19g-h</sup> we believe that a future work dealing with the *in vivo* efficacy of the most active compounds on xenograft models could give valuable information on the real potential of these gold(I) derivatives.

## Experimental

### Materials and methods

All complex syntheses were performed in air. Solvents and all other reagents were purchased and used as received without further purification unless otherwise stated. 1-thio-β-D-galactose tetraacetate and 1-thio-α-D-mannose tetraacetate were synthesized according to the procedure described by Doyle L. M. et al.<sup>21</sup> <sup>1</sup>H and <sup>13</sup>C{<sup>1</sup>H} Nuclear Magnetic Resonance (NMR) spectra were recorded on a Bruker Advance 400 Ultrashield spectrometer at 298K. Chemical shifts (expressed by parts per million) are referenced to residual solvent peaks.

Elemental analysis was carried out on a Flash EA 1112 series Thermo Finnigan elementary analyzer piloted by Eager Xperience software. The CHN oven was set up at 970°C, and the analysis were performed using helium (140 mL/min) as the vector gas and a catarameter as detector.

X-ray intensity data were collected at 100 K, on a Rigaku Oxford Diffraction Supernova Dual Source diffractometer equipped with an Atlas CCD detector.

### General procedure for complexes 5-8

The precursor [Au(NHC)Cl] 1-4 (100 mg), the thiosugar a-c (1 equiv.) and potassium carbonate (1 equiv.) were dissolved in technical grade acetone (0.05 M) and heated at 60°C for 1 hour. Then, the solvent was evaporated under vacuum, the crude product was dissolved in CH<sub>2</sub>Cl<sub>2</sub> and filtered through a pad of silica to remove the inorganic salts. The filtrate was concentrated in vacuo and triturated with pentane to afford the desired complexes as white powders.

### One-pot procedure for complexes 5-8

The NHC-HCl salt (100 mg), chloro(dimethylsulfide)gold(I) ([Au(DMS)Cl], 1 equiv.) and potassium carbonate (1 equiv.) were dissolved in technical grade acetone (0.05 M) and heated at 60°C for 1 hour. Afterwards, the thiosugar a-c (1 equiv.) and another portion of potassium carbonate (1 equiv.) were added, and the reaction was heated at 60°C for 1 additional hour.

The solvent was evaporated under vacuum, the crude product was dissolved in CH<sub>2</sub>Cl<sub>2</sub> and filtered through a pad of silica to remove the inorganic salts. The filtrate was concentrated in vacuo and triturated with pentane to afford the respective complexes as white powders.

### Synthesis of [Au(IPr)(1-thio-β-D-glucose tetraacetate)] (5a)

Yield general procedure: 89%

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.54 (t, *J* = 7.8 Hz, 1H), 7.34 – 7.31 (m, 4H), 7.15 (s, 2H), 4.93 (t, *J* = 9.3 Hz, 1H), 4.69 (t, *J* = 9.8 Hz, 1H), 4.55 (d, *J* = 9.6 Hz, 1H), 4.42 (t, *J* = 9.4 Hz, 1H), 3.93 (dd, *J* = 11.9, 5.5 Hz, 1H), 3.83 (dd, *J* = 12.0, 2.9 Hz, 1H), 3.37 (ddd, *J* = 10.0, 5.5, 2.9 Hz, 1H), 2.64 – 2.56 (m, 4H), 2.04 (s, 3H), 2.01 (s, 3H), 1.95 (s, 3H), 1.87 (s, 3H), 1.36 (dd, *J* = 6.7, 5.4 Hz, 12H), 1.22 (dd, *J* = 6.8, 5.5 Hz, 12H).

<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 186.9, 171.1, 170.5, 169.7, 169.3, 146.0, 145.9, 134.3, 130.8, 124.4, 124.3, 122.9, 82.7, 77.4, 75.2, 74.4, 69.7, 63.8, 29.0, 28.9, 24.6, 24.5, 24.3, 24.2, 21.1, 21.0, 20.9, 20.9.

Elemental Analysis for C<sub>41</sub>H<sub>55</sub>AuN<sub>2</sub>O<sub>9</sub>S (%): found C 51.74, H 5.65, N 2.95; calculated: C 51.90, H 5.84, N 2.95.

The data are in agreement with the reported values.<sup>16b-c</sup>

### Synthesis of [Au(IPr)(1-thio-β-D-galactose tetraacetate)] (5b)

Yield general procedure: 91%

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.49 (t, *J* = 7.8 Hz, 2H), 7.29 (d, *J* = 7.8 Hz, 4H), 7.16 (s, 2H), 5.27 (d, *J* = 2.6 Hz, 1H), 4.93 (t, *J* = 9.8 Hz, 1H), 4.75 (dd, *J* = 10.1, 3.4 Hz, 1H), 4.36 (d, *J* = 9.5 Hz, 1H), 3.92 (d, *J* = 7.2 Hz, 1H), 3.48 (t, *J* = 7.5 Hz, 1H), 2.61 – 2.54 (m, 4H), 2.06 (s, 3H), 2.04 (s, 3H), 1.92 (s, 3H), 1.87 (s, 3H), 1.34 (d, *J* = 6.8 Hz, 12H), 1.22 (dd, *J* = 6.9, 1.9 Hz, 12H).

<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 186.5, 170.7, 170.6, 170.5, 169.7, 145.9, 145.9, 134.3, 130.6, 124.3, 124.3, 122.9, 83.7, 73.5, 72.7, 72.5, 67.5, 61.1, 28.9, 24.6, 24.1, 24.1, 21.2, 20.9, 20.8.

Elemental Analysis for C<sub>41</sub>H<sub>55</sub>AuN<sub>2</sub>O<sub>9</sub>S (%): found C 51.92, H 5.80, N 2.96; calculated: C 51.90, H 5.84, N 2.95.

### Synthesis of [Au(IPr)(1-thio-α-D-mannose tetraacetate)] (5c)

Yield general procedure: 83%; Yield one-pot procedure: 81%

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.48 (t, *J* = 7.8 Hz, 2H), 7.30 – 7.26 (m, 4H), 7.15 (s, 2H), 5.69 (dd, *J* = 10.0, 3.4 Hz, 1H), 5.24 (d, *J* = 1.5 Hz, 1H), 5.17 (t, *J* = 10.1 Hz, 1H), 5.12 (dd, *J* = 3.4, 1.7 Hz, 1H), 4.48 (dt, *J* = 10.1, 2.6 Hz, 1H), 4.17 (dd, *J* = 12.4, 3.2 Hz, 1H), 3.54 (dd, *J* = 12.3, 2.2 Hz, 1H), 2.58 – 2.51 (m, 4H), 2.08 (s, 6H), 1.95 (s, 3H), 1.88 (s, 3H), 1.32 (dd, *J* = 7.6, 7.2 Hz, 12H), 1.21 (d, *J* = 6.9 Hz, 12H).

<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 186.4, 171.2, 170.0, 170.0, 169.7, 145.7, 145.7, 134.1, 130.7, 124.3, 124.3, 123.0, 80.7, 75.6, 69.7, 67.2, 66.9, 62.8, 28.9, 24.7, 24.1, 24.1, 21.3, 21.0, 20.9, 20.8.

Elemental Analysis for  $C_{41}H_{55}AuN_2O_9S$  (%): found C 51.94, H 5.83, N 3.00; calculated: C 51.90, H 5.84, N 2.95.

#### Synthesis of [Au(IMes)(1-thio- $\beta$ -D-glucose tetraacetate)] (6a)

Yield general procedure: 71%.

$^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  7.07 (s, 2H), 7.04 (d,  $J$  = 7.1 Hz, 4H), 4.97 (t,  $J$  = 9.3 Hz, 1H), 4.76 (t,  $J$  = 9.7 Hz, 1H), 4.64 (d,  $J$  = 9.5 Hz, 1H), 4.43 (t,  $J$  = 9.4 Hz, 1H), 3.92 (d,  $J$  = 4.2 Hz, 1H), 3.46 (dt,  $J$  = 10.0, 4.2 Hz, 1H), 2.36 (s, 6H), 2.15 (d,  $J$  = 6.7 Hz, 12H), 2.05 (s, 3H), 2.02 (s, 3H), 2.00 (s, 3H), 1.96 (s, 3H).

$^{13}C$  NMR (101 MHz,  $CDCl_3$ )  $\delta$  185.1, 171.1, 170.5, 169.8, 169.4, 139.7, 135.2, 135.1, 134.9, 129.5, 129.4, 121.9, 82.7, 77.3, 75.6, 74.5, 69.7, 63.8, 21.3, 21.2, 21.1, 20.9, 20.9, 17.9, 17.9.

Elemental Analysis for  $C_{37}H_{51}AuN_2O_9S$  (%): found C 49.14, H 4.93, N 3.17; calculated: C 48.61, H 5.01, N 3.24.

#### Synthesis of [Au(IMes)(1-thio- $\beta$ -D-galactose tetraacetate)] (6b)

Yield general procedure: 89%.

$^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  7.08 (s, 2H), 7.00 (d,  $J$  = 5.8 Hz, 4H), 5.31 (d,  $J$  = 2.8 Hz, 1H), 4.99 (t,  $J$  = 9.8 Hz, 1H), 4.82 (dd,  $J$  = 10.1, 3.3 Hz, 1H), 4.48 (d,  $J$  = 9.5 Hz, 1H), 4.07 – 3.94 (m, 2H), 3.56 (dd,  $J$  = 8.7, 5.7 Hz, 1H), 2.34 (s, 6H), 2.12 (s, 12H), 2.08 (s, 3H), 2.03 (s, 3H), 1.94 (s, 3H), 1.94 (s, 3H).

$^{13}C$  NMR (101 MHz,  $CDCl_3$ )  $\delta$  184.7, 170.7, 170.6, 170.5, 169.6, 139.7, 135.0, 134.9, 129.5, 129.4, 122.0, 83.1, 73.8, 73.0, 72.5, 67.6, 61.0, 21.2, 21.2, 20.9, 20.8, 17.9, 17.9.

Elemental Analysis for  $C_{35}H_{43}AuN_2O_9S$  (%): found C 48.28, H 4.90, N 3.16; calculated: C 48.61, H 5.01, N 3.24.

#### Synthesis of [Au(IMes)(1-thio- $\alpha$ -D-mannose tetraacetate)] (6c)

Yield general procedure: 92%; Yield one-pot procedure: 89%

$^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  7.06 (s, 2H), 6.99 (s, 4H), 5.76 (dd,  $J$  = 9.9, 3.4 Hz, 1H), 5.37 (d,  $J$  = 1.5 Hz, 1H), 5.20 (t,  $J$  = 10.0 Hz, 1H), 5.14 (dd,  $J$  = 3.4, 1.7 Hz, 1H), 4.52 (dt,  $J$  = 10.1, 2.7 Hz, 1H), 4.24 (dd,  $J$  = 12.3, 3.4 Hz, 1H), 3.67 (dd,  $J$  = 12.3, 2.1 Hz, 1H), 2.34 (s, 6H), 2.11 – 2.10 (m, 15H), 2.08 (s, 3H), 1.97 (s, 3H), 1.92 (s, 3H).

$^{13}C$  NMR (101 MHz,  $CDCl_3$ )  $\delta$  184.6, 171.1, 170.0, 169.9, 169.7, 139.6, 134.9, 129.6, 129.5, 122.1, 80.5, 75.8, 69.5, 67.4, 67.0, 62.7, 21.3, 21.0, 20.9, 20.9, 17.9, 17.9.

Elemental Analysis for  $C_{35}H_{43}AuN_2O_9S$  (%): found C 48.27, H 4.85, N 3.18; calculated: C 48.61, H 5.01, N 3.24.

#### Synthesis of [Au(SIMes)(1-thio- $\beta$ -D-glucose tetraacetate)] (7a)

Yield general procedure: 95%.

$^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  7.00 (d,  $J$  = 3.8 Hz, 4H), 4.93 (t,  $J$  = 9.3 Hz, 1H), 4.72 (t,  $J$  = 9.7 Hz, 1H), 4.54 (d,  $J$  = 9.5 Hz, 1H), 4.35 (t,  $J$  = 9.4 Hz, 1H), 3.96 (s, 4H), 3.91 (d,  $J$  = 4.2 Hz, 2H), 3.39 (dt,  $J$  = 10.0, 4.2 Hz, 1H), 2.36 (d,  $J$  = 6.8 Hz, 12H), 2.31 (s, 6H), 2.06 (s, 3H), 2.02 (s, 3H), 2.00 (s, 3H), 1.97 (s, 3H).

$^{13}C$  NMR (101 MHz,  $CDCl_3$ )  $\delta$  205.1, 171.1, 170.5, 169.7, 169.4, 138.9, 136.1, 135.9, 134.9, 129.8, 129.7, 82.6, 77.1, 75.5, 74.4, 69.6, 63.8, 50.9, 21.3, 21.1, 21.1, 20.9, 20.8, 18.2, 18.1.

Elemental Analysis for  $C_{35}H_{45}AuN_2O_9S$  (%): found C 48.41, H 5.06, N 3.15; calculated: C 48.50, H 5.23, N 3.23.

#### Synthesis of [Au(SIMes)(1-thio- $\beta$ -D-galactose tetraacetate)] (7b)

Yield general procedure: 91%.

$^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  6.95 (d,  $J$  = 8.2 Hz, 4H), 5.29 (d,  $J$  = 2.4 Hz, 1H), 4.95 (t,  $J$  = 9.8 Hz, 1H), 4.77 (dd,  $J$  = 10.1, 3.4 Hz, 1H), 4.31 (d,  $J$  = 9.5 Hz, 1H), 4.06 – 3.93 (m, 6H), 3.45 (dd,  $J$  = 8.3, 5.8 Hz, 1H), 2.33 – 2.29 (m, 18H), 2.08 (s, 3H), 2.04 (s, 3H), 1.96 (s, 3H), 1.93 (s, 3H).

$^{13}C$  NMR (101 MHz,  $CDCl_3$ )  $\delta$  204.8, 170.7, 170.6, 170.4, 169.6, 138.8, 135.9, 135.9, 134.9, 129.7, 129.6, 83.0, 73.8, 72.8, 72.5, 67.5, 61.0, 50.9, 21.3, 21.1, 20.9, 20.8, 18.2, 18.1.

Elemental Analysis for  $C_{35}H_{45}AuN_2O_9S$  (%): found C 48.28, H 5.10, N 3.25; calculated: C 48.50, H 5.23, N 3.23.

#### Synthesis of [Au(SIMes)(1-thio- $\alpha$ -D-mannose tetraacetate)] (7c)

Yield general procedure: 88%; Yield one-pot procedure: 82%

$^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  6.93 (d,  $J$  = 4.0 Hz, 4H), 5.73 (dd,  $J$  = 9.9, 3.4 Hz, 1H), 5.24 (d,  $J$  = 1.6 Hz, 1H), 5.17 (t,  $J$  = 10.0 Hz, 1H), 5.06 (dd,  $J$  = 3.4, 1.7 Hz, 1H), 4.53 – 4.41 (m, 1H), 4.22 (dd,  $J$  = 12.3, 3.6 Hz, 1H), 3.95 (s, 4H), 3.68 (dd,  $J$  = 12.3, 2.2 Hz, 1H), 2.31 (d,  $J$  = 5.0 Hz, 12H), 2.28 (s, 6H), 2.09 (s, 3H), 2.08 (s, 3H), 1.96 (s, 3H), 1.92 (s, 3H).

$^{13}C$  NMR (101 MHz,  $CDCl_3$ )  $\delta$  204.8, 171.1, 170.0, 169.9, 169.7, 138.8, 135.7, 135.7, 134.8, 129.8, 129.7, 80.2, 75.7, 69.5, 67.5, 67.0, 62.7, 50.9, 21.2, 21.2, 20.9, 20.9, 18.1, 18.0.

Elemental Analysis for  $C_{35}H_{45}AuN_2O_9S$  (%): found C 48.45, H 5.19, N 3.21; calculated: C 48.50, H 5.23, N 3.23.

#### Synthesis of [Au(IAd)(1-thio- $\beta$ -D-glucose tetraacetate)] (8a)

Yield general procedure: 85%.

$^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  7.06 (s, 2H), 5.17 – 5.12 (m, 2H), 5.02 – 5.01 (m, 2H), 4.23 (dd,  $J$  = 12.2, 5.0 Hz, 1H), 4.06 (dd,  $J$  = 12.1, 2.4 Hz, 1H), 3.70 (ddd,  $J$  = 9.4, 4.9, 2.4 Hz, 1H), 2.55 (d,  $J$  = 2.1 Hz, 12H), 2.27 (s, 6H), 2.07 (s, 3H), 2.03 (s, 3H), 2.00 (s, 3H), 1.97 (s, 3H), 1.77 (s, 12H).

$^{13}C$  NMR (101 MHz,  $CDCl_3$ )  $\delta$  179.8, 171.1, 170.6, 169.8, 169.7, 115.3, 83.5, 76.9, 75.8, 74.6, 69.3, 63.3, 59.2, 44.4, 36.0, 30.1, 21.2, 20.9, 20.9, 20.8.

Elemental Analysis for  $C_{41}H_{55}AuN_2O_9S$  (%): found C 49.03, H 5.60, N 3.02; calculated: C 49.55, H 5.73, N 3.12.

#### Synthesis of [Au(IAd)(1-thio- $\beta$ -D-galactose tetraacetate)] (8b)

Yield general procedure: 68%.

$^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  7.06 (s, 2H), 5.40 (d,  $J$  = 2.7 Hz, 1H), 5.21 (t,  $J$  = 9.8 Hz, 1H), 5.03 (d,  $J$  = 9.4 Hz, 1H), 4.99 (dd,  $J$  = 10.1, 3.5 Hz, 1H), 4.18 – 4.08 (m, 2H), 3.91 – 3.87 (m, 1H), 2.55 (d,  $J$  = 2.1 Hz, 12H), 2.26 (s, 6H), 2.11 (s, 3H), 2.08 (s, 3H), 2.00 (s, 3H), 1.96 (s, 3H), 1.76 (s, 12H).

$^{13}C$  NMR (101 MHz,  $CDCl_3$ )  $\delta$  179.8, 170.7, 170.6, 170.5, 169.9, 115.2, 84.4, 74.2, 73.9, 72.6, 67.9, 61.4, 5.2, 44.3, 36.0, 30.1, 21.3, 20.9, 20.9.

Elemental Analysis for  $C_{37}H_{51}AuN_2O_9S$  (%): found C 49.49, H 5.70, N 3.04; calculated: C 49.55, H 5.73, N 3.12.

#### Synthesis of [Au(IAd)(1-thio- $\alpha$ -D-mannose tetraacetate)] (8c)

Yield general procedure: 75%; Yield one-pot procedure: 92%  
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.05 (s, 2H), 6.02 (dd, *J* = 9.9, 3.4 Hz, 1H), 5.75 (d, *J* = 1.4 Hz, 1H), 5.50 (dd, *J* = 3.3, 1.7 Hz, 1H), 5.30 (t, *J* = 10.0 Hz, 1H), 4.83 (ddd, *J* = 10.1, 3.8, 2.5 Hz, 1H), 4.32 (dd, *J* = 12.2, 4.1 Hz, 1H), 4.03 (dd, *J* = 12.2, 2.3 Hz, 1H), 2.56–2.49 (m, 12H), 2.24 (br s, 6H), 2.13 (s, 3H), 2.05 (s, 3H), 2.02 (s, 3H), 1.96 (s, 3H), 1.74 (br s, 12H).

<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 179.0, 171.1, 170.3, 170.2, 169.9, 115.3, 81.5, 75.9, 69.7, 67.8, 67.5, 63.2, 59.2, 44.4, 36.0, 30.1, 21.3, 21.0, 20.9, 20.9.

Elemental Analysis for C<sub>37</sub>H<sub>51</sub>AuN<sub>2</sub>O<sub>9</sub>S (%): found C 49.82, H 5.80, N 3.12; calculated: C 49.55, H 5.73, N 3.12.

### Cell culture and cytotoxicity

A-549, HT-29 and MDA-MB-231 cells were obtained from DSMZ (German Collection of Microorganisms and Cell Cultures GmbH) and maintained by routine procedures. The cytotoxicity of complexes **5–8** was determined according to previously applied procedures.<sup>4f</sup> In short: The test compounds were prepared as stock solutions in dimethylformamide and diluted with cell culture media to graded concentrations. The cells were exposed to the compound containing cell culture media for a period of 72 h (A-549, HT-29) or 96 h (MDA-MB-231), after which the cell biomass was determined by crystal violet staining. The IC<sub>50</sub> values were calculated as the concentrations required to reduce cell proliferation by 50 % compared to the untreated control.

### Conflicts of interest

There are no conflicts to declare.

### Acknowledgements

CNRS, Université Côte d'Azur (UCA, Nice) and UM6P are gratefully acknowledged for financial support. For work conducted in Ghent, we are grateful to the Moonshot D2M project and the BOF (starting and senior grants) to SPN for financial support, as well as to the Research Foundation – Flanders (FWO) for a PhD fellowship to N.V.T (11I6921N). Umicore AG is gratefully acknowledged for generous gift of materials.

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