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Linking Flavonoids to Gold – A New Family of Gold Compounds for Potential Therapeutic Applications

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The flavone ligands 8-chloro-2-tetrahydrofuryl-1,4-benzopyrone and 8-chloro-2-(2-methyltetrahydrofuryl)-1,4-benzopyrone have been used to prepare the first examples of alkynyl phosphine gold compounds containing flavonoids which exhibit cytotoxicity towards human prostate cancer cells.

Introduction

Worldwide there are a significant number of deaths due to cancer;[1] however, a true medicinal cure to this disease remains elusive. Despite the success of existing clinical metal compounds such as cisplatin, *cis*-[$PtCl_2(NH_3)_2$], for the treatment of cancer,[2] there is continuing interest in new antitumour drugs in an effort to overcome the drawbacks of existing therapeutic agents, including high toxicity, which cause unwanted side-effects in the human body.[2]

Since the introduction of clinically accepted auranofin in 1985 for the treatment of arthritis, gold compounds have been the subject of investigation as a source of metal-based drugs.[3] Among the many gold compounds that have been tested for anticancer properties, gold(I)–phosphine derivatives have offered a promising scope for the development of gold-based drugs.[4] Initial interest concentrated on linear two-coordinate gold complexes such as auranofin and (triethylphosphine)gold(I) chloride; this was later expanded to include the cationic species bis[1,2-bis(diphenylphosphino)ethane]gold(I) chloride and bis[1,2-bis(di-*n*-pyridylphosphino)ethane]gold(I) chloride, which possess tetrahedral geometry about the metal centre.[4] Various ligands have been used to design effective gold-based anticancer agents,[4–16] many of which are less toxic than other metal compounds.[4,5,17] Alkynyl phosphine gold complexes have become the subject of attention recently due to their stable coordinative bond (strong gold–carbon σ-bond) and therefore their stability under physiological conditions.[18–21] Surprisingly, however, gold compounds that contain flavonoid ligands (Figure 1) have not been the subject of prior investigation. The role of dietary flavonoids, a class of antioxidants found in fruits, vegetables, tea, red wine and soybeans, is widely discussed in cancer prevention,[22–31] and in vitro and in vivo studies have demonstrated their anticancer properties.[32,33]

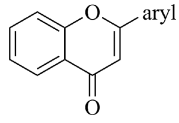

Figure 1. The flavone backbone.

Given our background in the synthesis of organogold complexes,[34] we were interested to design and prepare flavonoid derivatives of gold(I)–phosphine compounds, binding together two potentially anticancer-active components (namely a gold–phosphine and a flavonoid) through a gold–carbon σ-bond. Several factors were considered when designing these compounds, one being the introduction of a chlorine substituent into the phenyl ring of the flavone moiety, which has been shown to improve the cytotoxicity of flavone-based drugs.[35] Another factor was to incorporate a Au(PPh_3) component into the structure, since it has been reported that phenyl substituents on the phosphorus atom cause an increase in the cellular and nuclear uptake of AuCl(PR_3) (R = Ph, Me, Et, *t*Bu), hence an increase in the cytotoxicity.[36,37]

We now provide a detailed account of the preparation and biological activities of these complexes.

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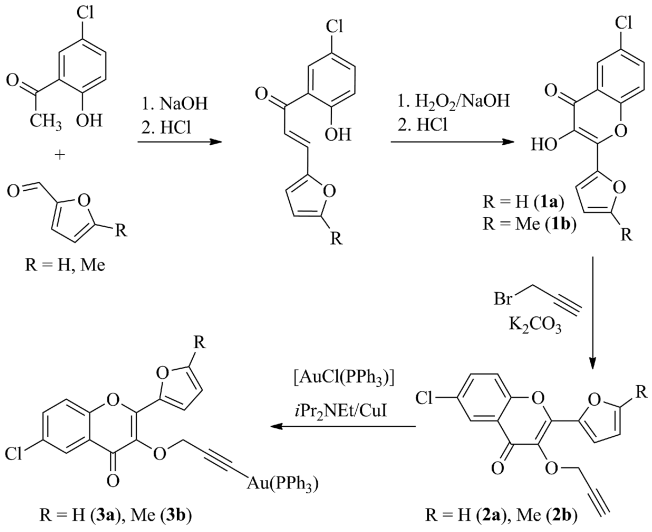
Results and Discussion

To bind a gold–phosphine moiety to a flavonoid, a propargyl ether group was employed,[18] which conveniently enabled the formation of the desired gold–carbon σ-bond by deprotonation of the alkyne. Thus, reaction of 3-hydroxybenzopyrans **1a** and **1b** with propargyl bromide gave aryl propargyl ethers **2a** and **2b** (Scheme 1).[38,39] Treatment of **2a** and **2b** with [AuCl(PPh$_3$)] in the presence of CuI and *i*Pr$_2$NEt afforded the desired gold(I) compounds **3a** and **3b** (Scheme 1) as air-stable solids in good yields (85–90%).



Scheme 1. Linking flavonoids to gold.

Complexes **3a** and **3b** were characterized by elemental analysis and spectroscopic techniques. The ^{1}H NMR spectroscopic data of **3a** and **3b** are generally similar to those of **2a** and **2b**,[39] respectively, with additional aromatic multiplets due to the phenyl protons of the PPh$_3$ ligand. The ^{31}P NMR spectra of **3a** and **3b** each showed a singlet resonance at δ = 41.8 ppm. The ESI mass spectra of **3a** and **3b** both show the expected $[M + H]^+$ peak at *m*/*z* 759.08 and 773.09, respectively, and elemental analyses are consistent with the proposed structures. The structures of **2a**, **2b**, **3a** and **3b** were also confirmed by X-ray diffraction. The molecular structures of **2a** and **2b** are shown in Figure 2 and those of **3a** and **3b** in Figure 3. Selected bond lengths and angles for **2a**, **2b**, **3a** and **3b** are listed in Tables 1 and 2.

The bond lengths and angles in the flavonoid compounds **2a** and **2b** are unexceptional (Tables 1 and 2). In general, the metrical parameters of gold complexes **3a** and **3b** are similar to those in the corresponding precursors **2a** and **2b**. Upon coordination of the Au(PPh$_3$) fragment, there is a slight lengthening of the C≡C bond by about 0.02 Å. As expected, the gold atom in **3a** and **3b** displays linear coordination.

The cytotoxicity of gold compounds **3a** and **3b**, flavonoid precursors **1a**, **2a**, **1b**, **2b** and gold precursor [AuCl(PPh$_3$)] were tested against human prostate cancer (PC-3) cells. Given the fact that androgen-independent prostate cancer is resistant to the common anticancer drug cisplatin, and a high dosage is required for chemotherapy, which generally leads to adverse side effects, we chose to investigate PC-3 cells for our experiments.[40,41] Another reason for choosing PC-3 cells is the fact that the activity of this cell line, when challenged with flavone compounds, has been well established.[35,42,43] In particular, chlorine substitution on the phenyl ring of flavones has been shown to change the steric and electronic characteristics of anticancer flavone-based drugs and favourably enhances their anticancer properties against PC-3 cells.[35]

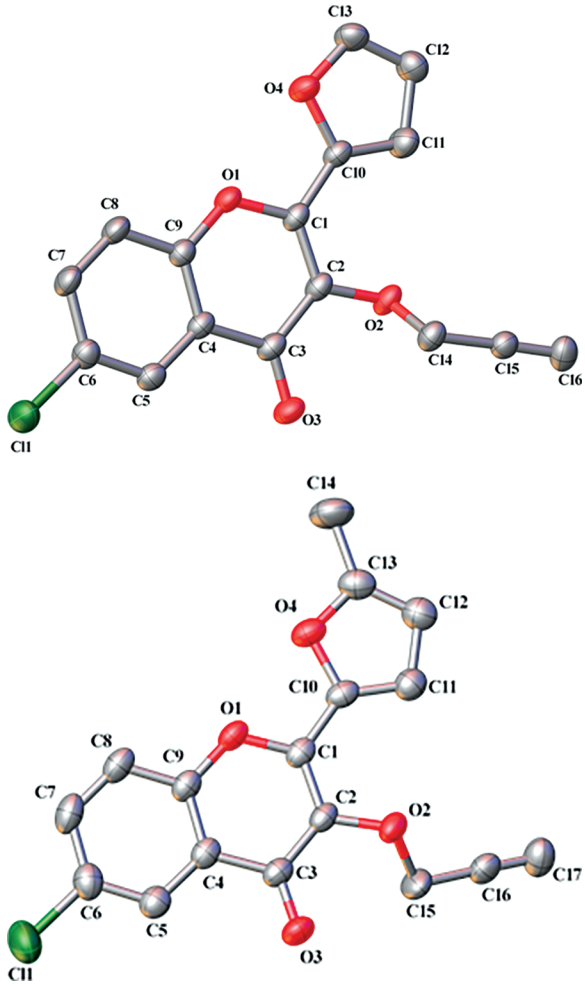


Figure 2. Molecular structure of **2a** (top) and **2b** (bottom). Ellipsoids show 50% probability levels. Hydrogen atoms have been omitted for clarity. The disordered benzene of crystallization in **2b** has been omitted.

Actively growing PC-3 cells in the log phase of their cell cycle were treated with increasing concentrations of compounds **1**–**3** for a period of 24 h, and the toxicity was assessed by using the 3-(4,5-dimethylazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay.[44] The MTT assay estimates cellular viability by measuring the mitochondrial dehydrogenase activity as indicated by the reduction of yellow tetrazolium MTT to purple needle-like formazan crystals, which, on solubilization, can be measured with a UV/Vis multiwell plate reader. The cell viability percentages were calculated for **1**–**3** and [AuCl(PPh$_3$)] and are shown in the

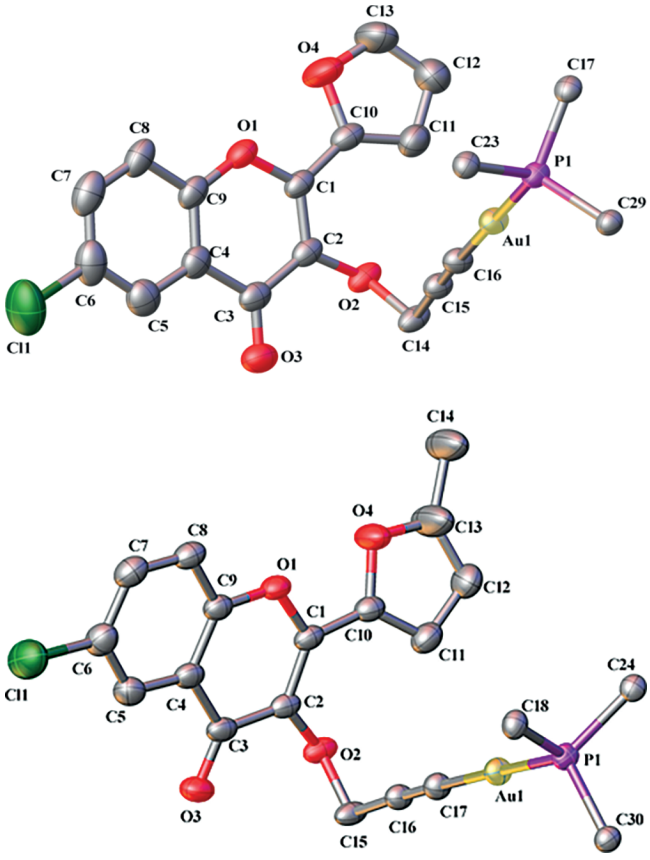


Figure 3. Molecular structure of **3a** (top) and **3b** (bottom). Ellipsoids show 50% probability levels. Hydrogen atoms and the CH_2Cl_2 of crystallization have been omitted for clarity. Only the *ipso* carbon atoms of the PPh_3 group are shown.

Table 1. Selected bond lengths [Å] and angles [°] in **2a** and **3a**.

	2a	**3a**
Au1–P1	–	2.2795(6)
Au1–C16	–	1.998(2)
C15–C16	1.180(2)	1.202(3)
C14–C15	1.459(2)	1.463(3)
C14–O2	1.4532(18)	1.467(3)
P1–Au1–C16	–	179.23(7)
C15–C14–O2	108.88(12)	113.15(19)
C14–O2–C2	112.42(11)	114.71(19)
C14–C15–C16	177.10(17)	178.2(3)

Table 2. Selected bond lengths [Å] and angles [°] in **2b** and **3b**.

	2b	**3b**
Au1–P1	–	2.2829(6)
Au1–C17	–	2.001(2)
C16–C17	1.161(3)	1.206(3)
C15–C16	1.447(3)	1.459(3)
C15–O2	1.438(2)	1.467(3)
P1–Au1–C17	–	178.54(7)
C16–C15–O2	108.61(15)	112.98(18)
C15–O2–C2	115.46(13)	114.75(19)
C15–C16–C17	177.3(2)	176.7(3)

Supporting Information, while the EC_{50} values are listed in Table 3. Since studies have shown that many flavonoid compounds react with MTT to form formazan crystals, which lead to false positive results,[45] compounds **1**–**3** were tested with MTT through cell-free controls. The results showed no formazan crystal formation, indicating that MTT was a suitable assay for testing the viability of these compounds. Vehicle control (1% DMSO) was tested with PC-3 cells and resulted in 97% viability, indicating that the highest concentration of DMSO used was not toxic to the cells.

Table 3. Cytotoxicity of compounds **1a**–**3a**, **1b**–**3b** and $[AuCl(PPh_3)]$ against human prostate cancer (PC-3) cells.

Compound	EC_{50} [μM][a]	Compound	EC_{50} [μM][a]
1a	84.69	**1b**	155.81
2a, **2b**	NA[b]	$[AuCl(PPh_3)]$	27.99
3a	37.73	**3b**	43.36

[a] The concentration of compound that gives half-maximum response. [b] Compounds **2a** and **2b** show no activity.

The results revealed that the presence of the hydroxyl group in compounds **1a** and **1b** is essential for their effectiveness as cytotoxic agents. The toxicities of **1a** and **1b** are diminished when the hydroxyl group is converted to a propargyl ether; compounds **2a** and **2b** exhibit no toxicity, leading to 100% viability of PC-3 cells under the conditions used. This may be explained by the fact that the hydroxyl group, due to its electron-donating capability, is able to disrupt the balance of reactive oxygen species (ROS) in the cells, leading to apoptosis.[46]

Upon coordination of the $Au(PPh_3)$ moiety to **2a** and **2b**, an increase in toxicity was observed (**3a**, EC_{50} = 37.73 μM; **3b**, EC_{50} = 43.36 μM). The toxicities of **3a** and **3b** are greater than those of their precursors **2a** and **2b** and even those of **1a** and **1b**. The presence of a methyl group in the furan ring resulted in a slight decrease in the cytotoxic potency of gold compound **3b** compared to that of **3a**; a similar trend was also observed between **1b** and **1a**. These observations highlight the importance of substituents in the furan ring for fine-tuning the activity profiles of these compounds. The toxicity of $[AuCl(PPh_3)]$ was also tested against PC-3 cells to determine the extent the gold moiety contributes to the cytotoxicity of **3a** and **3b**. The results show that $[AuCl(PPh_3)]$ has even greater activity than **1a**–**3a** and **1b**–**3b** at all concentrations tested (see Figure S1 in the Supporting Information), suggesting that the activities of **3a** and **3b** are mainly derived from the presence of the $Au(PPh_3)$ fragment. The results also indicate that the effectiveness of gold compounds **3a** and **3b** approaches that of $[AuCl(PPh_3)]$ at higher concentrations. The exact mechanism of action of these gold compounds remains to be investigated. It is also important to determine whether the cellular responses elicited by **3a** and **3b** arise from a synergistic effect of the flavone and $Au(PPh_3)$ moieties or are solely due to one or the other.

Conclusions

We have demonstrated the successful preparation of the first representatives of a family of organometallic gold com-

pounds containing flavone ligands that exhibit cytotoxicity against human prostate cancer (PC-3) cells. Growing evidence increasingly supports the role of flavonoids in cancer therapy alongside its prevention, wherein different flavonoids are found to selectively influence different proinflammatory signalling pathways.[47,48] Although the cytotoxicity of gold complexes **3a** and **3b** towards PC-3 cells was less than we had hoped, the results have provided further insights into the structural features that are important for activity. For example, the inactivity of compounds **2a** and **2b** compared to **1a** and **1b** highlights the importance that the phenol group plays in the cytotoxicity of these compounds. Similarly, the slightly greater activity of **3a** compared to that of **3b** illustrates the effect that relatively minor structural changes can play on anticancer activity. Nevertheless, given the results reported here, further investigations into the modification or functionalization of the furan ring, phosphine ligand or aryl halide group may lead to complexes that show even greater activity towards PC-3 cells.

Experimental Section

Compounds **2a** and **2b**, their starting materials[38,49] and [AuCl(PPh$_3$)][50] were prepared according to literature methods; all other reagents were commercially available and used as received. ^{1}H (300 MHz) and ^{31}P (121 MHz) NMR spectra were measured with a Bruker Avance 300 spectrometer at room temperature in $CDCl_3$. Coupling constants (J) are given in Hz and chemical shifts (δ) in ppm, internally referenced to residual solvent signals (^{1}H) or external 85% H_3PO_4 (^{31}P). Electrospray (ESI) mass spectra were measured with HP 5970 MSD and Waters spectrometers in the Mass Spectrometry Unit of the Research School of Chemistry, Australian National University (ANU). Elemental analyses were carried out by the Microanalytical Unit at the same school.

X-ray Crystallography

Crystals suitable for X-ray crystallography were obtained from methanol (for **2a**), benzene layered with hexane (for **2b**) or dichloromethane layered with hexane (for **3a** and **3b**). X-ray diffraction data were collected at 200 K with a D8 Bruker diffractometer with an APEX2 area detector using graphite-monochromated Mo-K_α radiation (λ = 0.71073 Å) from a 1 μS microsource. Geometric and intensity data were collected by using SMART software.[51] The data were processed with SAINT,[52] and corrections for absorption were applied by using SADABS.[53] The structures were solved by direct methods and refined with full-matrix least-squares methods on F^2 by using the SHELX-TL package.[54] OLEX2 was used to refine the structure of **3b** and to produce the molecular graphics.[55] Selected crystal data and details of data collection and structure refinement are listed in Table S1 (Supporting Information).

CCDC-1058881 (for **2b**), -1058882 (for **3b**), -105883 (for **2a**) and -105884 (for **3a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Complex 3a: A mixture of alkyne **2a** (110 mg, 0.36 mmol), [AuCl(PPh$_3$)] (181 mg, 0.36 mmol), CuI (5 mg) and iPr$_2$NEt (2 mL) in CH_2Cl_2 (8 mL) was stirred overnight in the dark. The solvent was removed in vacuo, and the residue was extracted with CH_2Cl_2. After filtration through Celite, the filtrate was concentrated to dryness and the solid was washed with Et_2O. Recrystallization from CH_2Cl_2/MeOH gave a pale yellow solid, which was isolated by filtration, washed with MeOH and dried in vacuo (252 mg, 91%). ^{1}H NMR: δ = 5.23 (s, 2 H, methylene), 6.61 (dd, J = 1.7, 3.6 Hz, 1 H, furan), 7.38–7.54 (m, 16 H, aromatics, furan), 7.57 (dd, J = 2.5, 8.9 Hz, 1 H, aromatic), 7.64 (d, J = 1.1 Hz, 1 H, furan), 7.74 (d, J = 3.5 Hz, 1 H, furan), 8.20 (d, J = 2.5 Hz, 1 H, aromatic) ppm. ^{31}P NMR: δ = 41.8 (s) ppm. ESI-MS: m/z = 759.08 [M + H]$^+$, 781.05 [M + Na]$^+$. $C_{34}H_{23}AuClO_4P$ (758.95): calcd. C 53.81, H 3.05, Cl 4.67; found C 53.41, H 2.76, Cl 4.73.

Complex 3b: A procedure similar to that described above using alkyne **2b** (105 mg, 0.33 mmol) and [AuCl(PPh$_3$)] (165 mg, 0.33 mmol) gave the desired product as a pale yellow solid (217 mg, 84%). ^{1}H NMR: δ = 2.43 (s, 3 H, methyl), 5.20 (s, 2 H, methylene), 6.22 (d, J = 2.8 Hz, 1 H, furan), 7.37–7.68 (m, 18 H, aromatics, furan), 7.65 (d, J = 3.4 Hz, 1 H, furan), 8.18 (d, J = 2.4 Hz, 1 H, aromatic) ppm. ^{31}P NMR: δ = 41.8 (s) ppm. ESI-MS: m/z = 773.09 [M + H]$^+$, 795.07 [M + Na]$^+$. $C_{35}H_{25}AuClO_4P$ (772.97): calcd. C 54.39, H 3.26, Cl 4.59; found C 54.02, H 3.08, Cl 4.71.

Cell Viability Assay: The cytotoxicity of the gold compounds and their precursors towards prostate cancer (PC-3) cells under in vitro conditions was examined by using the MTT assay. Briefly, 1×10^4 cells were seeded into each well of a flat-bottomed 96-well polystyrene-coated plate and incubated for 24 h in a CO_2 incubator at 5% CO_2 and 37 °C. 100X stock solutions of the compounds were prepared in DMSO, and the cells were treated with increasing concentrations of compounds ranging from 0 to 100 μM. Each concentration was run in triplicate and 1% DMSO, the highest DMSO concentration used for treatment, used as a vehicle control, was found to be nontoxic to the cells. After 24 h of incubation, 10 μL per well of MTT solution (stock solution of 5 mg/mL in phosphate buffered saline) was added and incubated for 4 h at 37 °C. The formazan crystals thus formed were dissolved in acidified 2-propanol (100 μL), and the intensity of the colour progression was measured with a microplate reader at 595 and 630 nm. The absorbance readings from the two wavelengths were subtracted and the percentage viability and EC_{50} were determined. The viability of untreated cells was comparable to those treated with the vehicle control, and untreated cells were considered to be 100% viable.

Acknowledgments

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