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HIGHLIGHT

Therapeutic applications of gold complexes: lipophilic gold(III) cations and gold(I) complexes for anti-cancer treatment

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Gold and its complexes have long been known to display unique biological and medicinal properties. Extensive cell-based (*in vitro*) and animal (*in vivo*) studies have revealed the potent anti-cancer activities of diverse classes of gold(I) and gold(III) complexes. Most of the reported anti-cancer active gold complexes are highly cytotoxic and unstable under physiological conditions, which hamper their development to be launched clinically. Several clinical reports showed that lipophilic organic cations are promising anti-cancer drug candidates targeting to mitochondria. Through metal–ligand coordination, gold(I) and gold(III) ions can form stable lipophilic cations containing organic ligands having tunable lipophilicity and diverse functionalities. The present highlight summarizes the recent development of lipophilic gold(III) cations and gold(I) complexes with promising anti-cancer activities.

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The oxidation states of gold range from −I to +V. Besides colloidal gold [gold(0)], gold(I) and gold(III) complexes are the commonly encountered forms of gold under physiological conditions. In 1890, Koch found that a gold(I) cyanide complex $K[Au^{I}(CN)_2]$ is effective for the treatment of tuberculosis.[1] Forestier in 1935 first demonstrated the anti-arthritic activity of sodium gold(I) thiopropanol-sulfonate (Allocrysine®),[2] which subsequently initiated the research on the discovery of other clinically useful Au(I)thiolate drugs including sodium aurothiomalate (Myochrysin®) and an acetylated glucose derivative of the

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triethylphosphine gold(I) complex (auranofin) for the treatment of rheumatoid arthritis.[3] The anti-HIV activity of several gold(I) and gold(III) complexes has also been uncovered recently.[4] In 1979, Lorber and co-workers first reported the anti-cancer properties of auranofin on HeLa cancer cells,[5] which subsequently blossomed the research on the discovery of other gold(I)-based anti-cancer complexes.[3b,6] The anti-cancer properties of various gold(I) phosphine and gold(I) carbene complexes have been reviewed recently.[7] Studies on the interactions of different gold(I) complexes with various proteins and enzymes have been extensively reviewed recently.[6g]

Berners-Price and Sadler have extensively studied the ligand exchange reactions of various gold(I) and gold(III) drugs.[8] In biological media, gold(III) is easily reduced to gold(I). Studies on the anti-cancer properties of gold(III) complexes are still in the rudimentary stage, although they are iso-structural (square planar) to the clinically-used cisplatin and its derivatives. Starting from the reports on the anti-cancer active gold(III) complexes bearing chelating N- and/or C-donor ligands including $[Au^{III}(terpy)Cl]Cl_2$ [terpy = 2,2′;6′,2″-terpyridine][9] and $[Au^{III}(dmamp)Cl_2]$ [dmamp = 2-(dimethylaminomethyl)-phenyl],[10] various classes of relatively stable gold(III) complexes displaying promising cytotoxic properties, including $[Au(bipy^c–H)(OH)][PF_6]$ [$bipy^c$ = 6-(1,1-dimethylbenzyl)-2,2′-bipyridine][11] and dioxo-bridged dinuclear gold(III) complexes with two 2,9-dimethylphenanthroline or bipyridyl ligands have been uncovered in recent years.[12,13]

Fregona and co-workers have reported a panel of neutral gold(III) dithiocarbamate derivatives as potential antineoplastic agents.[14] A $[(DMDT)Au^{III}Br_2]$ complex (wherein DMDT = *N*,*N*-dimethyldithiocarbamate) was found to significantly inhibit the activity of a purified rabbit 20S proteasome and a 26S proteasome in MDA-MB-231 breast cancer cells,[14e] resulting in accumulation of ubiquitinated proteins and induction of apoptosis. This complex could also induce apoptosis in cervical carcinoma (HeLa) cells *via* inhibition of the thioredoxin redox system and activation of the ERK pathway.[14d] Animal studies revealed that $[(DMDT)Au^{III}Br_2]$ could significantly suppress tumor growth in nude mice models bearing breast cancer. In a more recent study, the chloro derivative $[(DMDT)Au^{III}Cl_2]$ was found to inhibit tumor growth in PC3 prostate tumor-bearing nude mice.[14a]

Through gold–ligand coordination, gold(III) ions can be used as a template for the creation of lipophilic cations (positively-charged compounds which have the tendency to be dissolved in fat, oil, lipid and non-polar solvents). Structural modification of cationic gold(III) complexes can be achieved by varying the organic ligand(s). In the literature, an organic lipophilic planar cation such as a rhodacyanine dye (MKT-077) has been clinically-proven to be useful for treatment against various types of cancers.[7b,15] Previously, Berners-Price and Filipovska reported the construction of gold(I)-based lipophilic cations by using *N*-heterocyclic carbene (NHC) ligands.[7] Some gold(I)–NHC complexes were found to have adequate solubility and stability[16] in aqueous solutions, and display inimitable anticancer activities by targeting mitochondria[7] and thioredoxin reductase[16] in cancer cells.

In addition to these examples, in the past 8 years, our group has developed a series of cationic gold complexes displaying promising *in vitro* and *in vivo* anti-cancer activities.[17,18] Notable examples include the gold(III) complexes with dianionic porphyrinato ligands ($[Au^{III}–porphyrin]^+$),[19–21] gold(III) complexes with the dianionic tridentate ligands ($[Au^{III}(C^N^C)L]^+$, where HC^N^CH = 2,6-diphenylpyridine; L = neutral auxiliary ligand),[22,23] and gold(I) complexes with neutral thiourea ligands.[24]

Gold(III) complexes with dianionic porphyrinato ligands

A major problem hindering the development of gold(III) complexes for medicinal application is their poor stability in aqueous solutions.[3a] Among the various ligands used for the formation of gold(III) complexes, a porphyrinato ligand forms a stable gold(III)–ligand coordination scaffold. As revealed from the X-ray crystal structure of $[Au(TPP)]^+$ (gold–**1a**, Fig. 1),[20l] the Au(III) ion is located in the cavity of the TPP ligand with a square-planar geometry and with almost four identical Au–N bonds.[20h] Subsequent stability studies revealed that gold–**1a** is stable under physiologically-relevant solutions such as in phosphate-buffered saline (PBS) and in the PBS solutions containing a biological reductant glutathione (GSH) for 72 hours.[20l]

The monocationic gold(III)–porphyrin complex gold–**1a** displays promising *in vitro* anti-cancer activities against a panel of human cancer cell lines including nasopharyngeal carcinoma (NPC),[20e] hepatocellular carcinoma (HCC),[20i] colon cancer,[20d] neuroblastoma,[20f] melanoma,[20a] promyelocytic leukaemia and cervical epithelioid carcinoma,[20l] with IC_{50} values (dose required to inhibit 50% cellular growth) of 0.033 to 3.4 μM.[20] It also displays promising cytotoxic activity toward cisplatin- and multidrug-resistant variants. Compared to the cancerous cells, gold–**1a** displays a lower cytotoxicity (with larger IC_{50} values) towards the normal cells including the lung fibroblast and peripheral blood mononuclear cells (PBMCs).[19] The results reveal that gold–**1a** displays selectivity toward the fast-growing cancerous cells.

The *in vitro* cytotoxic activity of gold–**1a** was found to be unaffected by the presence of serum proteins such as human serum albumin (HSA).[20h] *In vitro* binding studies revealed that gold–**1a** interacts with HSA non-covalently. This non-covalent interaction is important since numerous clinically-used chemotherapeutic agents including oxaliplatin and the anti-arthritic auranofin would easily bind to plasma proteins, predominantly HSA, to form stable covalent adducts as revealed by the previous pharmacokinetics and mass spectrometric investigations.[25,26] Consequently, the serum protein competes with the molecular therapeutic target(s) such as DNA for binding with metal-based drug leads leading to lowering of their therapeutic efficacies.

The *in vivo* anti-cancer activity of gold–**1a** had first been demonstrated in an orthotopic rat HCC model with McA-RH7777 cells.[20i] Intra-tumoral injection of gold–**1a** significantly prolonged the survival of the rats compared to that of the vehicle-control group. The promising *in vivo* anti-cancer activities of gold–**1a** towards other types of cancers

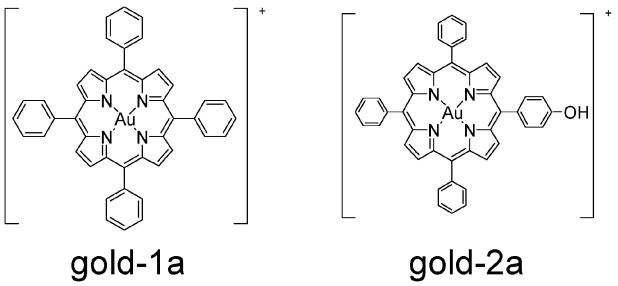

Fig. 1 Gold(III) porphyrins.

including NPC,[20e] colon,[20d] neuroblastoma[20f] and melanoma[20a] have also been demonstrated using different types of nude-mice models.

A more recent study also revealed that gold–**1a** prolonged the survival of NPC metastasis-bearing mice, concomitant with the inhibition of intrahepatic and lung metastasis.[20c] By means of histological examination, gold–**1a** was found to markedly reduce tumor microvessel formation. Several *in vitro* studies revealed that gold–**1a** could inhibit NPC cellular migration and invasion.[20a,c] Moreover, it could down-regulate the expression of genes playing roles in angiogenesis and inhibit microvessel formation of the epithelial cells as shown in the tube-formation assay. All of these data support the fact that gold–**1a** could be used for the treatment of cancer metastasis.

The anti-cancer mechanism has been proposed for the cytotoxic activity of gold–**1a**. Microscopic examination and flow cytometric analysis confirmed that gold–**1a** triggers apoptosis (a kind of programmed cell death) in cancer cells.[20l] By means of transcriptomic (cDNA array)[20i] and proteomic[20j,k] analyses as well as other biochemical techniques, gold–**1a** was found to cause depletion of mitochondrial potential shortly after the cellular uptake with suppression of Bcl-2 protein, and hence induce apoptosis by both the caspase-dependent and caspase-independent mitochondrial death pathways. Results from the proteomic analysis on NPC cells indicated that multiple factors including cellular oxidative stress and the induced change in the balance between pro-apoptotic and anti-apoptotic proteins are crucial to the gold–**1a**-induced apoptosis.[20j,k] A cell-cycle arrest study revealed that gold–**1a** partly inhibits cancer cell growth *via* abrogating the cell cycle at G_0–G_1, and is dependent on p53, a cell cycle-controlling and apoptosis-related protein.[20d]

Moreover, gold–**1a** is capable of activating $p38^{MARK}$ and inhibiting thioredoxin reductase *in vitro*.[20b,h] By means of a computational molecular modelling experiment, gold–**1a** was found to display a high binding affinity to the anti-apoptotic protein Bcl-2 (Fig. 2) with a calculated binding energy similar to that of the known Bcl-2 inhibitor, an acylsulfonamide-based ligand.[20b]

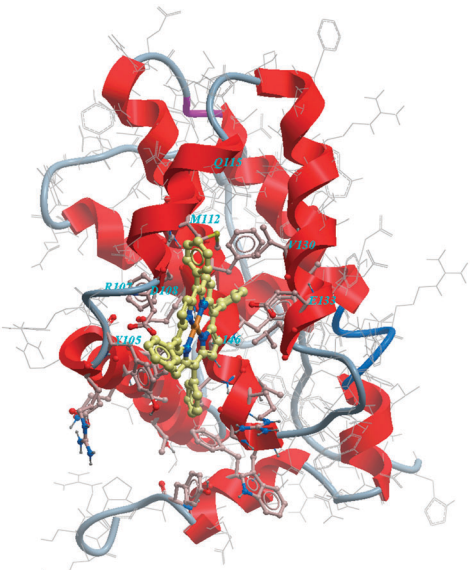

Fig. 2 Molecular docking studies of the Bcl-2 protein with gold–**1a**.[20b]

In neuroblastoma cells, gold–**1a** was found to trigger the release of cytochrome *c* from mitochondria and activate the caspase cascade.[20f] Alternatively, it also induces the expression of Akt, a survival protein in neuroblastoma cells. A subsequent study revealed that the cytotoxic activity of gold–**1a** was greatly enhanced in the presence of an Akt-specific inhibitor. Taken these results altogether, activation of Akt may slow down the gold–**1a** induced apoptosis and anti-proliferation on neuroblastoma cells and the anti-cancer activity of gold–**1a** towards neuroblastoma can be enhanced by the synergistic addition of Akt-specific inhibitor(s).

Gold–**1a** has been shown to be effective towards various kinds of cancers *in vivo*. Yet, an acute toxicological study revealed that the effective dose of gold–**1a** to combat tumor growth is close to its lethal dose.[17] To reduce the toxicity and to enhance the tumor-specificity, micro-encapsulation of gold–**1a** has been adopted to permit modulation of its concentration in biological media. Encapsulations of gold–**1a** by gelatin-acacia microcapsules (Fig. 3) were found to confer sustained-release properties with enhanced anti-cancer activity and reduced toxicity *in vivo*.[27]

A panel of 21 gold(III) porphyrin complexes with porphyrinato ligands bearing different peripheral substituents and with a dynamic range of lipophilicity and cytotoxic activities have been prepared.[20b] Their cytotoxic IC_{50} values ranging from 0.033 to >100 μM were found to correlate with their lipophilicity and cellular uptake. In one example, a gold(III) porphyrin with saccharide conjugation $[Au^{III}(4\text{-glucosyl-TPP})]^+$ (where H_2(4-glucosyl-TPP) = *meso*-tetrakis(4-β-D-glucosylphenylporphyrin)) was found to display a significant cytostatic, instead of the cytotoxic, property. Unlike the parental gold–**1a**, this gold(III) complex induces S-phase cell-cycle arrest, indicating that its cytostatic activity may be in part due to the disruption of DNA replication.

The monocationic status of the gold(III) porphyrin complexes is crucial to their anti-cancer activities. Introduction of charged *N*-methylpyridyl or sulfonyl substituents into the "[Au^{III}–porphyrin]$^+$" core changes the overall monocationic status resulting in a significant reduction in cytotoxicity.[20b]

Previous studies by Subha and Kumar revealed that the presence of hydroxy group(s) on anti-breast carcinoma agents can favor the anti-cancer activity by fitting into the active site of class I histone deacetylase (HDAC).[28] Recently, we have modified the structure of gold–**1a** by introducing a hydroxy group into one of the peripheral phenyl rings on the porphyrin core.[21] This gold(III) porphyrin complex [5-hydroxyphenyl-10,15,20-triphenylporphyrinato gold(III) chloride, (gold–**2a**), Fig. 1] was found to display improved aqueous solubility and is highly anti-cancer active toward breast carcinoma with an IC_{50} value down to 1 nM. Notably, it displays a 100- to 3000-fold higher cytotoxicity than the clinically-used cisplatin. Intraductal injection of gold–**2a** significantly suppressed the breast tumor growth in the nude mice model. These effects are in part associated with attenuation of Wnt/β-catenin signalling by inhibition of the class I HDAC activity.[21]

Gold(III) complexes with dianionic tridentate ligands

Apart from the gold(III) porphyrin complexes, complexation of gold(III) with a dianionic tridentate ligand and a neutral auxiliary ligand also gives a lipophilic complex cation. We reported the syntheses[29] and anti-cancer properties[22] of a series of cyclometallated gold(III) complexes $[Au^{III}(C\hat{}N\hat{}C)L]^+$ (wherein HC^N^CH = 2,6-diphenylpyridine; L = a neutral phosphine ligand), respectively, in 1998 and 2006. This class of complexes is stable in aqueous solutions containing GSH (2 mM), attributed to the dianionic $[C\hat{}N\hat{}C]^{2-}$ ligand, which stabilizes the electrophilic gold(III) ion. With triphenylphosphine as the auxiliary ligand, the cyclometallated gold(III) complex $[Au^{III}(C\hat{}N\hat{}C)(PPh_3)]^+$ was found to display cytotoxic activity towards the nasopharyngeal carcinoma (NPC) with IC_{50} values of ~4 μM. Contrasting to most of the gold(III) porphyrin complexes which display high binding affinities toward calf thymus DNA (ctDNA), $[Au^{III}(C\hat{}N\hat{}C)(PPh_3)]^+$ only weakly interacted with ctDNA and showed no significant alteration in the cell cycle of NPC cells.[22]

By using the bidentate bis-(diphenylphosphine)C_n ligands (wherein C_n is a saturated hydrocarbon linker with n = 1–6), binuclear gold(III) complexes of $[Au_2^{III}(C\hat{}N\hat{}C)_2(\mu\text{-bis-(diphenylphosphine)}C_n)]^{2+}$, each of which contains two $[Au^{III}(C\hat{}N\hat{}C)]^+$ cations, were obtained.[22] Compared to the mononuclear $[Au^{III}(C\hat{}N\hat{}C)(PPh_3)]^+$ complex, the cytotoxicity of these binuclear complexes was significantly enhanced. Among the $[Au_2^{III}(C\hat{}N\hat{}C)_2(\mu\text{-bis(diphenylphosphine)}C_n)]^{2+}$ complexes, $[Au_2^{III}(C\hat{}N\hat{}C)_2(\mu\text{-dppp})]^{2+}$ (dppp = bis(diphenylphosphine)propane, Fig. 4) displays the most potent cytotoxic activity toward human cervical epithelial carcinoma and nasopharyngeal carcinoma cells, with IC_{50} values down to ~50 nM.

We have examined the *in vivo* anti-cancer activity of $[Au_2^{III}(C\hat{}N\hat{}C)_2(\mu\text{-dppp})]^{2+}$ on rats bearing HCC orthografts. The rats were divided into sham operation and treatment groups ($[Au_2^{III}(C\hat{}N\hat{}C)_2(\mu\text{-dppp})]^{2+}$, 0.5 mg kg^{-1}). The median survival time of rats in the vehicle control was 30 days.[30] A dose of 0.5 mg kg^{-1} substantially prolonged the survival of rats (median, 43), indicating that this complex is effective in treating HCC-bearing rats (Fig. 4, right).

Apart from employing the toxic phosphine ligand, conjugation of an *N*-heterocyclic carbene (NHC) ligand to the $[Au^{III}(C\hat{}N\hat{}C)]^+$ moiety gives another class of anti-cancer active lipophilic gold(III) complex cations.[23] The non-toxic nature of the NHC ligands reduces the possibility of these complexes in producing additional toxic metabolites in biological systems. In a recent study, a $[Au^{III}(C\hat{}N\hat{}C)(NHC)]^+$ complex has been identified to display potent poisoning activity on topoisomerase I (TopoI), an enzyme that unwinds chromosomal DNA, which is an important cellular target for anti-cancer treatment. By means of computational molecular modelling, this complex was found to bind to TopoI-linked DNA with the carbene side chain pointing into the major groove of the DNA, with a calculated binding energy similar to that for topotecan, a known poison of the TopoI. The $[Au^{III}(C\hat{}N\hat{}C)(NHC)]^+$ complex shows promising *in vitro* cytotoxicity towards a panel of cancer cell lines with IC_{50} values spanning between 0.17 and 1.2 μM, and displays a 167-fold higher cytotoxicity to the non-small lung carcinoma cells than to the normal lung fibroblast cells. *In vivo* treatment of nude mice bearing HCC cells by this complex at 10 mg kg^{-1} $week^{-1}$ for 28 days significantly inhibited tumor growth compared to the vehicle control, and there was no apparent induced toxic side effect during the whole course of examination.

Guo and co-workers reported a series of anti-cancer active gold(III) cations with tridentate terpyridine and amino-quinoline ligands (Fig. 5).[31] The gold(III) aminoquinoline complexes are highly cytotoxic towards various melanoma and lung cancer cell lines, with IC_{50} values down to ~1 μM.

Messori and co-workers reported various lipophilic gold(III) cations with tridentate ligands showing promising anti-cancer activities (Fig. 6).[11] Two of them, $[Au^{III}(bipy^{dmb}–H)(OH)]^+$ and $[Au^{III}(bipy^{dmb}–H)(2,6\text{-xylidine}–H)]^+$ (wherein $bipy^{dmb}$ = 6-(1,1-dimethyl-benzyl)-2,2′-bipyridine), displayed potent

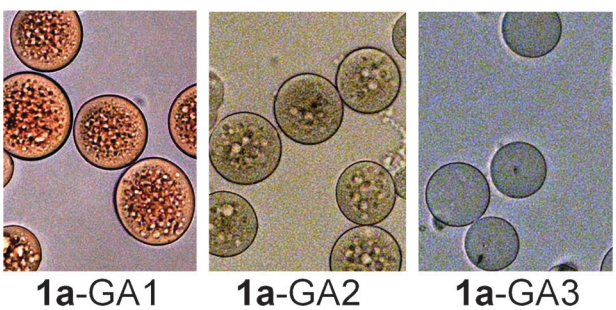

Fig. 3 Gelatin-acacia microcapsules of gold–**1a** with different weight percentage of gold–**1a**.[27]

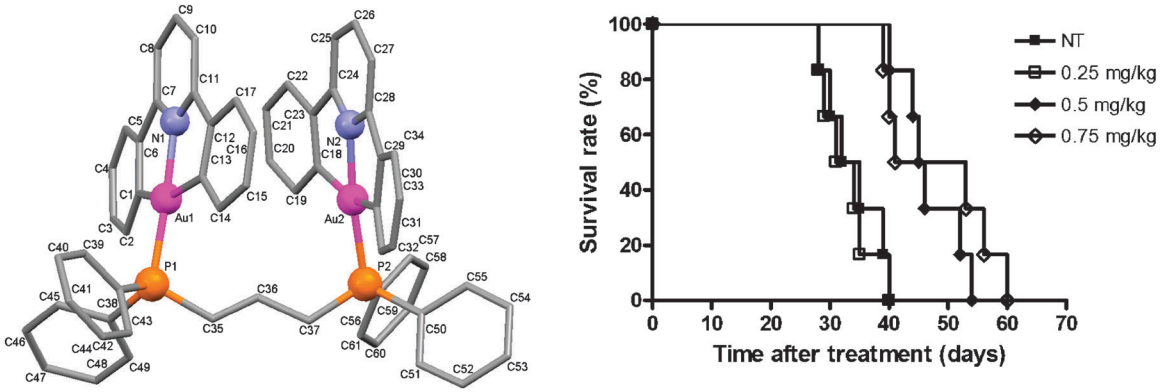

Fig. 4 (left) Balls and sticks representation of $[Au_2^{III}(C\hat{}N\hat{}C)_2(\mu\text{-dppp})]^{2+}$ and (right) survival curves of rats bearing HCC orthografts treated with $[Au_2^{III}(C\hat{}N\hat{}C)_2(\mu\text{-dppp})]^{2+}$.[30]

cytotoxic activities toward an ovarian carcinoma cell line (A2780/S) and its cisplatin-resistant variant (A2780/R) with IC_{50} values ranging from 1.0 to 9.0 μM. These complexes could induce apoptosis to a greater extent than cisplatin and oxaliplatin with modest cell-cycle alterations. A subsequent *in vitro* study revealed that these complexes could significantly inhibit mitochondrial thioredoxin reductase and mitochondrial respiration with an IC_{50} value down to 0.21 μM.[32]

Dioxo-bridged dinuclear gold(III) complexes

Messori, Cinellu and co-workers have reported the anti-cancer properties of various structurally related oxo-bridged binuclear gold(III) cations $[Au^{III}_2(\mu\text{-}O)_2(N\hat{}N)_2]^{2+}$ (wherein N^N = 2,2′-bipyridine or a substituted 2,2′-bipyridine) (Fig. 7).[12b,c] These complexes displayed cytotoxicity against the human ovarian cancer cell lines A2780/S and A2780/R with IC_{50} values ranging from 1.8 to 29.8 μM. More recently, a novel dinuclear complex $[Au^{III}_2(\mu\text{-}O)_2(phen^{2Me})_2]^{2+}$ (wherein $phen^{2Me}$ = 2,9-dimethyl-1,10-phenanthroline) has been found to display highly promising *in vitro* anti-proliferative activity towards a representative panel containing 36 different human tumor cell lines, with the mean IC_{70} value of 0.245 μg mL^{-1}.[12a] By means of COMPARE algorithm analysis, it was found that the induced cytotoxicity of this complex may involve histone deacetylase inhibition. Upon reaction with superoxide dismutase (SOD), this dimetallic $[Au^{III}_2(\mu\text{-}O)_2(phen^{2Me})_2]^{2+}$ complex breaks down, gold(III) reduction occurs, and two gold(I) ions are found associated to SOD with the free $phen^{2Me}$ ligands released.

Gold(I) complexes with neutral phosphine and carbene ligands

A variety of gold(I) complex cations with neutral phosphine ligand(s) have long been known to display potent *in vitro* and *in vivo* anti-cancer activities. These properties have been extensively reviewed in recent decades.[3b,6,7] In a more recent study, a panel of anti-cancer gold(I)–phosphine complexes have been found to display promising autophagy-inducing properties by enhancing the accumulation of autophagosomes.[33] In addition to the mononuclear complexes, a new bis-chelated Au^I bidentate phosphine complex with a novel water-soluble ligand 1,3-bis(di-2-pyridyl-phosphino)propane (d2pypp) has been found to induce apoptosis in breast cancer cells and target to mitochondria (Fig. 9).[6c] Berners-Price and co-workers recently reported a series of anti-cancer active mononuclear gold(I) complexes supported by *N*-heterocyclic carbene (NHC) ligands (Fig. 8).[7a,b] These complexes are cytotoxic to various kinds of cancer, and induce Ca^{2+}-sensitive mitochondrial swelling and apoptosis. In collaboration with Filipovska and co-workers, these complexes were found to be highly selective to cancer cells and target mitochondrial selenoproteins including the thioredoxin reductase.[6b]

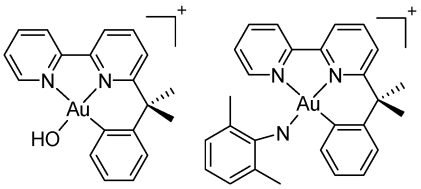

Fig. 6 Chemical structures of $[Au^{III}(bipy^{dmb}\text{–}H)(OH)]^+$ and $[Au^{III}(bipy^{dmb}\text{–}H)(2,6\text{-xylidine–H})]^+$.[11]

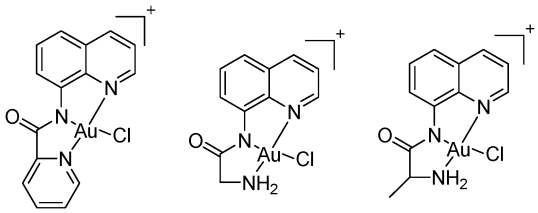

Fig. 5 Examples of gold(III) cations of aminoquinoline derivatives.[31b]

Gold(I) complexes with neutral thiourea ligands

As mentioned, various neutral phosphine and carbene ligands have been utilized to form bioactive gold(I) complexes.[6,7] To extend the horizon in search of new anti-cancer gold(I) complexes, thiourea ligands have been used to form gold(I) complexes as another type of lipophilic gold(I) cations.[24] The thiourea ligands are relatively non-toxic towards the normal lung fibroblast cells. We have identified that a gold(I) thiourea complex

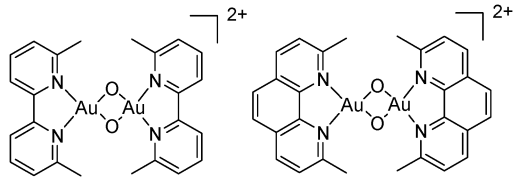

Fig. 7 Examples of dinuclear gold(III) oxo-bridged cations.[12]

with *N*,*N*′-disubstituted cyclic thiourea $[Au^{I}(imidazolidine\text{-}2\text{-}thione)_2]^+$ exhibits a tight-binding inhibition of thioredoxin reductase (TrxR) with the half maximal inhibition down to 1 nM (Fig. 9).

By means of progress curve analysis, it was found that the plot of the first-order rate inhibition constants of TrxR against the concentration of $[Au^{I}(imidazolidine\text{-}2\text{-}thione)_2]^+$ followed a hyperbolic function. The result indicates that $[Au^{I}(imidazolidine\text{-}2\text{-}thione)_2]^+$ inhibits TrxR *via* a two-step tight-binding mechanism. Besides, a size-exclusion-chromatography-inductively-coupled-plasma-mass spectrometric (SE-ICP-MS) analysis of TrxR treated with the $[Au^{I}(imidazolidine\text{-}2\text{-}thione)_2]^+$ complex showed the appearance of a peptide fraction co-eluted with Se and Au, indicating that formation of the tight enzyme–inhibitor complex is involved in the TrxR inhibition.

In vitro cytotoxicity studies showed that the gold(I) thiourea complex $[Au^{I}(imidazolidine\text{-}2\text{-}thione)_2]^+$ displays potent anti-cancer activities towards a panel of cancer cell lines with IC_{50} values spanned between 3.7 and 17.4 μM. An *in vivo* study revealed that intraperitoneal injection of this complex at 100 mg kg^{-1} twice a week resulted in significant size reduction of the tumor of non-small cell lung cancer cells by 38%.[24]

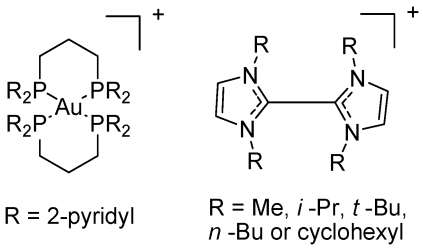

Fig. 8 Au^{I} bidentate phosphine cation of 1,3-bis(di-2-pyridylphosphino)propane and Au^{I}–NHC cations.[6,7]

Concluding remarks

The redox properties and rich coordination chemistry of metal ions render metal complexes to have diverse structures and intriguing chemical/biological properties, which are difficult to be attained by purely organic compounds. Gold(I) and gold(III) can form stable lipophilic cations with lipophilicity and anti-cancer properties that could easily be modified by varying auxiliary ligands.

The cationic (preferably mono-cationic) status together with the lipophilic scaffolds of the metal complexes would enhance cellular absorption. Previous studies on different types of gold-based lipophilic cations revealed that introduction of lipophilic substitution(s) generally enhances cellular uptake and hence cytotoxic activities. However, aqueous solubility of these complexes would decrease, resulting in lowering the bio-availability in the biological system. Thus in the design of metal-based drugs, there needs to be a more balanced consideration on the cytotoxic properties and aqueous solubility.

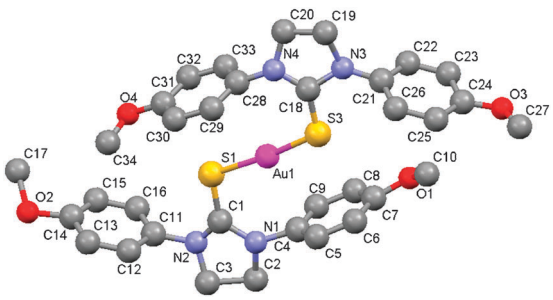

Fig. 9 Balls and sticks representation of the cation of $[Au^{I}(imidazolidine\text{-}2\text{-}thione)_2]^+$.[24]

Unless the metal-based lipophilic cations are designed to deliver the toxic coordinated ligands to specific cellular target(s), non-toxic ligands are preferably employed for the design of bioactive metal complexes so as to minimize the chance of having possible side-effect(s) rendered by these ligands especially after biological disintegration and metabolism. If the mechanism of drug action is based on non-covalent interactions of the metal complexes with molecular cellular targets, strong binding of ligand(s) to metal ions gives a physiologically stable metal complex, which is essential for the *in vivo* drug actions. To identify the molecular species which exerts the anti-cancer activities and at the same time displays toxic side effects, speciation(s) and metabolite(s) under *in vivo* conditions should be examined by means of mass-spectrometric and/or NMR-spectroscopic methods. Besides identifying the active molecular species, understanding the biological mechanisms by means of proteomics and trans-criptomics analyses provides crucial insights on the future drug optimization.

More *in vivo* studies are recommended for those lipophilic gold complexes which have already demonstrated to display promising *in vitro* activities. Extensive *in vivo* examinations such as biodistribution, biotransformation [metabolite(s) formation], pharma-cokinetics as well as safety pharmacological evaluation should also be conducted so as to provide more clinically-relevant information on the design of new gold complexes for clinical studies.

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