Gold(III) Compounds as Anticancer Drugs

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Abstract

Gold(III) complexes constitute a new class of metallodrugs, of potential interest for cancer treatment. During the past decade different kinds of gold(III) complexes have been reported to be appreciably stable under physiological-like conditions and to manifest relevant antiproliferative properties against selected human tumor cell lines. Some relevant examples are presented. Recent investigations point out that the interactions of cytotoxic gold(III) complexes with DNA are significantly different and weaker than those of platinum analogues; important interactions with model proteins and target proteins have been reported as well. Accordingly, the mechanisms of action of cytotoxic gold(III) complexes seem to be innovative and substantially different from that of cisplatin. Relevant antimitochondrial effects were demonstrated in some cases, eventually leading to cell apoptosis.

Gold(III) Compounds as Anti-tumour Agents

The serendipitous discovery of the anticancer properties of cisplatin, dating back to 1965, promoted a great deal of interest in the area of metal-based anti-tumour agents[1]. The large anticancer effects observed for cisplatin suggested that other metal-based compounds, at least in principle, might be similarly useful as anti-tumour drugs[2, 3]. Since Au(III) is isoelectronic and isostructural with Pt(II), square planar gold(III) complexes soon appeared to be suitable candidates for biological testing. However, in comparison with Pt(II) compounds, Au(III) analogues turned out to be relatively unstable and light-sensitive, and to undergo easy reduction to metallic gold, under physiological conditions. As a consequence of these difficulties, that heavily hindered their pharmaceutical applications, gold(III) compounds were rapidly abandoned and then neglected for several years[4].

However, during the early 90's, there was a revival of interest toward gold(III)-based anticancer compounds driven by a few novel compounds, endowed with improved stability and with encouraging pharmacological properties. For instance, a series of organogold(III) DAMP (DAMP = o-$C_6H_4CH_2NMe_2$) complexes, [Au(DAMP)X_2], were prepared and characterized by Buckley, Parish and Fricker, and screened for anti-tumour activity with positive results[5, 6]. Other gold(III) complexes, with putative anticancer properties, were prepared and tested in the same period, e.g. the gold(III) complex of streptonigrin[7] and the trichlorogold(III) derivatives of methylimidazole, methylbenzoxazole, and dimethylbenzoxazole described by Ponticelli *et al.*[8].

Later on, in the attempt of obtaining pharmaceutically useful substances with an even better stability profile, some classical square planar gold(III) complexes, based on a variety of structurally different ligands, were prepared and tested [9-11]. In order to enhance the stability of the gold(III) centre, multidentate ligands such as polyamines, cyclam, terpyridine and phenathroline were preferentially used. A few resulting compounds – namely [Au(en_2)]Cl_3 **1**, [Au(dien)Cl]Cl_2 **2**, [Au(cyclam)]$(ClO_4)_2Cl$ **3**, [Au(terpy)Cl]Cl_2 **4**, and [Au(phen)Cl_2]Cl-**5** – were characterised in detail, both in the solid state and in solution (Figure 1). Their solution behaviour was investigated through various physico-chemical methods including visible absorption spectroscopy, ESI mass spectrometry, and chloride-selective potentiometric measurements[10]; a quite satisfactory stability profile emerged from these studies that opened the way to extensive pharmacological testing *in vitro*.

Their cytotoxic properties were tested *in vitro*, by the sulforhodamine B assay, on the representative human ovarian tumor cell line A2780, either sensitive or resistant to cisplatin. In most cases, the investigated compounds showed relevant *in vitro* anticancer properties with IC_{50} values generally falling in the low μM range[10]; additionally, these compounds turned out to overcome largely resistance to cisplatin in cisplatin-resistant cell lines. Some relevant cytotoxicity data are reported in Table 1.

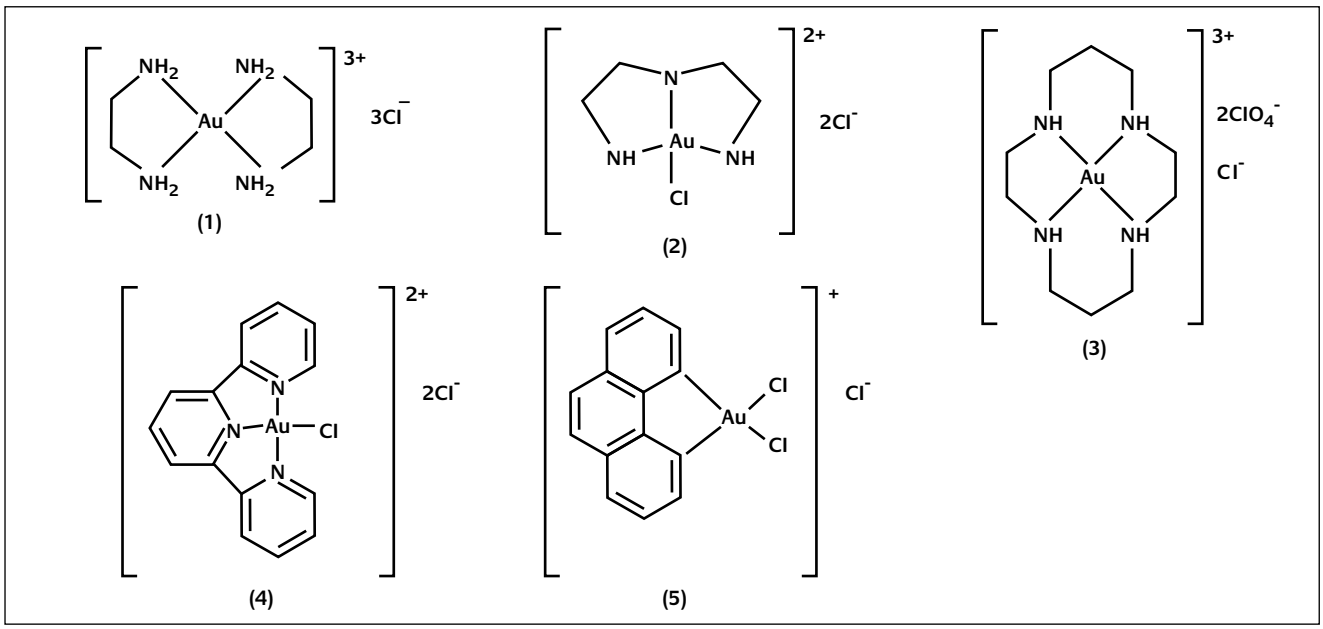

Figure 1

*Schematic drawing of (**1**) [Au(en$_2$)]Cl$_3$, (**2**) [Au(dien)Cl]Cl$_2$, (**3**) [Au(cyclam)](ClO$_4$)$_2$Cl, (**4**) [Au(terpy)Cl]Cl$_2$, and (**5**) [Au(phen)Cl$_2$]Cl.*

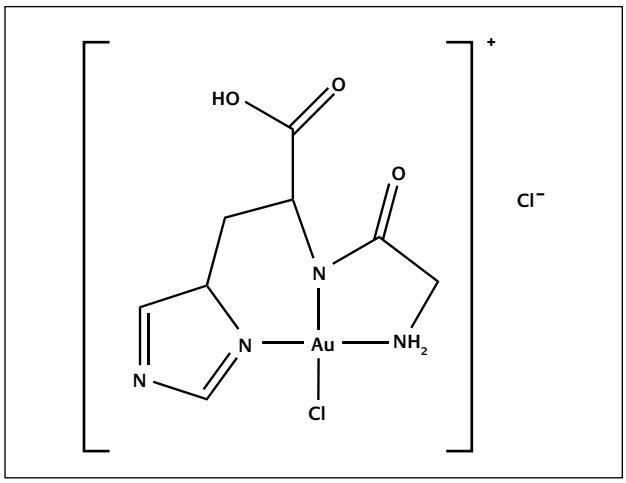

Figure 2

*Schematic drawing of of GHAu (**6**).*

In the same years, the solution behaviour and the cytotoxic properties of chloro- glycylhistidinate gold(III) (GHAu) **6** (Figure 2), a complex with promising chemical and biological properties[12, 13], was reported. Notably, this gold(III) peptide complex manifested a far higher cytotoxic activity towards the established A2780 ovarian carcinoma human cell line (see Table 1) compared to its zinc(II), palladium(II), platinum(II) and cobalt(II) analogues, proving that the gold(III) centre has a crucial role in determining the pharmacological effects[13].

A novel series of gold(III) compounds, of potential use as anticancer agents, namely the gold(III) phenylpyridine (ppy) derivatives were described by Fan and Ranford at the beginning of the 2000's[14]. [Au(ppy)Cl$_2$], forming a five-membered cycloaurated chelated ring with the bidentate ppy ligand, is the reference compound for this family. The two remaining coordination positions in [Au(ppy)Cl$_2$] are occupied by two chloride groups in *cis* to each other, thus conferring some structural analogy to cisplatin. Inspired by [Au(ppy)Cl$_2$], Fan and Ranford prepared and characterised a number of analogues containing carboxylate ligands in the place of chloride to improve aqueous solubility. The main structural aspects of these complexes were unambiguously elucidated by X-ray diffraction studies. All these gold(III) complexes were then tested for cytotoxic properties *in vitro* against MOLT-4 (human leukemia) and C2C12 (mouse tumour) cell lines. A cytotoxicity profile similar to cisplatin was found in the case of MOLT-4 cell line whereas no significant activity was observed on the C2C12 cell line.

In 2002, in collaboration with Minghetti and Cinellu (University of Sassari, Italy), we realised that some novel gold(III) complexes, bearing the bipyridyl motif (bipy), might be advantageously employed for cancer treatment. These compounds turned out to be reasonably stable within a physiological buffer and to produce relevant antiproliferative effects on various human tumor cell lines (Table1)[15]. A detailed description of these compounds is given in the next section. A number of analogues were subsequently prepared and characterized[16].

In the same years Fregona and coworkers prepared and characterised some novel gold(III) dithiocarbammate compounds showing a very promising chemical and biological profile[17]. The compounds containing N,N-dimethyldithiocarbamate and ethylsarcosinedithiocarbamate are the most representative members of this family. Early *in vivo* data looked very encouraging and led to the patenting of these novel compounds. Additionally, a conspicuous number of investigations have been carried out aimed at elucidating some aspects of their mechanism of action at a cellular and biochemical level.

Table 1

Cytotoxicity (IC_{50} μM) of the gold compounds studied in Florence during the last years towards different tumour cell lines. Cisplatin is reported as reference compound. Data were collected after 72 h exposure to drug.

Compounds	A2780/S	A2780/R	CCRF-CEM/S	CCRF-CEM/R	SK-OV-3	MCF7	HT29	A549
cisplatin	1.2±0.43	14±2.72	0.7±0.1	20.1±7.2	5.2	5.30±0.87	6.30±0.23	-
$[Au(en)_2]Cl3$	8.36±0.77	17.0±4.24	-	-	-	-	-	-
$[Au(dien)Cl]Cl_2$	8.2±0.93	18.7±2.16	12.6±2.0	32.7±6.6	-	-	-	-
$[Au(cyclam)](ClO_4)_2Cl$	99.0	>120.0	-	-	-	-	-	-
$[Au(Terpy)Cl]Cl_2$	0.2	0.37±0.032	-	-	-	-	-	-
$[Au(Phen)Cl_2]Cl$	3.8±1.1	3.49±0.91	2.3	6	-	-	-	-
GHAu	5.2±1.63	8.5±2.3	-	-	-	-	-	-
$[Au(bipy)(OH)_2][PF_6]$	8.8±3.9	24.1±8.7	52.9±11.6	58.6±0.9	34.4±4.7			
$[Au(bipy^{c}\text{-}H)(OH)][PF_6]$	3.3±1.4	8.2±1.5	11.9±2.1	51.2±5.6	13.3±1.6	35.30±8.8	24.60	>50
$Au(bipy^{dmb}\text{-}H)$ (2.6-xylidine-H)][PF_6]	2.50±0.43	5.7±0.3	-	-	-	5.20±0.40	~25	~35
$Au(py^{dmb}\text{-}H)(AcO)_2]$	2.90±0.34	6.40±1.0	-	-	-	17.70±0.44	8.60	~49
Auoxo1	22.8±1.53	23.3±0.35	-	-	-	-	-	-
Auoxo2	12.1±1.5	13.5±1.8	-	-	-	-	-	-
Auoxo3	25.4±2.47	29.8±3.1	-	-	-	-	-	-
Auoxo4	12.7±1.06	19.8±1.8	-	-	-	-	-	-
Auoxo5	11.0±1.5	13.2±1.2	-	-	-	-	-	-
Auoxo6	1.79±0.17	4.81±0.5	-	-	-	-	-	-

Some interesting gold(III) porphyrin compounds were first described by Chi Ming Che and Hongzhe Sun in 2003[18]. Notably, these compounds manifested some targeting specificity for DNA and seemed very promising for cancer treatment in terms of cytotoxic potency. Details of their chemistry and of their biological actions are given in the next section.

Finally, a series of dinuclear gold(III) complexes with a "Au_2O_2" diamond core and with bypiridyl ligands have been characterised and tested in our laboratory[19], exhibiting interesting *in vitro* biological properties (Table 1) as described in more detail in the next section.

Overall, the renewed interest for gold(III) compounds as potential anti-tumour agents, that started at the beginning of 90's, has resulted, until now, in the production of a conspicuous number of gold(III) and organogold(III) compounds characterised by a great structural variety and by encouraging pharmacological properties. Notably, most of

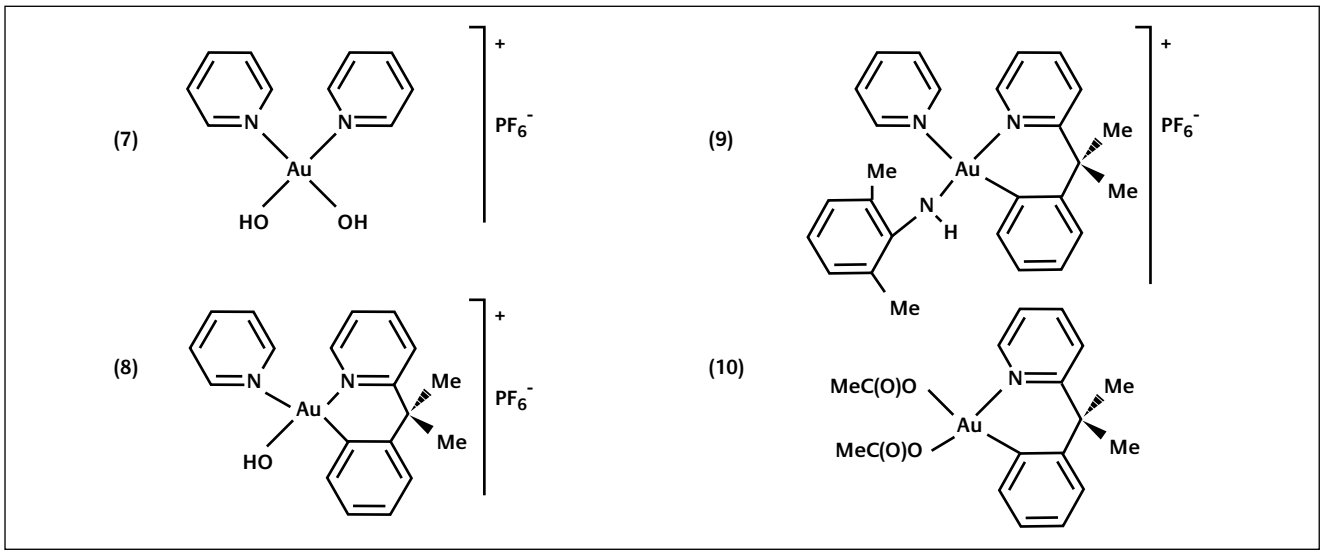

Figure 3

*Schematic drawing of $[Au(bipy)(OH)_2][PF_6]$ (**7**), $[Au(bipy^{c}\text{-}H)(OH)][PF_6]$ (**8**), $Au(bipy^{dmb}\text{-}H)$(2.6-xylidine-H)][PF_6] (**9**), $Au(py^{dmb}\text{-}H)(AcO)_2]$ (**10**), where $bipy^{dmb}$ = 6-(1,1-dimethylbenzyl)-2,2'-bipyridine); py^{dmb} = 2-(1,1-dimethylbenzyl)-pyridine).*

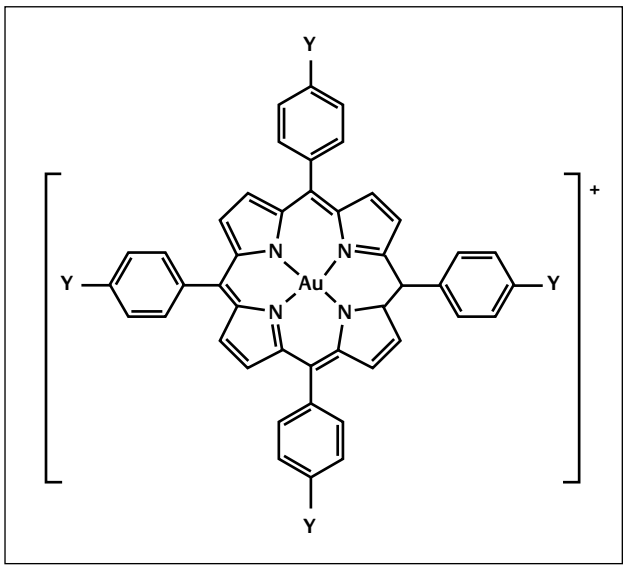

Figure 4
*Gold(III) meso-tetraarylporphyrins complexes. Y = H (**a**), Me (**b**), OMe (**c**), Br (**d**), Cl (**e**).*

these compounds revealed significant antiproliferative effects when tested *in vitro* against various tumor cell lines and are undoubtedly good candidates for further pharmacological evaluation. A few representative cases are described, below.

Some Representative Examples

a Gold(III) Bipyridyl compounds

$[Au(bipy)(OH)_2][PF_6]$ **7** and $[Au(bipy^c\text{-}H)(OH)][PF_6]$ **8**, two gold(III) compounds characterized by the presence of a bipyridyl ligand (Figure 3), were extensively investigated for their solution behaviour and their biological properties [16].

In $[Au(bipy)(OH)_2][PF_6]$, two adjacent coordination positions of the square planar gold(III) chromophore are occupied by two nitrogen atoms of the bipyridyl ligand, the remaining positions being occupied by two hydroxide groups. At variance, $[Au(bipy^c\text{-}H)(OH)][PF_6]$ (where $bipy^c$ = 6-(1,1-dimethylbenzyl)-2,2'-bipyridine) is an organogold(III) complex in which donors to the gold(III) centre are two nitrogens of the bipyridyl ligand, the C_2 carbon of the phenyl group, and a hydroxide group. Small deviations from square-planar geometry are observed in the classical bipyridyl complexes whereas such deviations are quite large in the case of cyclometallated derivatives due to a limited flexibility of the N,N,C-ligand.

The complexes **7** and **8** are soluble enough in aqueous buffers. The intense visible bands of these complexes, LMCT in nature, are diagnostic for the presence of gold +3; visible spectra were exploited to monitor the reactivity of these gold(III) compounds with biomolecular targets. Notably, these two complexes manifested a clearly different behaviour in the reaction with ascorbate: sodium ascorbate causes immediate disappearance of the main visible band of the $[Au(bipy)(OH)_2]$+ chromophore but does not modify the visible spectrum of $[Au(bipy^c\text{-}H)(OH)]^+$. This means that the oxidation state +3 is more stable in the case of the organogold(III) complex compared to $[Au(bipy)(OH)_2][PF_6]$, in line with previous indications from electrochemical studies, making the former complex a better candidate for pharmacological studies [20].

The *in vitro* cytotoxicity properties of these bipyridyl gold(III) complexes were analysed toward the human ovarian carcinoma cell line A2780, either sensitive (A2780/S) or resistant (A2780/R) to cisplatin. Both gold(III) complexes showed important cell killing effects, with IC_{50} values falling in the low micromolar range (see Table 1). $[Au(bipy^c\text{-}H)(OH)][PF_6]$ turned out to be the most active with a twofold higher activity than cisplatin in the A2780/R cell line. The cytotoxic properties of these complexes were also evaluated on the human ovarian cell line SKOV3 (inherently resistant to cisplatin) and on the CCRF-CEM leukemic cell line, either sensitive (CCRF-CEM/S) or resistant (CCRF-CEM/R) to cisplatin. In these cell lines both gold(III) complexes were generally less active compared to the A2780 line. Notably, these gold(III) complexes retain, to a large extent, their cytotoxic activity toward the cisplatin-resistant A2780/R and CCRF-CEM/R lines suggesting that the mechanisms of resistance to cisplatin - most likely intracellular detoxification and increased repair of DNA damage- are scarcely effective toward these gold(III) complexes, in line with previous findings on other gold(III) compounds.

The cytotoxic properties of the free 2,2'-bipyridyl ligand were also tested; this ligand is practically devoid of toxicity toward the A2780/S cell line while showing some partial activity, at high concentrations, in the other cell lines (Table 1).

In summary, these novel gold(III) complexes, bearing the bypiridyl motif, showed acceptable stability within physiological-like environments while exhibiting important cytotoxic properties. In addition, preliminary studies have pointed out that the interactions of these complexes with DNA are weak whereas relatively tight adducts are formed upon reaction with model proteins and serum proteins[16].

Given its greater stability within biological fluids, even in the presence of reducing agents, the organometallic $[Au(bipy^c\text{-}H)(OH)][PF_6]$ compound holds promise as a potential anti-tumour drug and is undergoing more extensive biological testing.

Very recently, other new organogold(III) analogues, $[Au(bipy^{dmb}\text{-}H)(2,6\text{-xylidine})](PF_6)$ **9** ($bipy^{dmb}$ = (1,1-dimethyl benzyl)-2,2'-bipyridine) and $[(Aupy^{dmb}\ CH_3COO)_2]$ **10** (py^{dmb} = 2-(1,1-dimethylbenzyl)-pyridine) (Figure 3) have been synthesized and successfully tested in our laboratory [21].

b Gold(III) Porphyrins

A series of interesting gold(III) meso-tetraarylporphyrins (TPP) complexes were recently described by Chi Ming Che, Hongzhe Sun and coworkers[23]. These compounds, of general formula [Au(III)(*p*-Y-TPP)]Cl, [with Y = H (**a**), Me (**b**), OMe (**c**), Br (**d**) and Cl (**e**)] (see Figure 4), were prepared and characterised by classical procedures[22]. Coordination to the tetrapyrrole ring results into a large stabilization of

the gold(III) centre. Accordingly, these gold(III) porphyrins exhibited excellent stability in solution around pH 7; no significant spectral changes were observed over large time intervals at room temperature based on UV-vis spectroscopy. Also, these gold(III) porphyrins revealed a high stability against glutathione (GSH), a biological reductant that is present, at high concentrations, inside cells.

The cytotoxic effects of compounds **a–e** toward established human cancer cell lines, including some drug resistant variants, were measured through the MTT assay. Remarkably, all gold(III) porphyrins showed relevant antiproliferative effects with IC_{50} ~ 0.1–1.5 μM. Importantly, **a** was found to be similarly cytotoxic toward cisplatin-resistant nasopharyngeal carcinoma (CNE1) cell lines with an IC_{50} value of 0.17 μM, which corresponds to *ca.* 240-fold higher potency compared to cisplatin. The lack of cross resistance suggests that gold(III) porphyrins and cisplatin induce cytotoxicity through different mechanisms.

For comparison purposes , a zinc(II) porphyrin [Zn(II)(TPP)] was also tested and found to be at least 100-fold less potent than the gold(III) porphyrins in killing cancer cells (IC_{50} > 50 μM). This experiment highlights again the crucial role of the gold(III) centre in producing the biological actions. Yet, the porphyrin ligand was found to be essential for the anticancer activities. So these authors concluded that the porphyrin ligand is crucial both in stabilizing the Au(III) centre and in carrying the metal to its cellular targets [23].

DNA is one of the major targets for anticancer drugs [24] and binding of metalloporphyrins to DNA has been studied extensively [25]. Hongzhe Sun and coworkers examined the interaction of representative gold(III) porphyrins with duplex DNA by UV-vis absorption titrations [23]. Isosbestic spectral changes and significant hypochromicity of the Soret band were noticed upon addition of calf thymus DNA suggesting a direct interaction of gold(III) porphyrins with the DNA double helix. Moreover, by using confocal microscopy, these authors reported that gold(III) porphyrins induce extensive apoptosis in HeLa cancer cells. In addition to morphological changes, fragmentation of genomic DNA was also observed after incubating the HeLa cells with compound **a** (Figure 4) for 15 h [26, 27]. In a subsequent study these authors reported that treatment with gold(III) porphyrins induces characteristic changes in protein expression profiles [26].

c Dinuclear gold(III) compounds

A common strategy in the field of anticancer metallodrugs is the design and the preparation of dimetallic or polymetallic compounds, derived from the "fusion" of two or more monometallic molecular fragments, in which the specific reactivity of each metal centre is further controlled by its interactions with the nearby metal centre(s) and by the overall molecular framework. This strategy has been successfully pursued by Farrell and his group in the case of anticancer platinum(II) compounds [29]. Notably, incorporation of two (or more) metal centres within an extended molecular framework may greatly affect the overall charge of the resulting

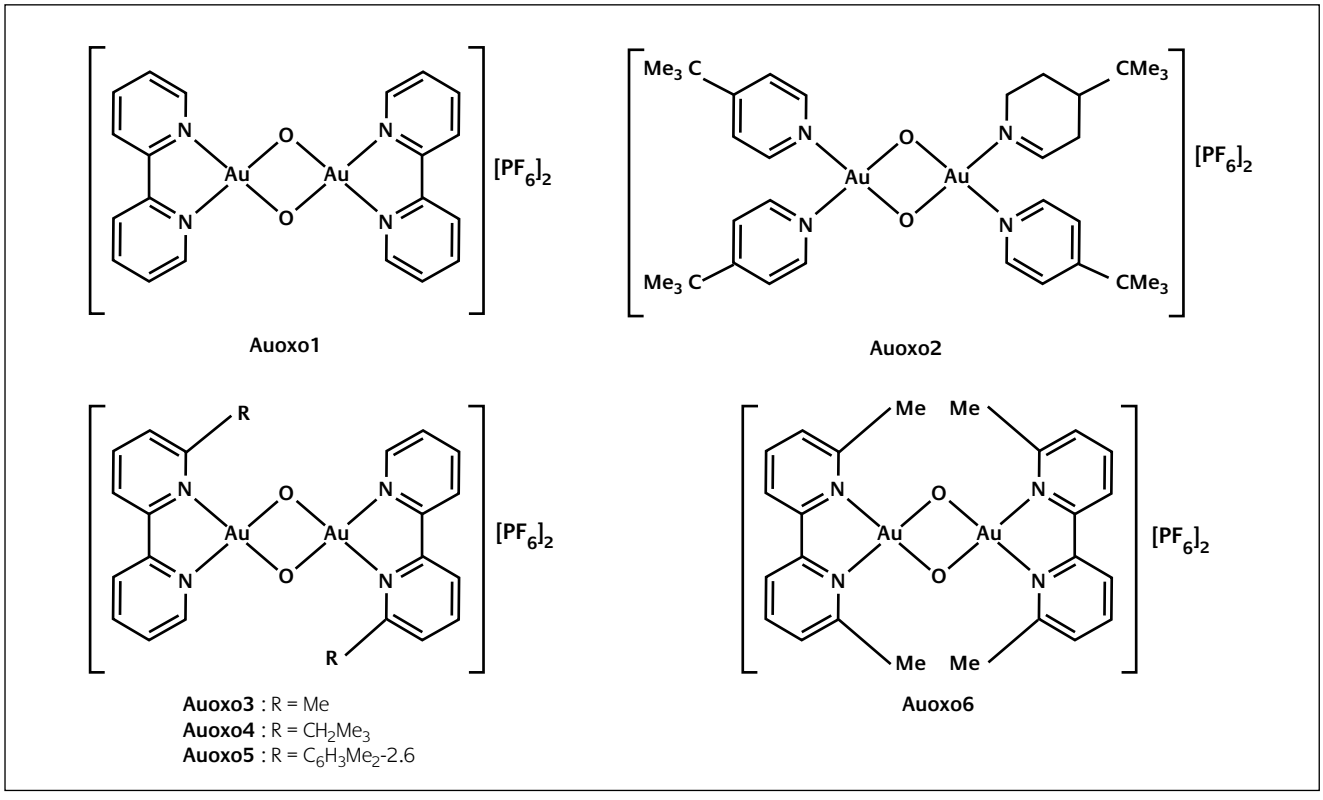

Figure 5

Schematic drawings of the dinuclear gold(III) complexes Auoxo. Auoxo3 is a ca. 1:1 mixture of the cis and trans isomer while Auoxo4 and Auoxo5 are, as depicted, only trans isomers.

polynuclear compound, its redox properties, the kinetics of hydrolysis, and its specific reactivity toward biomolecules in comparison to mononuclear analogues.

This led us to prepare novel dinuclear gold(III) compounds to be tested as anticancer agents, starting from the mononuclear gold(III) bipyridyl complexes described above [19]. Thus, a series of six dinuclear gold(III) oxo complexes with bipyridyl ligands (Figure 5), of general formula $[Au_2(N,N)_2(\mu\text{-}O)_2][PF_6]_2$ [where N,N = 2,2'-bipyridine (Auoxo1), 4,4'-di-tert-butyl- (Auoxo2), 6-methyl- (Auoxo3), 6-neopentyl- (Auoxo4), 6-(2,6-dimethylphenyl)- (Auoxo5), 6,6'-dimethyl-2,2'-bipyridine (Auoxo 6)] were prepared and characterised, and their antiproliferative properties evaluated *in vitro* toward the reference A2780 human ovarian carcinoma cell line (see Table 1).

While five compounds of this series manifested moderate cytotoxic properties (with IC_{50} ~10-30 micromolar), the sixth one (Auoxo6), turned out to be ~5-15 times more active against both cell lines, and will merit further pharmacological studies.

The interactions of two representative members of this series (Auoxo1 and Auoxo6) with a few model proteins (*serum albumin, cytochrome c, ubiquitin*) and with *calf thymus* DNA were analysed in detail by various spectroscopic methods. Both tested compounds manifested a high and peculiar reactivity toward the mentioned model proteins; oxidative damage to these proteins was observed. Also, at the end of the reaction, a number of bare gold atoms were found tightly associated to these model proteins. Specific differences were detected in their reactivity patterns with DNA. While Auoxo1 binds weakly and reversibly with DNA, mostly through electrostatic interactions, Auoxo6 was reported to give rise to redox reactions with DNA, thus causing extensive oxidative damage [17].

The mechanism of action: some insights

As described above, the renaissance of interest toward gold(III) complexes as potential anticancer metallodrugs has resulted in a number of structurally diverse gold(III) compounds, of appreciable chemical stability and of relevant biological activity, that merit further pharmacological and mechanistic investigations. Assessment of *in vitro* cytotoxicity has represented the main criterion for the initial biological screening of these substances. However, for some of these compounds, the pharmacological studies have been subsequently extended well beyond assessment of cytotoxicity by analysing their actions on a number of potentially relevant cellular processes such as direct DNA damage, modification of the cell cycle, mitochondrial effects, induction of apoptosis and so on. Moreover, the reactivity of some gold(III) complexes with specific biomolecular targets, such as DNA and proteins, has been studied in detail by a number of biochemical, biophysical and physico-chemical methods [30].

Yet, the molecular mechanisms through which the observed biological effects are produced remain largely unknown. However, on the ground of the available information, some considerations and suggestions may be anticipated.

The mechanistic studies carried out so far on gold(III) complexes have always been referred and compared to cisplatin; it emerges however that the respective molecular mechanisms are rather distinct. The few gold(III) compounds for which advanced pharmacological testing has been carried out offer a rather puzzling mechanistic profile. In some cases – *e.g.* gold(III) porphyrin complexes- evidence of direct DNA damage has been gathered; in the other cases the effects on DNA and on the cell cycle appear to be modest so that it is rather unlikely that DNA may represent, the ultimate target. For instance, we have shown that

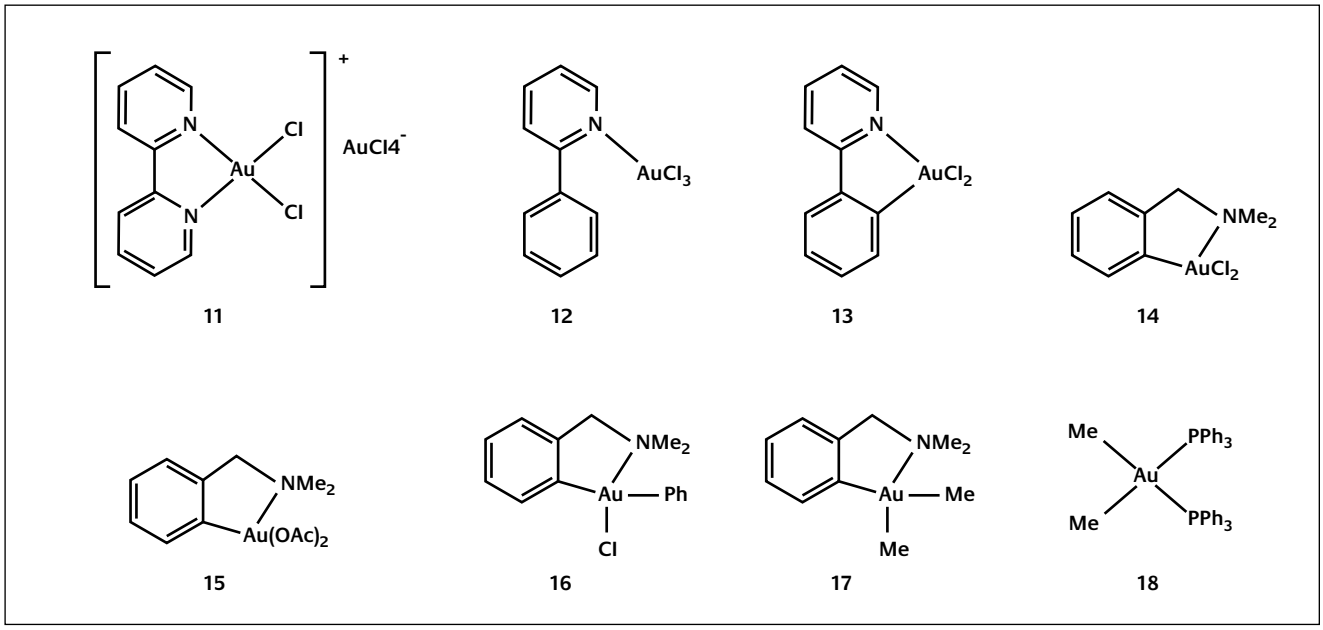

Figure 6

Schematic drawings of gold(III) complexes screened for the inhibition of human TrxR1.

Table 2

Inhibition (IC_{50} μM) of Thioredoxin reductase by gold compounds. Cisplatin is reported as reference compound.

Compound	IC_{50} (μM)		
	Rat Mitochondrial TrxR2	Rat Cytosolic TrxR1	Human TrxR1
Cisplatin	36.0		
Auranofin	0.020		
Au triethylphosphine chloride	0.065		
aurothiomalate	0.280	0.005	
[Au(2,2′-diethylendiamine)Cl]Cl_2	0.420		0.20
[(Au(2-(1,1-dimethylbenzyl)-pyridine) $(CH_3COO)_2$]	1.420		
[Au(6-(1,1-dimethylbenzyl)-2,2′-bipyridine)(OH)](PF_6)	0.280		
[Au(6-(1,1-dimethylbenzyl)-2,2′-bipyridine)-H)(2,6-xylidine)](PF_6)	0.210		
Tetrachloroaurate			0.0058
11			0.012
12			0.030
13			0.036
14			0.180
15			0.030
16			0.0022
17			1.80
18			0.68
Au triphenylphosphine chloride		0.001	
Au(III) chloride trihydrate		0.00075	
Au acetate		0.040	
Au thiosulfate Na^+		0.0005	

cytotoxicity caused by the gold(III) complexes [Au(phen)Cl_2]Cl and [Au(dien)Cl]Cl_2 only results in very marginal DNA damage; additionally only weak cell cycle effects were seen in comparison with cisplatin further suggesting a different molecular mechanism. A similar situation was previously found for gold(III) DAMP compounds exhibiting modest DNA binding properties [6]. Thus, DNA is likely not to be the primary target for several of the investigated gold(III) compounds. Even in the cases where some evidence of a direct interaction with DNA has been reported, -*e.g.* the gold(III) porphyrin complexes- the mechanisms of DNA damage and cell death seem to be distinct from those induced by platinum metallodrugs.

Based on newly obtained experimental evidence it is tempting to propose that gold(III) compounds may exert their cytotoxic effects by causing direct mitochondrial damage through modification of specific proteins. For example, in a recent study conducted in collaboration with the group of Bindoli and Rigobello in Padova, we observed that a few gold(III) complexes are tight inhibitors of the selenoenzyme thioredoxin reductase (TrxR) (see Table 2), a crucial enzyme for cell protected against oxidative stress. Accordingly, these compounds were found to perturb greatly the mitochondrial functions[16,31]. This hypothesis is further reinforced by the observation that antiarthritic gold(I) compounds such as auranofin are known as potent inhibitors of thioredoxin reductase and as effective antimitochondrial agents [32,33].

Very recently Powis *et al*. reported on the inhibitory properties of a series of gold(III) complexes (Figure 6), including some containing the DAMP group, against the human thioredoxin reductase 1 (TrxR1).

Table 2 contains some representative literature data of the inhibition of TrxR by the gold compounds reported in this review.

According to these data, it is very likely that direct antimitochondrial effects are at the ground of the large proapoptotic and cytotoxic effects produced by anticancer gold(III) compounds.

Other recent studies identified the thiol-dependent cathepsin enzymes as possible targets for novel anticancer agents[35]. These lysosomal enzymes are mainly cysteine proteases responsible for extracellular matrix degradation, bone resorption and joint destruction. Their inhibition by coordination of gold complexes to their active site has recently been reported [36,37].

Concluding Remarks

Gold(III) complexes represent today an interesting family of cytotoxic agents. A number of structural diverse gold(III) complexes, prepared and characterised in the last 15 years, exert outstanding antiproliferative effects. The observed biological effects are mediated by innovative and distinct molecular mechanisms in dependence of the coordination chemistry of the gold(III) centre and of the nature of its ligands. Relevant antimitochondrial effects have been highlighted. Additionally, gold complexes can inhibit disease-specific, thiol-containing, cysteine protease cathepsins. Owing to their peculiar chemical and biological properties, gold(III) complexes have now the potential of being further developed as experimental anticancer drugs.

About the Authors

Luigi Messori PhD in Chemical Sciences (1987), Associate Professor of General and Inorganic Chemistry, is a member of the Department of Chemistry, University of Florence. His main research interests are in the field of bioinorganic chemistry. In a first phase he has been involved in the study of the solution behaviour of metalloproteins, with emphasis on metal carrier proteins. Later on, his research interests moved to consider the role of metal ions in medicine. In particular, he has directed his attention towards anti-tumour metal complexes (mainly ruthenium(III) and gold(III) complexes) and to their interactions with nucleic acids and proteins. Recent achievements of his scientific activity are a number of studies on anticancer gold(III) complexes and a few biophysical studies concerning the adducts of platinum drugs with some proteins. He has been the Coordinator of a COST D20 WG focusing on the interactions of anticancer metallodrugs with plasma proteins. He has given several invited lectures in Italy and abroad on the above topics. He is author of more than 130 papers, published on international scientific journals.

Dr. Chiara Gabbiani graduated in Chemistry at the University of Florence in 2003. She is presently working as a PhD student in Prof. Messori's research group in Florence. The main subject of her studies is the investigation of gold(III) complexes as anticancer agents.

Dr. Angela Casini received her BSc from the University of Florence in 1998 and was awarded a PhD grant from the same University in 2001. She has worked first on the mechanisms of action of metal complexes as anti-cancer agents investigated through a variety of spectroscopic and molecular biology techniques. Her PhD research project concerned the development of novel metallo-enzyme inhibitors with particular focus on carbonic anhydrase inhibitors. She is presently holding a post-doc position to perform studies on the interactions of metal complexes with biomolecules with particular attention to proteins as possible targets for the pharmacological activity of this type of drugs.

References

1 B. Rosenberg, L. VanCamp, J.E. Trosko, V.H. Mansour, Nature, 1969, **222**, 385

2 B. Lippert, 1999, Cisplatin: Chemistry and Biochemistry of a Leading Anticancer Drug, John Wiley & Sons, Inc., New York

3 E. Wong, C.M. Giandomenico Chem. Rev., 1999, **99**, 2451

4 C.F. Shaw III, Chem. Rev., 1999, **99**, 2589

5 R.V. Parish, B.P. Howe, J.P. Wright, J. Mack, R.G. Pritchard, R.G. Buckley, A.M. Elsome, S.P. Fricker, Inorg. Chem., 1996, **35**, 1659

6 R.G. Buckley, A.M. Elsome, S.P. Fricker, G.R. Henderson, B.R. Theobald, R.V. Parish, B.P. Howe, L.R. Kelland, J. Med. Chem., 1996, **39**, 5208

7 A., Moustatih, A., Garnier-Suillerot, J. Med. Chem., 1989, **32**, 1426

8 F. Cossu, Z. Matovic, D. Radanovic, G. Ponticelli, Farmaco, 1994, **49**, 301

9 S. Carotti, A. Guerri, T. Mazzei, L. Messori, E. Mini, P. Orioli, Inorg. Chim. Acta, 1998, **281**, 90

10 L. Messori, F. Abbate, G. Marcon, P. Orioli, M. Fontani, E. Mini, T. Mazzei, S. Carotti, T. O'Connell, P. Zanello, J. Med. Chem., 2000, **43**, 3541

11 F. Abbate, P. Orioli, B. Bruni, G. Marcon, L. Messori, Inorg. Chim. Acta, 2000, **311**, 1

12 M. Wienken, , B. Lippert, E. Zangrando, L. Randaccio, Inorg. Chem., 1992, **31**, 1983

13 S. Carotti, , M. Marcon, M. Marussich, T. Mazzei, L. Messori, E. Mini, P. Orioli, Chem. Biol. Interact., 2000, **125**, 29

14 D. Fan, C.-T. Yang, J.D. Ranford, , P.F. Lee, J.J. Vittal, J. Chem. Soc., Dalton Trans., 2003, **13**, 2680

15 G. Marcon, S. Carotti, M. Coronnello, L. Messori, E. Mini, P. Orioli, T. Mazzei, M. A. Cinellu, G. Minghetti, J Med Chem., 2002, **45**, 1672

16 M. Coronnello, E. Mini, B. Caciagli, M.A. Cinellu, A. Bindoli, C. Gabbiani, L. Messori., J. Med. Chem. 2005 , **48**, 6761

17 L. Ronconi, L. Giovagnini, C. Marzano, F. Bettio, R. Graziani, G. Pilloni, D. Fregona, Inorg. Chem. 2005, **44**, 1867-81

18 C.M. Che, R.W.-Y. Sun, W.-Y. Yu, C.-B. Ko, N. Zhu, H. Sun, Chem. Commun., 2003, **14**, 1718

19 A. Casini, M. A. Cinellu, G. Minghetti, C. Gabbiani, M. Coronnello, E. Mini, L. Messori, J. Med. Chem. In the press

20 A. Vaccini, thesis 2002, University of Florence

21 L. Messori, G. Marcon, M.A. Cinellu, M. Coronello, E. Mini, C. Gabbiani, P. Orioli, Biorg. Med. Chem., 2004, **12**, 6039

22 E.B. Fleischer, A. Laszlo, Inorg. Nucl. Chem. Lett., 1969, **5**, 373

23 C.M. Che, R.W. Sun, W.Y. Yu, C.B. Ko, N. Zhu, H. Sun, Chem. Commun. (Camb), 2003, **21**, 1718

24 L. H. Hurley, Nat. Rev. Cancer , 2002, **2**, 188

25 L.A. Lipscomb, F.X. Zhou, S.R. Presnell, R.J. Woo, M.E. Peek, R.R. Plaskon, L.D. Williams, Biochemistry, 1996, **35**, 2818

26 M.O. Hengartner, Nature, 2000, **407**, 770

27 A. Hunt, G. Evan, Science, 2001, **293**, 1784

28 Wang Y, He QY, Che CM, Chiu JF. Proteomics, 2006, **6**, 131-42

29 N. Farrell, Polynuclear platinum drugs. Met. Ions. Biol. Syst. 2004, **42**, 251

30 L. Messori, G. Marcon, P. Orioli, M.A. Cinellu, G. Minghetti, Eur. J. Biochem., 2003, **270**, 4655

31 M.P. Rigobello, L. Messori, G. Marcon, M. Bragadin, A. Folda, G. Scutari, A. Bindoli, J. Inorg. Biochem, 2004, **98**, 1634

32 M.P. Rigobello, G. Scutari, A. Folda, A. Bindoli, Biochem. Pharmacol., 2004, **67**, 689

33 Y.Omata, M. Folan, M. Shaw, R.L. Messer, P.E. Lockwood, D. Hobbs, S. Bouillaguet, H.Sano, J.B. Lewis, J.C.Wataha,Toxicol In Vitro. 2006, **20**, 882-90

34 L. Engman, M. McNaughton, M. Gajewska, S. Kumar, A. Birmingham, G. Powis, Anticancer Drugs. 2006, **17**, 39

35 V. Turk, B. Turk, D.Turk, EMBO J. 2001, **20**, 4629

36 A. Chircorian A, A.M. Barrios, Bioorg. Med. Chem. Lett., 2004, **14**, 5113

37 S.P. Fricker, R. Skerjl, B. R. Cameron, R. Mosi, Y. Zhu, "Recent developments in gold drugs", contribution to the Gold 2003 conference: new industrial applications for gold.