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Synthesis of Gold(I) and Palladium(II) Complexes Bearing *N*-Heterocyclic Carbene Thioglucosides with Selective Cytotoxicity Towards Ovarian Cancer Cells

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We report the development of an efficient and versatile synthetic protocol for the preparation of gold(I) and palladium(II) complexes bearing N-heterocyclic carbene (NHC) thioglucosides and their azolium precursors. Gold(I) and Nolan-type palladium(II)-allyl complexes were synthesized under mild aerobic conditions using potassium carbonate as a base. Additionally, allyl palladate complexes were prepared via a straightforward solvent-free method. In vitro assays on three ovarian cancer cell lines (OVCAR-5, A2780, and its cisplatin-resistant clone A2780cis) revealed interesting structure-activity relationships (SARs). Gold(I) complexes with saturated NHC ligands showed enhanced activity, while Nolan-type palladium(II)-allyl complexes with unsaturated NHC ligands exhibited higher efficacy. Allyl palladates demonstrated similar activity regardless of whether the ligand was saturated or not. The most promising compounds display high selectivity for cancer cells, with cytotoxicity comparable to cisplatin on A2780 and OVCAR-5 lines and superior activity against the A2780cis line. Notably, these compounds showed minimal toxicity towards non-cancerous MRC-5 cells. This selective anticancer activity is likely due to the presence of glucoside units, suggesting their role as targeting agents.

Introduction

Carbohydrates, or glycans, are essential biomolecules that play crucial roles in various biological processes, such as cell-cell communication, immune response, and pathogen recognition.[1,2] In cancer, carbohydrate structures on cell surfaces often undergo significant alterations, leading to the overexpression of specific glycan patterns.[3,4] These cancer-specific glycan profiles present a unique opportunity for the selective targeting of tumour cells. This specificity has driven interest in using carbohydrates as targeting agents in the design of metallodrugs for cancer therapy.[5–7]

Indeed, cancer cells typically exhibit altered glycosylation patterns compared to normal cells, including increased sialylation, fucosylation, and branching of *N*- and *O*-glycans.[8] These changes are not simple markers of malignancy but also contribute to the cancer's ability to evade immune surveillance, invade tissues, and metastasize. Glycan-binding proteins, such as lectins, recognize these cancer-specific carbohydrates, and targeting these interactions with carbohydrate-based strategies could improve the selectivity of cancer therapies.[5–7]

Among the various therapeutic options, chemotherapy remains the most widespread and is usually combined with surgery and radiotherapy.[9,10] In this context, metal-based chemotherapeutic agents, especially platinum complexes, are used in about half of the clinical protocols.[11–17] However, their lack of selectivity often results in severe side effects and toxicity. To overcome this limitation, research has focused on designing metallodrugs that can selectively target tumour cells, minimizing damage to healthy tissues.[18–20] One promising approach involves using carbohydrates as targeting moieties to enhance the specificity of these drugs.

By incorporating carbohydrates into the design of metallodrugs, researchers can take advantage of the selective binding between cancer-specific glycans and glycan-recognition proteins.[5–7] Carbohydrate-metallodrug conjugates are designed to improve the drug's affinity for cancer cells through glycan-receptor interactions, increasing their accumulation in tumour tissues.[7] These conjugates may also benefit from multivalency effects, where multiple glycan moieties interact with cell surface receptors, enhancing binding strength and specificity.

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The key to using carbohydrates as targeting agents lies in their ability to interact with lectins that are proteins that recognize and bind specific glycan structures on cell surfaces. Many tumours overexpress certain lectins, such as galectins, C-type lectins, and sialic acid-binding immunoglobulin-like lectins (Siglecs).[3,4] By attaching carbohydrate moieties that are recognized by these lectins to a metallodrug, selective drug delivery to cancer cells can be achieved.[7] This strategy exploits the *"glycocalyx"* of cancer cells, which is often denser and more complex than that of normal cells, to enhance tumour targeting.[21]

Recent research has explored various metal ions, such as platinum, gold, ruthenium, and copper, in combination with carbohydrate moieties.[22–27] For instance, carbohydrate-conjugated platinum drugs have been developed with improved selectivity towards cancer cells, reducing off-target effects.[24] Similarly, gold-based complexes functionalized with sugars have demonstrated selective cytotoxicity against cancer cells, showing promise as anticancer agents with reduced systemic toxicity.[25,26]

An example of this approach is the design of metal complexes conjugated to glucose molecules. Cancer cells often exhibit high glucose uptake due to their increased metabolic demands (the Warburg effect), making glucose an ideal targeting ligand.[28] By linking glucose, especially in its acetylated form, to a metallodrug, researchers have shown enhanced uptake of the drug in cancer cells, leading to increased efficacy.[7]

Taking all these aspects into consideration, we wondered if it might be possible to combine the carbohydrate chemistry with our expertise in the synthesis of metal-carbene complexes with the aim of designing new potential anticancer agents, particularly for the treatment of ovarian cancer. The latter expresses itself as a malignant tumor that begins in the ovaries, the female reproductive organs responsible for producing eggs and hormones like oestrogen and progesterone.[29] It is often referred to as a "silent killer" because its symptoms–such as bloating, abdominal pain, and difficulty eating–are subtle and easily mistaken for common digestive or menstrual issues. As a result, ovarian cancer is frequently diagnosed at an advanced stage, when it is most challenging to treat. Common risk factors include age, family history, genetic mutations (like BRCA1 and BRCA2), and reproductive history.[30]

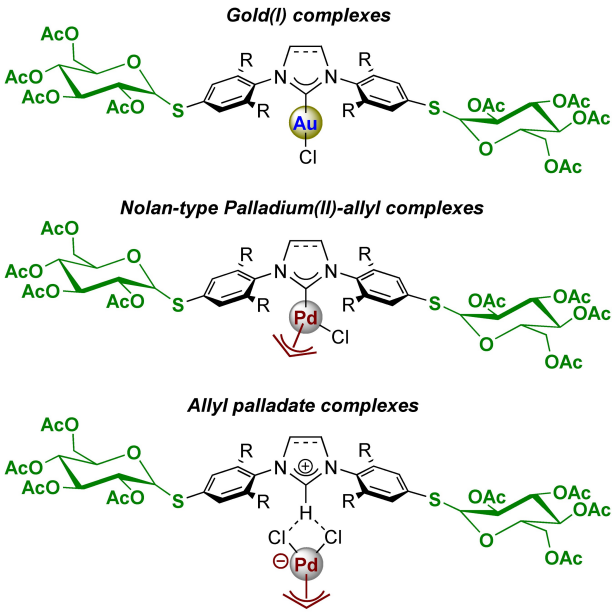
Examining the literature, the first examples of organometallic compounds containing a carbohydrate substituent on the *N*-heterocyclic carbene (NHC) ligand did not appear until after 2007.[31–33] These included iridium, rhodium and palladium derivatives, produced through deprotonation of an imidazolinium salt or by transmetalation of silver complexes with the appropriate metals. Despite these advances, there has been little exploration of their therapeutic potential, with only a few platinum complexes featuring carbohydrate-substituted NHCs described in a study aimed at developing anticancer agents.[24]

While numerous NHC complexes have been developed,[34] including several that exhibit excellent anticancer properties,[35] only a few NHC-carbohydrate complexes have been reported, primarily where the sugar moiety is attached to nitrogen heterocycles like imidazole or triazole.[27,31–33,36] Hybrid cyclodextrin-NHC ligands have also been investigated, introducing metal centers such as gold, silver, or copper into the cyclodextrin cavity, resulting in unique reactivity and selectivity.[37,38]

Curiously, a limited number of studies have focused on introducing carbohydrates into the aromatic substituents of the most commonly used *N*-heterocyclic carbenes in catalysis and medicinal chemistry, such as IPr (*N,N'*-bis(2,6-diisopropylphenyl)imidazol-2-ylidene) and IMes (*N,N'*-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene), along with their saturated derivatives (SIPr and SIMes).[39,40]

In particular, Gautier, Lamaty, and Messaoudi have recently reported an interesting synthetic protocol for the introduction of thioglucosides at the *para* position of aromatic rings anchored to the nitrogen atoms of azolium salts.[39] Their corresponding silver complexes exhibited promising bioactivity as well as remarkable stability, which is ensured by maintaining the classic structure of IPr, IMes, SIPr, and SIMes ligands, while introducing thioglucoside functions. These functions are expected to improve the compatibility of such carbenes with biological environments and act as targeting agents.

Herein, we explored the coordination chemistry of this fascinating class of NHC-thioglucosides, employing gold(I) and palladium(II) as metal centres (Scheme 1). More specifically, we focused on the synthesis and evaluation of the antiproliferative activity of three families of complexes, namely [Au(NHC-thioglucosides)Cl], [Pd(NHC-thioglucosides)Cl(allyl)], and [azolium-thioglucosides][$PdCl_2$(allyl)], which have recently shown interesting anticancer properties with conventional/classical *N*-heterocyclic carbenes.



Scheme 1. Gold(I) and Palladium(II) complexes bearing NHC-thioglucosides reported in this work.

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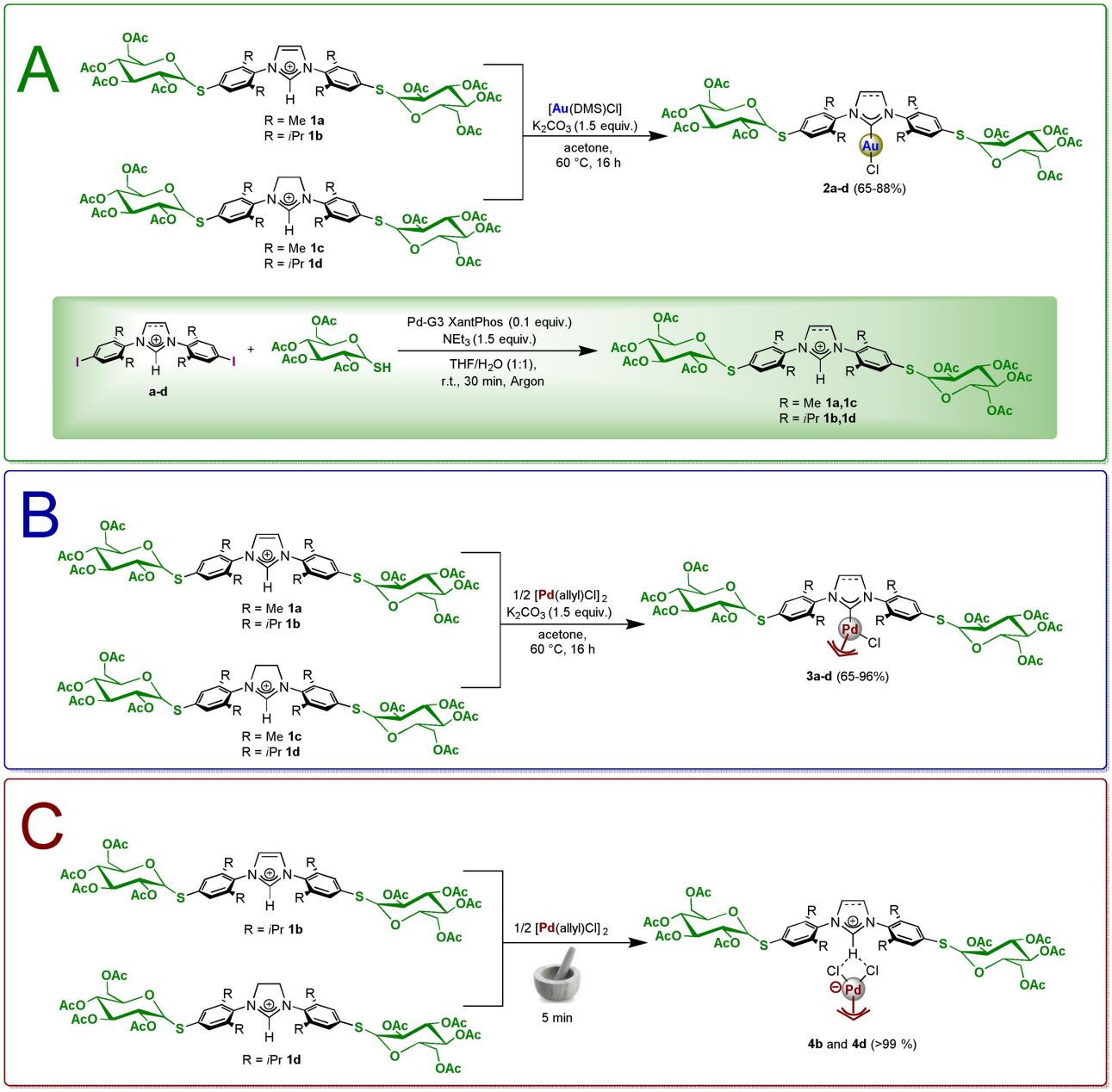
Results and Discussion

Synthesis of [Au(NHC-thioglucosides)Cl] Complexes

Following the procedure reported in the literature, both saturated and unsaturated azolium thioglucosides (**1 a-d**) were obtained through a palladium-catalyzed Migita cross-coupling between tetra-*O*-acetylated 1-thio-β-D-glucopyranose and di-iodinated imidazolium and imidazolinium salts (**a–d**, Scheme 2A, green window).[41,42] The latter were easily synthesized using a well-established three-step procedure.

By reacting azolium salts **1 a-d** with [Au(DMS)Cl] (DMS = dimethyl sulfide) in the presence of a weak and inexpensive base such as potassium carbonate, it was possible to fully convert the reagents into the desired Au-NHC complexes **2 a-d**. All reactions proceeded under aerobic conditions in technical grade acetone (green acetone) at 60 °C for 16 hours (Scheme 2A). The target complexes were isolated by filtering the reaction mixture through a pad of silica, followed by solvent removal *in vacuo*.

Given that the use of a weak base has become the simplest and most popular method (*weak base route*) for synthesizing [Au(NHC)Cl] complexes,[35,43–45] the identity of the obtained products was easily confirmed by ^{1}H and $^{13}C\{^{1}H\}$ NMR spectroscopy.



Scheme 2. Synthetic route to: (A) azolium thioglucosides (green window) and Au(I) complexes bearing NHC-thioglucoside ligands; (B) Nolan-type Pd(II)-allyl complexes bearing NHC-thioglucoside ligands and (C) allyl palladates with azolium thioglucosides.

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Specifically, in the ^{1}H NMR spectra, the disappearance of the NC*H*N proton is observed in the 8.5–11 ppm range, depending on the type of azolium salt used. Additionally, the deprotonation-metalation process causes a slight shift in the signals of the aryl and glycosidic protons compared to the starting azolium salt. In the $^{13}C\{^{1}H\}$ NMR spectra, all signals corresponding to the carbene ligand can be identified, though they are also slightly shifted with respect to the starting material. Particularly diagnostic is the signal of the carbenic carbon coordinated to the gold(I) center at 170–205 ppm (depending on the nature of NHC ligand).

It should be remembered that gold-NHC complexes have gained attention in the last two decades as promising anticancer agents due to their unique properties and mechanisms of action.[46,47] These complexes exhibit high stability and can effectively bind biomolecules, interfering with cancer cell growth. They usually induce apoptosis by disrupting mitochondrial function and inhibiting key enzymes such as thioredoxin reductase, which plays a vital role in cancer cell survival.[48–50] Their versatility and potential to overcome drug resistance make them a promising class of chemotherapeutic agents.

The compounds described above are specifically aimed at expanding the portfolio of easily accessible gold-NHC derivatives, with the hope of improving selectivity towards cancer cells and reducing side effects through the introduction of two thioglucosidic moieties.

Synthesis of [Pd(NHC-thioglucosides)Cl(allyl)] Complexes

The second class of organometallic compounds examined in this work consists of [Pd(NHC)Cl(allyl)] complexes. These compounds have been extensively studied in homogeneous catalysis due to their ability to efficiently promote a wide range of homo- and hetero-cross-coupling reactions under extremely mild conditions (Nolan catalysts).[51–53] However, palladium-allyl complexes, particularly those containing both an NHC and a phosphine as ancillary ligands, have recently been studied by some of us as promising antitumor agents.[27,54] Their high cytotoxicity against a wide range of cisplatin-sensitive and cisplatin-resistant cancer cell lines, especially ovarian cancer, combined with a mechanism of action completely different from classical platinum-based agents–namely, early mitochondrial damage–makes these derivatives extremely interesting in the broad field of metal-based antitumor agents.

Taking advantage, once again of the *weak base route*,[35,52] neutral palladium-allyl complexes **3 a-d** were obtained by direct reaction between azolium salts **1 a-d** and the dimeric precursor $[Pd(\mu\text{-}Cl)(\eta^{3}\text{-allyl})]_2$ in the presence of potassium carbonate as the base (Scheme 2B). The reactions were performed under the same conditions used for the gold-NHC complexes, specifically in technical grade acetone at 60 °C for 16 hours. The products were isolated in good to excellent yields using the same purification procedure as for the gold complexes.

The analysis of the ^{1}H NMR spectra of palladium-allyl complexes **3 a-d** shows a slight shift in the signals of the aryl and glycosidic protons compared to the starting azolium salt, as well as the disappearance of the imidazolium NC*H*N proton in the 8.5–11 ppm range. Additionally, five distinct signals for the allyl protons are observed due to the presence of two different ancillary ligands: *i) anti* allyl proton *trans* to chloride at ca. 2.2 ppm; *ii) anti* allyl proton *trans* to carbene at ca. 2.6 ppm; *iii) syn* allyl proton *trans* to chloride at ca. 3.6 ppm; iv) *syn* allyl proton *trans* to carbene at ca. 4 ppm and v) *central* allyl proton at ca. 5 ppm.

In the $^{13}C\{^{1}H\}$ NMR spectra, the allyl carbons can be observed at ca. 45, 70, and 125 ppm, as well as the signal of the carbene carbon coordinated to palladium at 170–200 ppm, along with the remaining aromatic and aliphatic signals of the NHC-thioglucoside ligand.

Synthesis of Allyl Palladate Complexes

The last compounds discussed in this work are the allyl palladates. These compounds display a unique interaction between the proton of an azolium salt and two chloride ligands in the Pd-allyl fragment. We have recently shown that these species are crucial intermediates in synthesizing [Pd(NHC)Cl(allyl)] precatalysts.[52,55] Notably, they can be prepared by simply grinding an azolium salt with the $[Pd(\mu\text{-}Cl)(\eta^{3}\text{-allyl})]_2$ dimer using a mortar and pestle. The significant antitumor activity of allyl palladates containing conventional imidazol(in)ium salts, observed across several cancer cell lines and validated in patient-derived organoids, has motivated us to explore this unique class of compounds further.[56]

In addition, these compounds have demonstrated higher cytotoxicity when bulky azolium salts are employed, as well as a remarkable ability to inhibit thioredoxin reductase, suggesting this protein as the primary target in the mechanism of action of these fascinating compounds. However, when conventional azolium salts are used, the corresponding allyl palladates show comparable cytotoxicity in both cancer and non-cancerous cells.

To enhance the selectivity of this family of organopalladium derivatives, the two bulkiest azolium salts proposed in this work (**1 b** and **1 d**) were reacted with the $[[Pd(\mu\text{-}Cl)(\eta^{3}\text{-allyl})]_2$ dimer under solvent-free conditions (Scheme 2C).

^{1}H and $^{13}C\{^{1}H\}$ NMR spectra confirmed the formation of the desired palladates, showing a general shift in signals compared to the starting materials. Specifically, in the ^{1}H NMR spectra, the diagnostic signals include the NC*H*N proton at 7–8 ppm and the three sets of allyl signals at *ca.* 3 (H^{anti}), 4 (H^{syn}), and 5 ($H^{central}$) ppm.

Antiproliferative Activity on Ovarian Cancer and Normal Cell Lines

The antiproliferative effects of the newly synthesized metal-carbene complexes were assessed using A2780, A2780*cis* and OVCAR-5 ovarian cancer cell lines. Their biological activity was compared to cisplatin, a widely used chemotherapeutic agent in ovarian cancer treatment, and to those of gold(I) and

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palladium(II) complexes bearing conventional NHCs ([Au(IMes)Cl], [Pd(IPr)Cl(allyl)] and [IPr·H][$PdCl_2$(allyl)]). Notably, preliminary experiments on A2780*cis* cancer cells confirmed the low cytotoxicity ($IC_{50} > 50$ μM) of azolium salts **1a-d**. This result is consistent with the observations of Lamaty and colleagues with HCT-116 cells.[39] Additionally, the synthesized complexes were tested on MRC-5 normal human lung fibroblasts cells to confirm their selective action against cancer cells (Table 1).

Preliminarily, we evaluated the stability of the synthesized complexes in a 1:1 D_2O/DMSO-d_6 solution through NMR spectroscopy. After 48 hours, there were no notable changes detected in the spectra, indicating the complexes maintained their structural integrity (Figures S21–23 in ESI). The same results can be obtained in the presence of 50 mM of ammonium bicarbonate (buffer at pH = 7.4). Upon closely examining the IC_{50} values obtained, it can first be stated that all compounds, including cisplatin, are more active in the A2780 cell line compared to the OVCAR-5 one. This aligns with the fact that OVCAR-5 cells belong to a more aggressive form of ovarian cancer, known as high-grade serous ovarian cancer.

Within the class of [Au(NHC)Cl] complexes, compounds containing saturated NHC ligands (**2c** and **2d**) are generally more active than their unsaturated counterparts (**2a** and **2b**). Particularly interesting is complex **2d**, which was found to be more active than cisplatin in the A2780 line, and while less active than cisplatin, it still showed good activity against the aggressive OVCAR-5 cancer cells. Complexes **2a** and **2b** were found to be inactive in the OVCAR-5 line. The former showed IC_{50} values in both lines comparable to those of a complex containing a carbene ligand lacking the thioglucoside function, such as [Au(IMes)Cl].

An opposite trend was observed in the case of Nolan-type Pd(II)-allyl complexes **3a-d**. In fact, the most active complexes are those containing unsaturated NHC ligands (**3a-b**). Particularly promising are the results obtained for complex **3b**, which showed activity comparable to that of cisplatin in both cancer cell lines. High cytotoxicity was also observed for the complex [Pd(IPr)Cl(allyl)], which represents the non-thioglucosylated version of complex **3b**.

The allyl palladate complexes **4b** and **4d** exhibited promising cytotoxicity in both cancer cell lines, with IC_{50} values slightly higher than those of cisplatin and the allyl palladate complex [IPr·H][$PdCl_2$(allyl)], which represents the non-functionalized form of complex **4b**.

The data obtained from the A2780*cis* cell line, which represents the cisplatin-resistant form of A2780 cells, allow for several interesting considerations. First, the higher cytotoxicity of the gold(I) complexes bearing saturated NHC ligands (**2c-d**) compared to their unsaturated congeners (**2a-b**) and the [Au(IMes)Cl] complex is confirmed. In this cell line, cisplatin exhibits moderate cytotoxicity, which is approximately 50 times lower than that observed in the cisplatin-sensitive A2780 line. Complexes **2c-d** retain significant cytotoxicity in this cell line as well, with IC_{50} values almost one order of magnitude lower than that of cisplatin.

Regarding the Nolan-type Pd(II)-allyl complexes **3a-c**, they exhibit IC_{50} values in the A2780*cis* line that are essentially identical to those obtained in the A2780 line. This suggests a mechanism of action different from that of cisplatin. Compound **3b**, as well as its non-thioglucosylated version ([Pd(IPr)Cl(allyl)]), display the highest cytotoxicity, approximately 100 times greater than that of cisplatin against A2780*cis* cancer cells.

The allyl palladate complexes **4b/4d** and [IPr·H][$PdCl_2$(allyl)] show an IC_{50} of *ca.* 2 μM on the A2780*cis* cell line, making them at least 10 times more active than cisplatin. Once again, the similar IC_{50} values observed for these allyl palladates between the A2780 and A2780*cis* lines suggest a different mechanism of action compared to cisplatin. As previously discussed, in depth

Table 1. IC_{50} (μM) of Au(I) and Pd(II) complexes bearing *N*-heterocyclic carbene thioglucosides complexes and cisplatin on cancer (A2780, A2780*cis* and OVCAR-5) and non-cancerous (MRC-5) cell lines.

Complex	A2780	A2780*cis*	OVCAR-5	MRC-5
Cisplatin	0.6 ± 0.2	27 ± 5	1.0 ± 0.1	6 ± 2
[Au(IMes)Cl]	5 ± 2	> 100	> 100	8 ± 3
2a	2.1 ± 0.2	80 ± 30	> 100	> 100
2b	11 ± 2	> 100	> 100	> 100
2c	3.4 ± 0.6	4.1 ± 0.2	12 ± 2	> 100
2d	0.25 ± 0.03	3.4 ± 0.3	9.5 ± 0.4	> 100
[Pd(IPr)Cl(allyl)]	0.23 ± 0.01	0.30 ± 0.02	0.52 ± 0.04	3.2 ± 0.2
3a	2.9 ± 0.6	3.7 ± 0.4	44 ± 6	70 ± 20
3b	0.32 ± 0.03	0.33 ± 0.02	2.8 ± 0.2	7.8 ± 0.4
3c	3.0 ± 0.5	3.3 ± 0.4	24 ± 2	> 100
3d	> 100	> 100	> 100	> 100
[IPr·H][$PdCl_2$(allyl)]	0.4 ± 0.1	2.0 ± 0.1	0.6 ± 0.3	0.84 ± 0.03
4b	1.3 ± 0.8	2.0 ± 0.1	3.64 ± 0.09	> 100
4d	1.22 ± 0.05	2.3 ± 0.5	4.8 ± 0.1	> 100

Data after 76 h of incubation. Stock solutions in DMSO for all complexes; stock solutions in H_2O/NaCl for cisplatin. A2780, A2780*cis* (cisplatin-sensitive and cisplatin-resistant ovarian cancer cells, respectively); OVCAR-5, high-grade serous ovarian cancer cells; MRC-5, normal lung fibroblasts.

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mechanistic studies of this type of complexes have already been conducted with conventional carbenes and are currently a subject of ongoing investigation in our group.

Analyzing the data for MRC-5 non-cancerous cells provides further insights into the selectivity of the compounds examined. In particular, all compounds that do not present a thioglucoside function, such as cisplatin, [Au(IMes)Cl], [Pd(IPr)Cl(allyl)], and [IPr·H][$PdCl_2$(allyl)], although they exhibit antitumor activity comparable to or even greater than that of the complexes synthesized in this work, show similar cytotoxic effects on both cancerous and non-cancerous cells.

Conversely, most complexes studied here, owing to the presence of thioglucoside moieties, were found to be poorly active or inactive (IC_{50} > 100 μM) towards normal cells. This indicates that they exhibit selectivity towards ovarian cancer cells over non-cancerous ones.

Overall, the most promising complexes are those that exhibit high cytotoxicity towards cancer cells while maintaining reduced cytotoxicity towards MRC-5 non-cancerous cells. In this study, these criteria are particularly met by the gold(I) complexes **2c-d**, the Nolan-type Pd(II)-allyl complex **3c**, and the allyl palladates **4b/4d**. These latter complexes likely represent the most promising class of compounds for further investigation.

Conclusions

We have developed an efficient and versatile synthetic protocol for the preparation of gold(I) and palladium(II) complexes bearing *N*-heterocyclic carbene (NHC) thioglucosides or their azolium precursors. Specifically, gold(I) and Nolan-type palladium(II)-allyl complexes were obtained by reacting the metal precursors ([Au(DMS)Cl] or [PdCl(allyl)]$_2$) with a selection of both saturated and unsaturated azolium salts in the presence of potassium carbonate as a base. All reactions were carried out under aerobic and mild conditions (green acetone, 60 °C). An even simpler method was used for the preparation of allyl palladate complexes (**4b** and **4d**), which involved the direct grinding of the imidazolium salt with the dimeric precursor [PdCl(allyl)]$_2$.

All synthesized compounds were fully characterized by ^{1}H and ^{13}C{1H} NMR spectroscopy and elemental analysis. *In vitro* tests on three ovarian cancer cell lines (OVCAR-5, A2780, and its cisplatin-resistant clone A2780*cis*) revealed intriguing structure-activity relationships (SARs). Specifically, for gold(I) complexes, the most active compounds contained saturated NHC ligands, while for the Nolan-type palladium(II)-allyl complexes, higher activity was observed with unsaturated NHC ligands. In the case of the allyl palladates, saturated azolium salts performed similarly to their unsaturated counterparts.

The most striking biological aspect of this study was the high selectivity of compounds bearing thioglucoside moieties towards cancer cells compared to those containing conventional azolium or NHC ligands. Particularly interesting were the gold(I) complexes **2c-d**, the Nolan-type Pd(II)-allyl complex **3c**, and the allyl palladates **4b/4d**. These compounds, especially the allyl palladates, exhibited cytotoxicity comparable to that of cisplatin against the A2780 and OVCAR-5 cell lines and display up to two orders of magnitude greater cytotoxicity against the A2780*cis* line. This high efficacy against ovarian cancer cells was surprisingly coupled with minimal cytotoxicity (IC_{50} > 100 μM) towards non-cancerous MRC-5 cells.

The remarkable selective anticancer activity of the most promising compounds reported here is likely attributable to the presence of glucoside units, which act as efficient targeting agents. Ongoing research in our laboratory focus on evaluating the most promising compounds in more complex biological systems (*e.g.* organoids and animal models), as well as on a detailed exploration of their mechanism of action and the origin of their observed selectivity.

Experimental

Materials and Methods

All solvents, potassium carbonate and the metal precursors ([Au(DMS)Cl] and [Pd(allyl)Cl]$_2$ were used as purchased (Sigma-Aldrich). Azolium salts **1a-d** were synthesized following the published procedures.[41,42] NMR spectra were recorded by a Bruker 400 MHz spectrometer. Elemental analyses were carried out using an Elemental CHN 'CUBO Micro Vario' analyzer.

Synthesis of Au(I)-NHC Complex 2a

A small capped vial was charged, under air, with 30.1 mg of azolium salt **1a** (0.03 mmol), 8.8 mg of [Au(DMS)Cl] (0.03 mmol) and suspended in acetone (2 mL). The mixture was stirred at 60 °C for 10 min and then 6.2 mg of K_2CO_3 (0.04 mmol, 1.5 equiv.) was added. The reaction mixture was stirred at 60 °C for 16 h. The reaction mixture was then filtered through silica which was washed with MeOH (3x1 mL). The solvent was removed *in vacuo*, and the product obtained as a colorless solid in 82% yield (30.2 mg).

^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 2.01 (s, 6H, OCH_3), 2.04 (s, 6H, OCH_3), 2.11 (s, 6H, OCH_3), 2.13 (s, 6H, OCH_3), 2.15 (s, 6H, NCH_3), 2.16 (s, 6H, NCH_3), 3.85 (ddd, *J* = 10.1, 5.0, 2.5 Hz, 2H, H^5 glucose), 4.25 (dd, *J* = 12.3, 5.1 Hz, 4H, $\underline{CH_2}OAc$), 4.84 (d, *J* = 10.1, 2H, H^1 glucose), 5.05 (t, *J* = 9.6 Hz, 2H, H^4 glucose), 5.11 (t, *J* = 9.8 Hz, 2H, H^2 glucose), 5.27 (t, *J* = 9.3 Hz, 2H, H^3 glucose), 7.16 (s, 2H, Aryl-H), 7.18 (s, 2H, Aryl-H), 7.40 (s, 2H, Im–H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm) δ: 17.8, 18.0, 20.6, 20.6, 20.8, 20.9, 62.2, 68.1, 69.9, 73.9, 75.9, 85.6, 132.3, 132.4, 134.5, 135.7, 135.8, 136.7, 169.4, 169.5, 170.1, 170.6, 173.6 (C, carbene). Elemental analysis calcd (%) for $C_{47}H_{56}AuClN_2O_{18}S_2$: C, 45.77; H, 4.58; N, 2.27; found: C, 45.98, H, 4.45; N, 2.36.

Synthesis of Au(I)-NHC Complex 2b

Complex **2b** was prepared in an analogous manner to that described for **2a** starting from 33.6 mg of azolium salt **1b**, 8.6 mg of [Au(DMS)Cl] and 6.1 mg of K_2CO_3.

Yield: 30.2 mg (77%).

^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 1.23 (d, *J* = 6.8 Hz, 12H, $CH(\underline{CH_3})_2$), 1.32 (d, *J* = 6.8 Hz, 6H, $CH(\underline{CH_3})_2$), 1.33 (d, *J* = 6.9, 6H, $CH(\underline{CH_3})_2$),2.01 (s, 6H, OCH_3), 2.03 (s, 6H, OCH_3), 2.10 (s, 6H, OCH_3), 2.14 (s, 6H, OCH_3), 2.54 (m, 4H, $\underline{CH}(CH_3)_2$) 3.84 (ddd, *J* = 10.1, 4.8, 2.2 Hz, 2H, H^5 glucose), 4.16–4.35 (m, 4H, $\underline{CH_2}OAc$), 4.83 (d, *J* = 9.9, 2H, H^1 glucose),

5.03 (t, $J=9.6$ Hz, 2H, H^4 glucose), 5.11 (t, $J=9.8$ Hz, 2H, H^2 glucose), 5.28 (t, $J=9.3$ Hz, 2H, H^3 glucose), 7.23 (s, 2H, Im–H), 7.31 (d, $J=1.9$ Hz, 2H, Aryl-H), 7.46 (d, $J=1.9$ Hz, 2H, Aryl-H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm) δ: 20.6, 20.9, 20.9, 23.8, 24.0, 24.4, 24.4, 29.0, 62.2, 68.0, 69.8, 74.0, 76.1, 77.2,

85.3, 123.0, 128.6, 128.7, 133.8, 134.7, 146.4, 169.4, 169.4, 169.5 (C, carbene), 170.0, 170.6. Elemental analysis calcd (%) for $C_{55}H_{72}AuClN_2O_{18}S_2$: C, 49.09; H, 5.39; N, 2.08; found: C, 48.75, H, 5.51; N, 2.19.

Synthesis of Au(I)-NHC Complex 2 c

Complex **2 c** was prepared in an analogous manner to that described for **2 a** starting from 36.1 mg of azolium salt **1 c**, 10.6 mg of [Au(DMS)Cl] and 7.4 mg of K_2CO_3.

Yield: 28.7 mg (65 %).

^1H NMR (400 MHz, $CDCl_3$, ppm) δ: 2.00 (s, 6H, OCH_3), 2.03 (s, 6H, OCH_3), 2.11 (s, 6H, OCH_3), 2.12 (s, 6H, OCH_3), 2.31 (s, 12H, NCH_3), 3.83 (m, 2H, H^5 glucose), 3.97 (s, 4H, CH_2-CH_2), 4.18–4.30 (m, 4H, $\underline{CH_2}OAc$), 4.80 (dd, $J=10.1$, 1.8, 2H, H^1 glucose), 5.03 (t, $J=9.7$ Hz, 2H, H^4 glucose), 5.09 (t, $J=9.7$ Hz, 2H, H^2 glucose), 5.25 (t, $J=9.3$ Hz, 2H, H^3 glucose), 7.52 (s, 4H, Aryl-H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm) δ: 17.7, 18.1, 18.2, 20.6, 20.9, 50.5, 62.3, 68.2, 69.9, 74.0, 75.8, 85.7, 95.3, 129.2, 132.7, 136.7, 137.9, 138.1, 169.5, 170.0, 170.1, 170.6, 204.0 (C, carbene). Elemental analysis calcd (%) for $C_{47}H_{58}AuClN_2O_{18}S_2$: C, 45.69; H, 4.73; N, 2.27; found: C, 45.84, H, 4.62; N, 2.34.

Synthesis of Au(I)-NHC Complex 2 d

Complex **2 d** was prepared in an analogous manner to that described for **2 a** starting from 40.0 mg of azolium salt **1 d**, 10.2 mg of [Au(DMS)Cl] and 7.2 mg of K_2CO_3.

Yield: 41.3 mg (88 %).

^1H NMR (400 MHz, $CDCl_3$, ppm) δ: 1.21–1.33 (m, 18H, $CH(\underline{CH_3})_2$), 1.48 (m, 6H, $CH(\underline{CH_3})_2$), 1.97 (s, 3H, OCH_3), 1.99 (s, 3H, OCH_3), 2.02 (s, 6H, OCH_3), 2.09 (s, 3H, OCH_3), 2.10 (s, 9H, OCH_3), 3.35–3.61 (m, 4H, $\underline{CH}(CH_3)_2$), 3.82 (ddd, $J=10.1$, 5.0, 2.2 Hz, 2H, H^5 glucose), 4.05 (m, 4H, CH_2-CH_2), 4.16 (m, 2H, $\underline{CH_2}OAc$), 4.33 (m, 2H, $\underline{CH_2}OAc$), 4.73 (d, $J=10.0$ Hz, 2H, H^1 glucose), 4.95 (m, 2H, H^4 glucose), 5.07 (m, 2H, H^2 glucose), 5.23 (m, 2H, H^3 glucose), 7.26 (m, 1H, Aryl-H), 7.29 (m, 2H, Aryl-H), 7.34 (d, $J=2.0$ Hz, 1H, Aryl-H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm) δ: 20.6, 20.9, 24.0, 26.6, 26.7, 28.5, 28.7, 54.0, 62.2, 68.0, 74.1, 76.0, 77.4, 85.5, 124.3, 127.8, 128.5, 133.1, 135.6, 146.3, 169.4, 169.5, 170.2, 170.7, 184.3 (C, carbene). Elemental analysis calcd (%) for $C_{55}H_{74}AuClN_2O_{18}S_2$: C, 49.02; H, 5.53; N, 2.08; found: C, 48.75, H, 5.51; N, 2.19.

Synthesis of Pd(II)-allyl Complex 3 a

A small capped vial was charged, under air, with 30.0 mg of azolium salt **1 a** (0.03 mmol), 5.5 mg of $[Pd(allyl)Cl]_2$ (0.015 mmol) and suspended in acetone (2 mL). The mixture was stirred at 60 °C for 10 min and then 6.2 mg of K_2CO_3 (0.04 mmol, 1.5 equiv.) was added. The reaction mixture was stirred at 60 °C for 16 h. The reaction mixture was then filtered through silica which washed with MeOH (3x1 mL). The solvent was removed *in vacuo* and the product with obtained as a pale-yellow solid in 65 % yield (20.3 mg).

^1H NMR (400 MHz, $CDCl_3$, ppm) δ: 2.00 (s, 6H, OCH_3), 2.03 (s, 6H, OCH_3), 2.10 (s, 6H, OCH_3), 2.10 (s, 6H, OCH_3), 2.17 (m, 1H, *anti* allyl-H *trans*-Cl), 2.25 (s, 6H, NCH_3), 2.26 (s, 3H, NCH_3), 2.27 (s, 3H, NCH_3), 2.63 (m, 1H, *anti* allyl-H *trans*-C), 3.73 (m, 1H, *syn* allyl-H *trans*-Cl), 3.82 (m, 2H, H^5 glucose), 4.04 (m, 1H, *syn* allyl-H *trans*-C), 4.15–4.30 (m, 4H, $\underline{CH_2}OAc$), 4.78 (dd, $J=10.1$, 2.4 Hz, 2H, H^1 glucose), 5.00 (m, 2H, H^4 glucose), 4.81 (m, 1H, *central* H allyl), 5.10 (t, $J=9.7$ Hz, 2H, H^2 glucose), 5.25 (t, $J=9.3$ Hz, 2H, H^3 glucose), 7.17 (s, 2H, Aryl-H), 7.22 (s, 2H, Aryl-H), 7.30 (d, 2H, $J=4.6$ Hz, Im–H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm) δ: 19.2, 19.3, 20.6, 20.6, 20.8, 20.9, 47.5, 62.2, 68.1, 69.0, 69.8, 74.0, 75.9, 85.4, 123.2, 132.0, 132.1, 134.1, 135.8, 136.3, 136.5, 169.5, 170.1, 170.3, 170.6, 171.3 (C, carbene). Elemental analysis calcd (%) for $C_{50}H_{61}ClN_2O_{18}PdS_2$: C, 50.72; H, 5.19; N, 2.37; found: C, 50.91, H, 5.08; N, 2.30.

Synthesis of Pd(II)-allyl Complex 3 b

Complex **3 b** was prepared in an analogous manner to that described for **3 a** starting from 33.6 mg of azolium salt **1 b**, 5.3 mg of $[Pd(allyl)Cl]_2$ and 6.1 mg of K_2CO_3.

Yield: 30.3 mg (80 %).

^1H NMR (400 MHz, $CDCl_3$, ppm) δ: 1.00 (m, 6H, $CH(\underline{CH_3})_2$), 1.13 (m, 6H, $CH(\underline{CH_3})_2$), 1.24 (m, 6H, $CH(\underline{CH_3})_2$), 1.35 (m, 6H, $CH(\underline{CH_3})_2$), 1.85 (m, 1H, *anti* allyl-H *trans*-Cl), 1.92 (s, 3H, OCH_3), 1.93 (s, 3H, OCH_3), 1.96 (s, 6H, OCH_3), 2.03 (s, 6H, OCH_3), 2.05 (s, 6H, OCH_3), 2.58 (m, 1H, *anti* allyl-H *trans*-C), 2.80 (m, 2H, $\underline{CH}(CH_3)_2$), 3.13 (m, 2H, $\underline{CH}(CH_3)_2$) 3.53 (m, 1H, *syn* allyl-H *trans*-Cl), 3.74 (m, 2H, H^5 glucose), 3.99 (m, 1H, *syn* allyl-H *trans*-C), 4.09 (m, 2H, $\underline{CH_2}OAc$), 4.28 (m, 2H, $\underline{CH_2}OAc$), 4.70 (m, 1H, *central* H allyl), 4.77 (d, $J=10.0$, 2H, H^1 glucose), 4.97 (m, 2H, H^4 glucose), 5.08 (m, 2H, H^2 glucose), 5.25 (m, 2H, H^3 glucose), 7.21 (s, 2H, Aryl-H), 7.30 (d, $J=2.1$ Hz, 1H, Im–H), 7.35 (s, 2H, Aryl-H), 7.39 (d, $J=2.1$ Hz, 1H, Im–H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm) δ: 20.6, 20.6, 20.8, 20.8, 20.9, 22.8, 22.9, 23.3, 25.6, 25.7, 26.4, 26.5, 28.8, 43.7, 62.2, 68.0, 68.2, 69.6, 69.7, 74.0, 76.0, 85.2, 85.5, 124.4, 128.0, 128.1, 128.3, 133.4, 136.0, 146.6, 146.9, 23.8, 24.0, 24.4, 24.4, 29.0, 62.2, 68.0, 69.8, 74.0, 76.1, 77.2, 85.3, 123.0, 128.6, 128.7, 133.8, 134.7, 146.4, 169.0, 169.2, 169.4, 170.2, 170.7, 173.7 (C, carbene). Elemental analysis calcd (%) for $C_{58}H_{77}ClN_2O_{18}PdS_2$: C, 53.74; H, 5.99; N, 2.16; found: C, 54.06, H, 5.73; N, 2.09.

Synthesis of Pd(II)-allyl Complex 3 c

Complex **3 c** was prepared in an analogous manner to that described for **3 a** starting from 36.1 mg of azolium salt **1 c**, 6.6 mg of $[Pd(allyl)Cl]_2$ and 7.4 mg of K_2CO_3.

Yield: 28.5 mg (67 %).

^1H NMR (400 MHz, $CDCl_3$, ppm) δ: 1.99 (s, 6H, OCH_3), 2.03 (s, 6H, OCH_3), 2.04 (m, 1H, *anti* allyl-H trans-Cl), 2.09 (s, 6H, OCH_3), 2.11 (s, 6H, OCH_3), 2.47 (s, 12H, NCH_3), 2.53 (m, 1H, *anti* allyl-H *trans*-C), 3.80 (m, 1H, *syn* allyl-H *trans*-Cl), 3.80 (m, 2H, H^5 glucose), 4.00 (m, 1H, *syn* allyl-H *trans*-C), 4.00 (s, 4H, CH_2-CH_2), 4.15–4.30 (m, 4H, $\underline{CH_2}OAc$), 4.70 (m, 1H, *central* H allyl), 4.75 (dd, $J=10.1$, 2.0 Hz, 2H, H^1 glucose), 4.98 (m, 2H, H^4 glucose), 5.06 (t, $J=9.7$ Hz, 2H, H^2 glucose), 5.24 (t, $J=9.5$ Hz, 2H, H^3 glucose), 7.17 (d, $J=7.6$ Hz, 2H, Aryl-H), 7.24 (d, $J=7.6$ Hz, 2H, Aryl-H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm) δ: 19.3, 19.4, 20.6, 20.8, 20.9, 47.9, 51.2, 62.2, 68.1, 69.7, 69.8, 74.0, 75.8, 85.4, 85.5, 125.7, 132.0, 132.2, 132.3, 132.5, 137.3, 138.4, 169.3, 169.5, 170.1, 170.6, 199.7 (C, carbene). Elemental analysis calcd (%) for $C_{50}H_{63}ClN_2O_{18}PdS_2$: C, 50.63; H, 5.35; N, 2.36; found: C, 51.01, H, 5.11; N, 2.27.

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Synthesis of Pd(II)-allyl Complex 3 d

Complex **3 d** was prepared in an analogous manner to that described for **3 a** starting from 40.0 mg of azolium salt **1 d**, 6.4 mg of $[Pd(allyl)Cl]_2$ and 7.2 mg of K_2CO_3.

Yield: 43.4 mg (96 %).

^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 1.29–1.41 (m, 36H, CH($\underline{CH_3}$)$_2$), 1.99 (s, 3H, OCH_3), 2.02 (s, 6H, OCH_3), 2.09 (s, 6H, OCH_3), 2.10 (m, 1H, *anti* allyl-H *trans*-Cl), 2.11 (s, 6H, OCH_3), 3.03 (m, 5H, *anti* allyl-H *trans*-C, $\underline{CH}(CH_3)_2$), 3.82 (m, 2H, H^5 glucose)4.00–4.05 (m, 5H, CH_2-CH_2, *syn* allyl-H *trans*-Cl), 4.17 (m, 2H, $\underline{CH_2}$OAc), 4.21 (m, 1H, *syn* allyl-H *trans*-C), 4.32 (m, 2H, $\underline{CH_2}$OAc), 4.78 (d, J = 9.9 Hz, 2H, H^1 glucose), 4.80 (m, 1H, *central* H allyl), 5.00 (m, 2H, H^4 glucose), 5.09 (m, 2H, H^2 glucose), 5.27 (m, 2H, H^3 glucose), 7.39 (d, J = 2.0 Hz, 2H, Aryl-H), 7.53 (s, 2H, Aryl-H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm) δ: 20.6, 20.8, 20.9, 24.0, 24.1, 24.9, 25.0, 29.0, 29.1, 48.9, 53.4, 62.2, 68.0, 69.7, 74.0, 76.0, 85.4, 96.8, 124.6, 129.2, 133.7, 134.2, 147.4, 148.8, 169.2, 169.4, 170.0, 170.7, 191.6 (C, carbene). Elemental analysis calcd (%) for $C_{58}H_{81}ClN_2O_{18}PdS_2$: C, 53.66; H, 6.13; N, 2.16; found: C, 53.43, H, 6.22; N, 2.29.

Synthesis of Allyl Palladate Complex 4 b

In air, 33.5 mg (0.03 mmol) of the azolium salt **1 b** and 5.3 mg (0.015 mmol) of $[Pd(allyl)(\mu\text{-}Cl)]_2$ were added to a mortar. The two solids were mixed and grinded using a pestle for 5 min. A yellow/brownish powder was obtained in a quantitative yield.

^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 1.06–1.40 (24H, CH($\underline{CH_3}$)$_2$), 1.99 (s, 6H, OCH_3), 2.02 (s, 6H, OCH_3), 2.10 (s, 6H, OCH_3), 2.12 (s, 6H, OCH_3), 2.49 (m, 2H, *anti* allyl-H), 3.04 (m, 4H, $\underline{CH}(CH_3)_2$) 3.86 (m, 2H, H^5 glucose), 4.13–4.37 (m, 6H, $\underline{CH_2}$OAc, *syn* allyl-H), 4.84 (d, J = 10.0, 2H, H^1 glucose), 4.99 (m, 2H, H^4 glucose), 5.08 (m, 2H, H^2 glucose), 5.26 (m, 2H, H^3 glucose), 5.34 (m, 1H, *central* H allyl), 7.26–7.34 (m, 4H, Aryl-H), 7.45 (d, J = 2.1 Hz, 2H, Im–H), 8.10 (s, 1H, NCHN). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm) δ: 20.6, 20.8, 24.0, 24.4, 29.2, 43.7, 62.1, 68.0, 69.6, 74.0, 76.0, 84.9, 110.0, 129.2, 145.7, 145.8, 169.3, 170.0, 170.6.Elemental analysis calcd (%) for $C_{59}H_{82}Cl_2N_2O_{18}PdS_2$: C, 52.54; H, 6.13; N, 2.08; found: C, 52.87, H, 5.98; N, 1.94.

Synthesis of Allyl Palladate Complex 4 d

In air, 60.9 mg (0.05 mmol) of the azolium salt **1 d** and 9.7 mg (0.025 mmol) of $[Pd(allyl)(\mu\text{-}Cl)]_2$ were added to a mortar. The two solids were mixed and grinded using a pestle for 5 min. A yellow/brownish powder was obtained in a quantitative yield.

^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 1.46–1.23 (24H, CH($\underline{CH_3}$)$_2$), 1.97 (s, 6H, OCH_3), 2.00–2.36 (20H, OCH_3, anti allyl-H), 3.10 (m, 4H, s, 6H, OCH_3), 3.81 (dd, J = 10.0, 2.4 Hz, 2H, H^5 glucose), 4.14–4.34 (6H, $\underline{CH_2}$OAc, *syn* allyl-H), 4.73 (d, J = 10.0 Hz, 2H, H^1 glucose), 4.91 (6H, H^4 glucose, CH_2-CH_2), 5.08 (t, J = 9.8 Hz, 2H, H^2 glucose), 5.24–5.30 (3H, H^3 glucose, *central* H allyl), 7.38 (d, J = 2.0 Hz, 2H, Aryl-H), 7.43 (d, J = 1.9 Hz, 2H, Aryl-H), 7.60 (d, J = 1.6 Hz, 1H, NCHN). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm) δ: 20.7, 20.9, 20.9, 23.9, 24.1, 25.4, 25.5, 25.6, 29.2, 29.3, 62.2, 68.0, 69.6, 74.1, 76.3, 77.4, 84.8, 129.6, 130.1, 134.7, 135.3, 147.2, 148.6, 169.2, 169.6, 170.2, 170.7 ppm. Elemental analysis calcd (%) for $C_{59}H_{84}Cl_2N_2O_{18}PdS_2$: C, 52.46; H, 6.27; N, 2.07; found: C, 52.80, H, 6.04; N, 1.98.

Cell Viability Assay

Cells were cultured following the supplier's (Sigma-Aldrich) protocol and incubated at 37 °C with 5 % CO_2. A total of 500 cells were seeded into 96-well plates and exposed to six different concentrations of gold and palladium complexes (0.001, 0.01, 0.1, 1, 10, and 100 μM). After 96 hours, cell viability was assessed using the CellTiter-Glo assay (Promega, Madison, WI, USA) on a Tecan M1000 instrument. IC_{50} values were determined from triplicate experiments, with error bars representing standard deviations.

More in detail, for each cell line, the appropriate culture medium was employed. Specifically, RPMI-1640 medium was used for the A2780, A2780*cis*, and OVCAR-5 cell lines whereas MEM was used for the MRC-5 cell line. After preparing the cell cultures and confirming their health status with a microscope, the cells were detached from the plates where they had proliferated, counted, and subsequently seeded. The seeding procedure involved adding 100 μL of a solution containing cells and medium into each well of a 96-well multiwell plate. An appropriate number of wells were filled, ensuring that six concentrations of each compound were tested in triplicate (a total of 18 wells per compound).

The plates were incubated for 24 hours, after which the cell health was verified, and the treatment procedure was initiated. A 10 mM stock solution of each compound was prepared in DMSO, from which the necessary aliquots were taken for dilution in the culture medium, yielding six final concentrations: 100 μM, 10 μM, 1 μM, 0.1 μM, 0.01 μM, and 0.001 μM. The same concentration values were also used for cisplatin, which served as the reference for determining the IC_{50} value in all cell lines.

The plates were incubated for 96 hours at 37 °C. At the end of the incubation period, the cells were again observed under a microscope to visually assess cell viability.

Subsequently, the medium was removed from the wells, and a 1 : 1 solution of CellTiter-Glo® (a mixture of Substrate and Buffer) and PBS was added. CellTiter-Glo® enables the assessment of cell viability by inducing cell lysis and producing a luminescent compound in reaction with ATP. The luminescent signal, which is proportional to ATP levels, was measured and plotted as a function of the logarithm of the complex concentration in the analysed well, resulting in sigmoidal curves. Non-linear regression analysis was then performed to calculate the IC_{50} value.

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

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