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## Solution chemistry and cytotoxic properties of novel organogold(III) compounds

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**Abstract**—The solution behaviour of some novel organogold(III) compounds was investigated, and their cytotoxic properties evaluated against a few human tumour cell lines (A2780/S, A2780/R, MCF7, HT29 and A549). Specifically, the following compounds were considered:  $[\text{Au}(\text{bipy}^{\text{dmb}}\text{-H})(2,6\text{-xylylidine-H})][\text{PF}_6]$  (AuXyl) and  $[\text{Au}(\text{bipy}^{\text{dmb}}\text{-H})(p\text{-toluidine-H})][\text{PF}_6]$  (AuTol) (in which  $\text{bipy}^{\text{dmb}} = 6\text{-}(1,1\text{-dimethylbenzyl})\text{-}2,2'\text{-bipyridine}$ ),  $[\text{Au}(\text{py}^{\text{dmb}}\text{-H})(\text{AcO})_2]$  (AuPyAcO) (in which  $\text{py}^{\text{dmb}} = 2\text{-}(1,1\text{-dimethylbenzyl})\text{-pyridine}$ ) and  $[\text{Au}(\text{pz}^{\text{Ph}}\text{-H})\text{Cl}_3]\text{K}$  (AuPzCl) (in which  $\text{pz}^{\text{Ph}} = 1\text{-phenylpyrazole}$ ). The solution chemistry of these compounds, under physiological-like conditions, was investigated through UV–vis absorption and <sup>1</sup>H NMR spectroscopies. Significant cytotoxic effects in vitro were observed in selected cases.

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### 1. Introduction

We have recently shown that various gold(III) complexes exhibit promising cytotoxic effects in vitro and are good candidates for further evaluation as antitumour agents.<sup>1</sup> Additional reports on the antitumour properties of selected gold(III) complexes are the result of the research activities of other groups.<sup>2–6</sup> Notably, gold(III) compounds seem to exert their growth inhibitory effects through mechanisms that are distinct from those of the classical anticancer platinum(II) complexes.<sup>7</sup> Among the recently tested compounds, the organogold(III) complex,  $[\text{Au}(\text{bipy}^{\text{dmb}}\text{-H})(\text{OH})][\text{PF}_6]$ , characterised by an appreciable stability within physiological conditions, has proved to be very active against the A2780 cell line;<sup>8</sup> at variance with the platinum(II) complexes, its biological activity seems to be unrelated to a direct interference with DNA function and metabolism.<sup>8</sup> This prompted us to consider the solution behaviour and the biological properties of some additional gold(III) compounds characterised by the pres-

ence of a direct carbon–gold(III) bond; we believe that this latter feature is very important for the stabilisation of the oxidation state +3 of the gold centre. For this purpose, we took advantage of various recent studies on the synthesis, characterisation and reactivity of gold(III) cyclometallated derivatives.<sup>9–11</sup>

In particular, we report here on the solution chemistry and the biological properties of four organogold(III) compounds:  $[\text{Au}(\text{bipy}^{\text{dmb}}\text{-H})(2,6\text{-xylylidine-H})][\text{PF}_6]$  (AuXyl) and  $[\text{Au}(\text{bipy}^{\text{dmb}}\text{-H})(p\text{-toluidine-H})][\text{PF}_6]$  (AuTol) (in which  $\text{bipy}^{\text{dmb}} = 6\text{-}(1,1\text{-dimethylbenzyl})\text{-}2,2'\text{-bipyridine}$ ),<sup>12</sup>  $[(\text{Au}(\text{py}^{\text{dmb}}\text{-H})(\text{AcO})_2)]$  (AuPyAcO) (in which  $\text{py}^{\text{dmb}} = 2\text{-}(1,1\text{-dimethylbenzyl})\text{-pyridine}$ )<sup>12</sup> and  $[\text{Au}(\text{pz}^{\text{Ph}}\text{-H})\text{Cl}_3]\text{K}$  (AuPzCl) (in which  $\text{pz}^{\text{Ph}} = 1\text{-phenylpyrazole}$ ).<sup>13</sup> The AuXyl and AuTol compounds, both featuring the same terdentate C, N, N ligand, inspired us by the encouraging results recently attained with the parent compound  $[\text{Au}(\text{bipy}^{\text{dmb}}\text{-H})(\text{OH})][\text{PF}_6]$ . Specifically, we wanted to establish whether the introduction of a bulkier ligand in the fourth coordination position might have effects on the solution behaviour and the pharmacological profile of this organogold(III) compound. At variance, AuPyAcO, having a cyclometallated C, N ligand, and AuPzCl, with a monodentate C ligand, represent examples of compounds in which the gold(III) centre is less protected than in the

**Keywords:** Organogold(III) complexes; UV–vis absorption spectroscopy; <sup>1</sup>H NMR spectroscopy; Cytotoxicity; Gold; Cancer.

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former cases. Remarkably, AuPyAcO presents two accessible coordination positions occupied by two acetate groups whereas AuPzCl bears three exchangeable chlorides that might undergo facile hydrolysis within an aqueous environment.

Overall, we have observed that the organogold(III) moieties of all these compounds, except AuPzCl, are generally stable under physiological conditions, and exhibit significant cytotoxic properties towards a restricted panel of human tumour cell lines. Based on these observations, the present compounds may be of interest for further evaluation as anticancer agents.

## 2. Results

### 2.1. Main structural aspects

The following compounds have been considered in the present study: AuXyl, AuTol, AuPyAcO and AuPzCl (see Scheme 1). The structure in the solid state has been determined only for AuXyl;<sup>12</sup> that of the analogous compound AuTol can be deduced from spectroscopic data and other physicochemical measurements. Equally, the organometallic fragments of AuPzCl and AuPyAcO are confidently assumed to match those of the related complexes  $[\text{Au}(\text{pz}^{\text{Ph}}\text{-H})(3,5\text{-Me}_2\text{py})\text{Cl}_2]$ <sup>13</sup> and  $[\text{Au}(\text{py}^{\text{dmb}}\text{-H})\text{Cl}_2]$ ,<sup>14</sup> respectively, whose crystal structures have been ascertained by X-ray diffraction analysis.

Notably, all these compounds are characterised by the presence of a direct carbon–gold bond. AuXyl and AuTol, obtained by proton exchange of  $[\text{Au}(\text{bipy}^{\text{dmb}}\text{-H})(\text{OH})][\text{PF}_6^-]$  with 2,6-xylylidine and *p*-toluidine, respectively, show a significant enhancement of the hydrophobic properties compared to the parent complex.<sup>12</sup> In AuPyAcO the cyclometallated benzylpyridine provides a nitrogen and a carbon donor to the square planar gold(III) centre; the remaining coordination sites of the square plane being occupied by two acetate ligands. In AuPzCl the gold(III) centre is coordinated to a carbon atom of the 1-phenylpyrazole ligand and to three chlorides. In all cases, the presence of the carbon–gold

bond is believed to confer sufficient redox stability to the gold(III) centre.

### 2.2. Solution chemistry

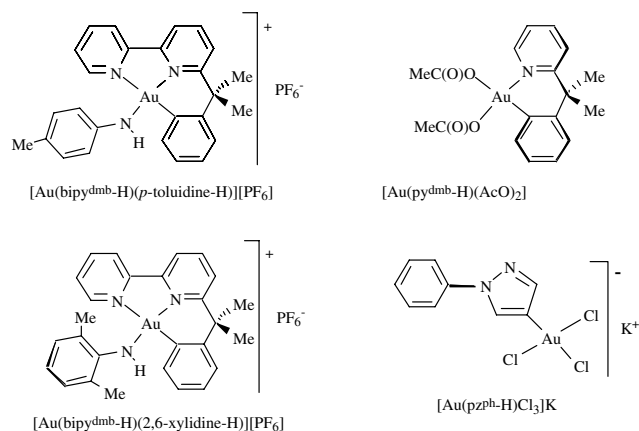
The stability in solution of the various organogold(III) compounds was assayed by simple spectrophotometric measurements. Measurements were carried out within different solvents (DMSO, dichloromethane, water and the reference physiological buffer containing 50 mM sodium phosphate 100 mM NaCl, pH = 7.4). Some significant spectrophotometric results are shown in Figure 1.

AuXyl and AuTol are stable in organic solvents such as dichloromethane or DMSO. Under these conditions both compounds exhibit an intense band in the visible (centred around 420 nm) that is tentatively assigned as a  $\text{N}^-$  to gold(III) charge transfer. The hydrolysis of both compounds, either in water or in a physiological-like buffer, is very fast and results into nearly complete disappearance of the 420 nm band; notably, hydrolysis in water is accompanied by a significant pH decrease. However, the UV transitions characteristic of the Aubipy<sup>dmb</sup> scaffold (centred at 320 nm)<sup>8</sup> are not perturbed upon hydrolysis. The  $[\text{Au}(\text{bipy}^{\text{dmb}}\text{-H})(\text{OH})]^+$  species is most likely formed in both cases by proton exchange of the amidogold complexes AuXyl and AuTol with water; concomitant release of the aromatic amine takes place. Indeed, these compounds can be quantitatively obtained by the reaction of  $[\text{Au}(\text{bipy}^{\text{dmb}}\text{-H})(\text{OH})][\text{PF}_6^-]$  with an excess of the corresponding amines, only providing that water, produced by the reaction, is removed.<sup>12</sup>

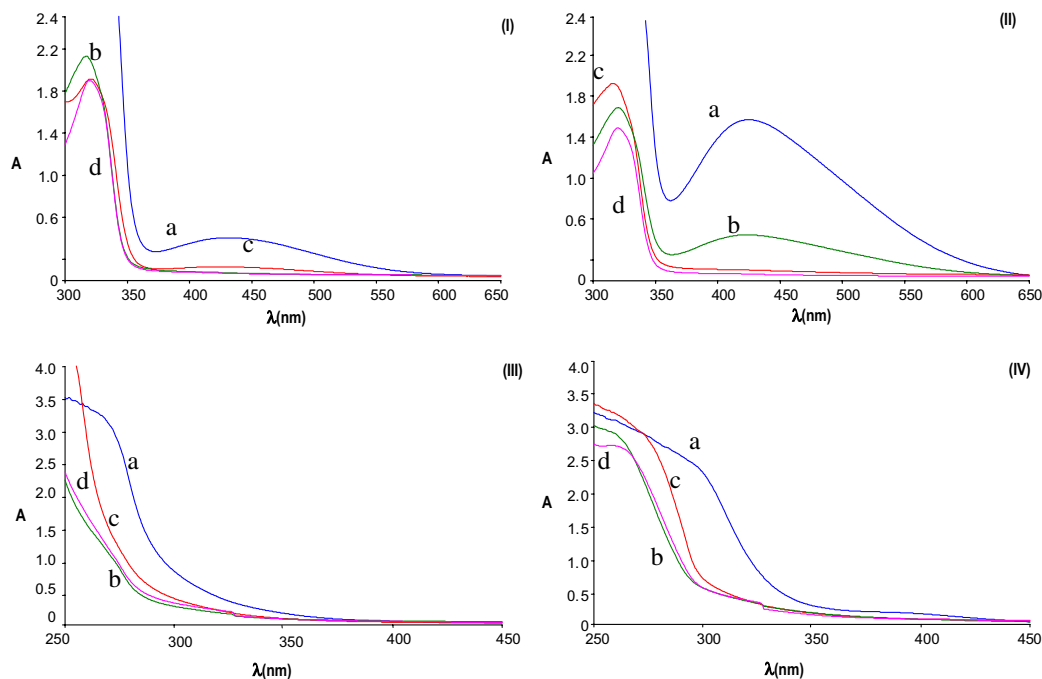
Solutions of AuPyAcO, either in water or in organic solvents, are colourless. When dissolved in water or in the reference buffer, AuPyAcO exhibits some characteristic bands in the near UV, around 260 nm that are stable with time. Upon considering that the acetate moieties generally behave as good leaving groups in aqueous solutions, we may expect their hydrolysis and replacement by hydroxide. Apparently, the resulting species is stable in solution for several hours.

When dissolved within organic solvents, AuPzCl imparts a characteristic yellow colour to the solution. In water, or in the reference buffer, fast fading of the colour is observed ascribed to rapid hydrolysis of gold(III) coordinated chlorides as in the case of the  $\text{AuCl}_4^-$  anion.<sup>15</sup> The process is accompanied by a drastic decrease in pH. However, this process may be reversed, almost completely, by addition of excess chloride, for example, LiCl. Notably, the UV spectrum of AuPzCl, dissolved in the buffer, shows a slow, progressive decrease of the main band centred at 250 nm (Fig. 1, IV). The process reaches completion within about 12 h at 25 °C. We interpret this behaviour in terms of a progressive modification of the hydrolysed species.

Overall, from the above reported spectrophotometric experiments, it emerges that the first three compounds, following quick hydrolysis of their respective labile ligands, produce organogold(III)-containing species that



Scheme 1. Schematic drawing of the four gold(III) complexes.



**Figure 1.** UV-vis spectra of AuXyl (I), AuTol (II), AuPyAcO (III) and AuPzCl (IV). Traces a represent the compounds dissolved in DMSO at 5 mM concentration. Then the DMSO mother solutions of the four compounds were diluted 1:4 either in pure DMSO (traces b) or in the reference phosphate buffer (traces c) or in water (traces d).

are stable for several hours under physiological-like conditions. At variance, the hydrolysis product of AuPzCl manifests a lower stability and undergoes further transformations.

The behaviour in solution of AuXyl and AuTol was further analysed by  $^1\text{H}$  NMR spectroscopy. The spectra were recorded either in deuterated DMSO or in deuterated aqueous solutions. Notably, the  $^1\text{H}$  NMR spectra of AuXyl and AuTol, in DMSO, exhibit the resonances characteristic of the cyclometallated bipyridine ligand, plus resonances assigned to the xylylidine or tolylidine moieties coordinated to the gold(III) centre. Upon hydrolysis within the reference deuterated buffer, the  $^1\text{H}$  NMR spectra exhibit some characteristic modifications that are ascribed to release of either xylylidine or tolylidine from gold(III) coordination; at the same time loss of the characteristic colour is detected. In the final  $^1\text{H}$  NMR spectra signals characteristic of free xylylidine or free tolylidine are easily recognised (at 6.87, 6.60 and 2.06 ppm for xylylidine; at 6.97, 6.65 and 2.13 ppm for tolylidine) in agreement with our hypothesis.

Thus, the  $^1\text{H}$  NMR results confirm the picture coming out from the spectrophotometric measurements. AuXyl and AuTol dissolved in the buffer rapidly hydrolyse their amide ligands. However, the molecular scaffold of these compounds, characterised by the presence of a direct carbon-to-gold bond, is pretty stable and does not show any sign of reduction of the gold(III) centre.

### 2.3. Cytotoxic effects

Owing to the appreciable stability of the various organogold(III)-containing fragments under physiological-like

conditions, all the above compounds could be evaluated *in vitro* as potential cytotoxic agents.

These organogold(III) compounds were tested against the following human tumour cell lines: A2780/S, A2780/R (ovarian cancer), MCF7 (breast cancer), HT29 (colon cancer) and A549 (lung cancer). Their growth inhibitory properties were analysed through the classical sulforhodamine-B method.<sup>12</sup> Results are shown in Table 1. For comparison purposes, results obtained with  $[\text{Au}(\text{bipy}^{\text{dmb}}\text{-H})(\text{OH})][\text{PF}_6]$ —the precursor of AuXyl and AuTol; oxaliplatin and cisplatin (both currently used as anticancer drugs in the clinics) are also reported.

Notably, AuPyAcO and AuXyl proved to be significantly active against the two ovarian carcinoma cell lines, with  $\text{IC}_{50}$  values of  $2.90 \pm 0.34 \mu\text{M}$  and  $2.50 \pm 0.43 \mu\text{M}$ , respectively, on the A2780/S cell line. Cross-resistance is relatively modest as it emerges from inspection of the data obtained on the A2780/S and A2780/R lines. Lower but still important cytotoxic effects were produced by AuTol ( $6.15 \pm 1.40 \mu\text{M}$ ) and  $[\text{Au}(\text{bipy}^{\text{dmb}}\text{-H})(\text{OH})][\text{PF}_6]$  ( $8.20 \pm 2.0 \mu\text{M}$ ) on the same A2780/S line. Modest effects were observed on the MCF7 cell line, except for AuXyl ( $5.20 \pm 0.40 \mu\text{M}$ ) ( $5.30 \pm 0.87 \mu\text{M}$ ); negligible effects were generally measured on the HT29 and A549 lines. At variance with the other organogold(III) compounds, AuPzCl turned out to be virtually devoid of cytotoxicity towards all tested cell lines, probably in relation to its lower chemical stability profile.

It is worthwhile noting that the three compounds  $[\text{Au}(\text{bipy}^{\text{dmb}}\text{-H})(\text{OH})][\text{PF}_6]$ ,  $[\text{Au}(\text{bipy}^{\text{dmb}}\text{-H})(2,6\text{-xylylidine-H})][\text{PF}_6]$  and  $[\text{Au}(\text{bipy}^{\text{dmb}}\text{-H})(p\text{-toluidine-H})][\text{PF}_6]$

**Table 1.** IC<sub>50</sub> (μM) values of organogold(III) compounds in human tumour cells, sensitive or resistant to cisplatin

Compounds	IC <sub>50</sub> (μM) <sup>a</sup>				
	A2780/S	A2780/R	MCF7	HT29	A549
AuPzCl	30.20 ± 0.24	31.30 (1.0)	33.70 ± 2.15	>50	>50
[Au(bipy <sup>dmb</sup> -H)(OH)][PF <sub>6</sub> ]	8.20 ± 2.00	12.70 ± 1.42 (1.6)	35.30 ± 8.80	24.60	>50
AuPyAcO	2.90 ± 0.34	6.40 ± 0.10 (2.2)	17.70 ± 0.44	8.60	~49
AuXyl	2.50 ± 0.43	5.70 ± 0.03 (2.3)	5.20 ± 0.40	~25	~35
AuTol	6.15 ± 1.40	14.30 ± 0.94 (2.3)	18.10 ± 0.64	~25	~35
Cisplatin	0.33 ± 0.04	6.40 ± 0.87 (19.3)	5.30 ± 0.87	6.30 ± 0.23	—
Oxaliplatin	0.40 ± 0.12	0.20 ± 0.02 (0.5)	0.13 ± 0.10	0.40 ± 0.16	—

Data were collected after 72 h exposure to the drugs.

<sup>a</sup> IC<sub>50</sub> is defined as the concentration of drug required to inhibit cell growth by 50% compared to control; it is expressed as mean ± SE of at least three determinations or mean of two determinations; values in parentheses ( ) denote the ratios of IC<sub>50</sub> of cisplatin-resistant cell line and IC<sub>50</sub> of parental sensitive cell line.

exhibit significant variations in their cytotoxic properties against the tested cell lines, in spite of the fact that all of them most likely transform into the same species when dissolved in the reference buffer. This observation implies that the presence of the 2,6-Me<sub>2</sub>C<sub>6</sub>H<sub>3</sub>NH<sup>-</sup> or 4-MeC<sub>6</sub>H<sub>5</sub>NH<sup>-</sup> ligand affects somehow the biological activities of the common organogold(III) centre.

### 3. Discussion

Owing to the encouraging *in vitro* antitumour properties recently observed for Au(bipy<sup>dmb</sup>-H)(OH)[PF<sub>6</sub>], new organogold(III) complexes were prepared, characterised and tested as potential cytotoxic agents. The solution behaviour and the stability within a physiological-like environment of these novel organogold(III) compounds was investigated. In all cases, the gold(III) centre does not undergo reduction, being adequately stabilised by the direct carbon-to-gold bond. However, important hydrolysis processes take place. Specifically, in the case of AuXyl and AuTol, hydrolysis and release of either xylylidine or toluidine are clearly observed resulting in the formation of the parent hydroxo-complex. Both AuPyAcO and AuPzCl undergo to some extent hydrolysis of the anionic coligands. Afterwards, further degradation is observed in the case of the pyrazolato derivative, which bears a monodentate C ligand.

The cytotoxic properties of all these compounds were tested against the A2780/S, A2780/R, MCF7, HT29 and A549 human tumour cell lines. Notably, the investigated organogold(III) compounds, with the exception of AuPzCl, proved significantly active against the former tumour cell lines, with cytotoxicity values falling in the low micromolar range. Some differences were observed in the activity patterns of AuXyl and AuTol compared to the reference [Au(bipy<sup>dmb</sup>-H)(OH)][PF<sub>6</sub>] compound.<sup>7</sup> Moderate effects were observed on the MCF7 and HT29 lines, whereas negligible effects were measured on the A549 line. Overall, similar trends of biological activity were identified among the three active compounds that are suggestive of a similar mechanism of action. We believe that the specificity of their biological effects may be ascribed to the presence of a gold(III) centre, characterised by an acceptable stability profile under physiologi-

cal-like conditions. In the light of these observations, the gold(III) containing molecular fragment is very likely to be responsible for the observed cytotoxic effects, although the actual mechanism is not yet understood.

## 4. Experimental

### 4.1. Chemicals

Common chemical reagents were purchased from SIGMA Chemical Co. (Milano, Italy) and Pharmacia. Fetal calf serum (FCS), antibiotics, and RPMI-1640 medium were obtained from Gibco Life Technologies Italia (Milano, Italy).

Synthesis of [Au(bipy<sup>dmb</sup>-H)(2,6-xylylidine-H)][PF<sub>6</sub>] (AuXyl),<sup>12</sup> [Au(bipy<sup>dmb</sup>-H)(*p*-toluidine-H)][PF<sub>6</sub>] (AuTol),<sup>12</sup> [Au(py<sup>dmb</sup>-H)(CH<sub>3</sub>COO)<sub>2</sub>] (AuPyAcO)<sup>12</sup> and [Au(pz<sup>Ph</sup>-H)Cl<sub>3</sub>]K (AuPzCl).<sup>13</sup> The title compound was prepared according to Refs. 12 and 13.

### 4.2. Electronic spectra

The absorption spectra in the UV–vis region were recorded on a Perkin–Elmer Lambda 20 Bio spectrophotometer operating at room temperature. The electronic spectra were recorded at room temperature, adding small amounts of freshly prepared, concentrated solutions of the individual complexes in DMSO to, respectively, DMSO, water or to the reference buffer (50 mM phosphate, pH 7.4, 100 mM NaCl); the concentrations of each gold(III) compound was  $1.25 \times 10^{-4}$ . The hydrolysis experiments were carried out monitoring the electronic spectra of  $5 \times 10^{-4}$  M gold(III) complexes solutions in DMSO over 24 h.

### 4.3. <sup>1</sup>H NMR studies

Solution <sup>1</sup>H NMR spectra of the gold(III) complexes were recorded on a Varian Gemini 2000 spectrometer operating at 300 MHz. The  $2.5 \times 10^{-3}$  M solutions were prepared in *d*<sup>6</sup>-DMSO and in 50 mM PO<sub>4</sub><sup>3-</sup>, 4 mM NaCl, pH 7.4 deuterated buffer. The spectra were recorded immediately after dissolution.

#### 4.4. Cell culture and cytotoxicity assay

Cytotoxicity studies were carried out on the A2780/S, A2780/R, MCF7, HT29 and A549 human tumour cell lines. The cisplatin-resistant A2780/R cell line was produced by repeated 1 h weekly exposure to 50  $\mu$ M of the sensitive parental cell line.<sup>8</sup> Cell lines were cultured in RPMI-1640 medium (GIBCO Life technologies Product catalog, RPMI 1640 medium, Cat. no 11817) supplemented with 10% FCS and antibiotics (streptomycin 100  $\mu$ g/mL and penicillin 100 U/mL) at 37 °C in a 5% CO<sub>2</sub> atmosphere and subcultured twice weekly. Experiments were conducted on exponentially growing cells. Drugs were dissolved in DMSO. Inhibition of cell growth was determined after a 72 h drug exposure through the Sulforhodamine-B (SRB) assay<sup>16</sup> for the ovarian carcinoma cell lines.

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