ChemComm

FEATURE ARTICLE

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View Journal

Recent developments in gold(I) coordination chemistry: luminescence properties and bioimaging opportunities

Cite this: DOI: 10.1039/c4cc03259d

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Received 1st May 2014,
Accepted 3rd June 2014

DOI: 10.1039/c4cc03259d

www.rsc.org/chemcomm

The fascinating biological activity of gold coordination compounds has led to the development of a wide range of complexes. The precise biological action of such species is often poorly understood and the ability to map gold distribution in cellular environments is key. This article discusses the recent progress in luminescent Au(I) complexes whilst considering their utility in bioimaging and therapeutics.

1. Introduction

The development of luminescent coordination complexes has been driven by a detailed understanding of their photochemical and photophysical properties and mechanisms, and their resultant diverse applicability, including photovoltaic components, light-emitting devices, sensor platforms and biological imaging. Over the past several decades the photophysical and photochemical properties of $[Ru(bipy)_3]^{2+}$ derivatives have been studied more than any other metal complex,[1] and derivatives of this structure have been widely applied to numerous investigations. This has led to countless studies on related complexes with d^6 and d^8 electronic configurations (Fig. 1), with luminescent Re(I), Os(II), Rh(III), Ir(III) and Pt(II) species of particular interest.[2–10] The excited state properties of many of these compounds have been investigated in great detail[11,12] and, although a crass generalisation, can often fall into two classes of either metal-to-ligand charge transfer (MLCT) and ligand-centred (LC) excited (often triplet) states or admixtures of the two.

The opportunities presented by d^{10} complexes have, perhaps, been less well investigated.[13] Certain diimine (Fig. 2) and/or diphosphine complexes of Cu(I) are known to possess promising phosphorescent properties, often based upon MLCT character.[14] In the context of applications, particularly biological ones, chemical stability remains a problematic issue for many Cu(I) species. However, a recent report by Li suggests that this challenge can be met through robust mixed-ligand Cu(I) complexes that

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Simon Pope was born in York, UK and grew up in Essex; he is currently a Reader in the School of Chemistry at Cardiff University. He obtained his BSc and PhD (supervisor Prof. Gillian Reid) degrees from the University of Southampton. He then completed postdoctoral research at the Universities of Bristol (with Prof. Michael Ward) and Manchester (with Prof. Stephen Faulkner and Dr Benjamin Coe) before moving to Cardiff University in 2006. His research encompasses a breadth of interests related to the application of d- and f-block coordination complexes to optical devices, sensing and biological imaging. He is also a STEM ambassador.

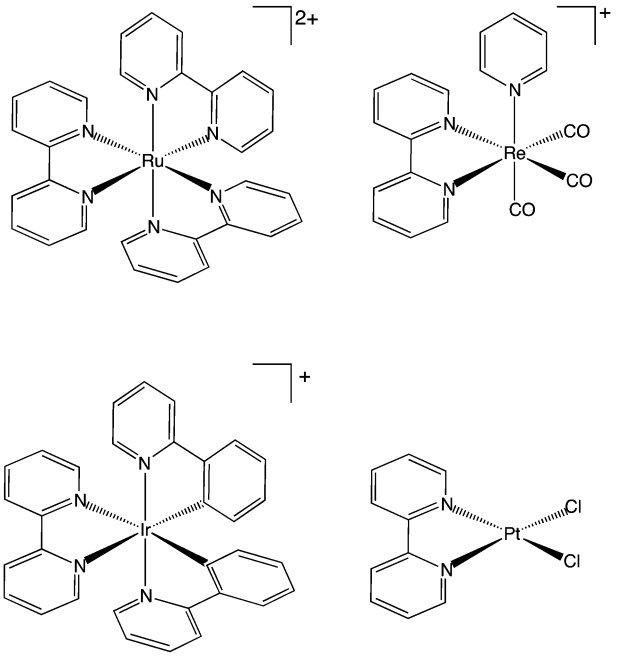


Fig. 1 The core structures of some common d^6 and d^8 metal-based luminophores.

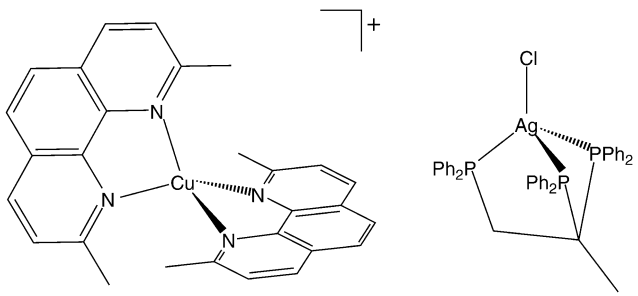


Fig. 2 Examples of d^{10} metal-based luminophores.

emit *via* aggregation induced emission, and have been successfully applied to cell imaging.[15]

Stable Ag(I) complexes are accessible with a variety of ligand architectures, and solid state structures often reveal the propensity for Ag(I) to form aggregated polymetallic structures supported by metallophilic interactions. The different redox character of Ag(I) prohibits low energy MLCT type transitions, with emission often dominated by ligand-centred, inter-ligand (in heteroleptic species), LMCT and/or metal-centred character.[13] The presence of the heavy metal Ag(I) can often promote intersystem crossing, favouring excited states of triplet character.[16]

Complexes of Au(I) display a fascinating range of both structural and photophysical properties. The pronounced relativistic effect of gold enhances the formation of weak (*ca.* 10 kcal mol^{-1}) Au–Au bonds (aurophilicity), supporting the formation of polymetallic structures.[17] Previous reviews have highlighted some of the key photophysical properties of a range of different Au(I) complexes.[18–21]

The aim of this feature article is to summarise recent progress in the development of luminescent Au(I) complexes, whilst considering the utility of such compounds in cell imaging amidst the context of the often cytotoxic nature of many Au(I) species.

2. Brief comment on the therapeutic activity of Au(I) complexes

By definition, chrysotherapy is the use of gold-based compounds in medicinal practice.[22–25] In this context, the most common class of gold coordination complex that has been used in a clinical setting are species incorporating Au(I) and thiolate ligands, for example sodium aurothiomalate (Fig. 3).[26–29] Such coordination compounds are often polymeric and water soluble, and have been successfully used in the treatment of rheumatoid arthritis, an inflammatory autoimmune condition.[30] Related Au(I) agents have been developed as mixed ligand, discrete molecular species, for example auranofin (Fig. 3), which combines a lipophilic triethylphosphine (PEt_3) and a biocompatible tetraacetatothioglucose ligand. The biological action of these drugs is likely to be through the inhibition of implicated cathepsins, slowing the advancement of rheumatoid arthritis. Lysosomal cysteine proteases can be targeted by Au(I) complexes, inhibiting cathepsin B activity.[31] The induction of oxidative cellular stress by antirheumatic Au(I) compounds may also be a pharmacologically important pathway.[32] More recently, the inhibition of selenium-glutathione peroxidase, emphasising the thio- and selenophilic nature of Au(I), has also been described.[33,34] However, the toxicity from many Au(I) complexes, and the unclear biological mode of action of such compounds[35] in the treatment of rheumatoid arthritis still detract from the established medical benefits.[36]

In addition to the focused studies on developing treatments for rheumatoid arthritis, a wide range of Au(I) complexes have been assessed for their anti-tumour properties.[37,38] Auranofin and its structural analogues (*i.e.* phosphine gold thiolates) have been studied and displayed significant cytotoxicity against B16 melanoma and P388 leukemia cell lines.[39] A key outcome of the work was the importance of the ancillary tertiary phosphine ligand and its substitution (for example for a given thiolate ligand, triethyl derivatives were generally more cytotoxic than triphenyl), which induced additional potency to the complex. A number of subsequent studies, summarised by Tiekink,[29] have evaluated the cytotoxicity of a large range of Au(I) complexes, screening for structure–property relationships amongst tetrahedral Au(I) complexes with charged and/or bidentate thiols, chiral phosphines and thiols labelled with biologically active moieties.

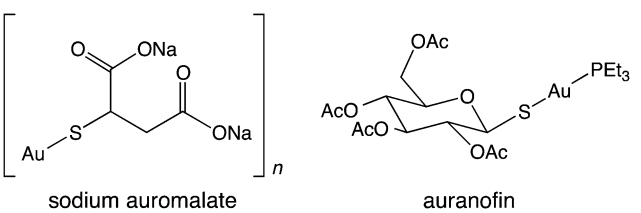


Fig. 3 Examples of Au(I)-based therapeutic agents.

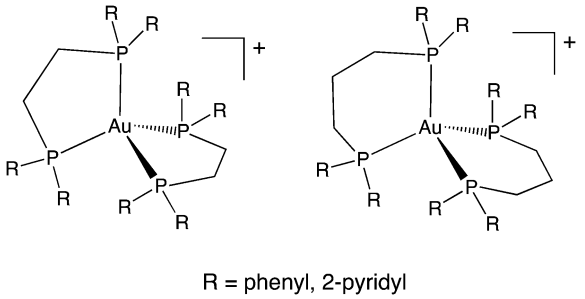


Fig. 4 Tetrahedral geometry, tertiary diphosphine complexes of Au(I) with controlled amphiphilicity *via* the phosphorus substituent (R).

Lipophilicity is an important factor in determining the cellular uptake and anti-tumour activity of gold phosphine complexes.[40] For example, the tetrahedral (Fig. 4) cationic complex $[Au(dppe)_2]^+$ (where dppe = 1,2-bis(diphenylphosphino)ethane) has shown mitochondrial targeting behaviour[41] and subsequent disruption of mitochondrial function.[42] Structurally related complexes with increasing hydrophilic character, achieved by replacing the phenyl substituents with pyridyl groups, have also been studied. A careful balance of the amphiphilic nature can modulate protein binding, excretion pathways and overall toxicity. It is noteworthy that four coordinate Au(I) complexes are less reactive to thiols, compared to linear two-coordinate species, presumably on steric grounds. $[Au(d2\text{-}pypp)_2]Cl$ (where d2-pypp = 1,3-bis(di-2-pyridylphosphino)propane) selectively induces apoptosis (*via* a mitochondrial pathway) in breast cancer cells at submicromolar concentrations; inhibition of Trx (thioredoxin) and TrxR (thioredoxin reductase) are enhanced in the cancer cells *versus* normal cells.[43] More recently Ott has comprehensively reviewed the medicinal aspects of anti-tumour gold complexes,[44] highlighting comparisons with more established metallodrugs based on Pt(II) coordination chemistry.

Current opinion has focused upon the inhibitive character of gold complexes against the enzyme TrxR, which is a member of the glutathione reductase class of enzymes. Mammalian TrxR is a high molecular weight (*ca.* 55 000 Da) species that contains a selenocysteine residue in its active site.[45] TrxR is involved in several metabolic pathways, but it is its antioxidant capability that is thought to protect cells from oxidative stress.[46] Elevated levels of TrxR have been noted in a variety of cancer cell lines.[14] Auranofin has demonstrated remarkable selectivity for TrxR when compared to other structurally comparable enzymes.[47] The soft, electrophilic Au(I) ion has a high affinity for both sulfur and selenium donors, and an example of a binding interaction between a Au(I) complex and glutathione reductase has been revealed through X-ray crystallography.[48,49] The key observation from the structure is that the gold centre had liberated both ligands and was bound by two cysteine residues within the active site.

Ligand exchange is clearly a fundamental contributory factor to the biological activity and behaviour of Au(I) coordination complexes. It is generally accepted that the rate of ligand exchange for Au(I) species in aqueous solution is $X^- > RS^- > PR_3$.[50] However, only limited details of these characteristics exist and speculation is often invoked to explain any observed trends. In this context, there is an additional and, in a sense, complementary interest in the use of [Au(L)Cl] type complexes in homogeneous catalysis. A range of 14-electron, linear two-coordinate Au(I) complexes that incorporate tertiary phosphines (*e.g.* $[Au(PR_3)(X)]$ where X = halide, OH, trifluoromethanesulfonate) have acted as useful catalytic precursors, although the active species is often thought to be the $[Au(PR_3)]^+$ cation.[51] Solution calorimetry studies have been used to investigate ligand exchange reactions of the [Au(L)Cl] system (where L = phosphine or phosphite), correlating reaction enthalpies with the steric and electronic properties of the P-donor ligands and thus deriving Au–P bond dissociation enthalpies. It is the electronics parameters of the phosphorous ligand that dominate: typical bond dissociation enthalpies for tertiary phosphines from Au(I) were estimated at 58–65 $\pm$ 5 kcal mol^{-1}.[52]

3. Luminescent monometallic Au(I) complexes

The nature of the coordinated ligands dictates the luminescence properties of d^{10} Au(I) complexes. Also, the propensity of a coordinatively unsaturated Au(I) complex to aggregate through metallophilic interactions can perturb excited states with ligand-centred and/or CT parentage, as well as produce new excited states due to aurophilic interactions. Of course, these observations often become more important when considering the spectroscopic properties of compounds in the solid state.

A rigid, chelating di-tertiary phosphine ligand, 1,2-bis(diphenylphosphinyl)benzene, has been used to synthesise tetrahedral geometry Au(I) complexes from $[AuCl(PPh_3)]$ (Fig. 5). The cationic complexes absorb at 360–420 nm with visible phosphorescence emission in the solid state, which was dependent upon the nature of the counter anion (Cl^- *vs.* BF_4^- *vs.* PF_6^-). Supporting density functional theory (DFT) calculations suggest that the emitting state is of CT character, involving the P (donor) and Ph (acceptor) groups of the chelated phosphine.[53] The small conformational changes induced by the anion perturb the excited state behaviour.

Water-soluble three-coordinate Au(I) complexes (Fig. 5) have been obtained using triphenylphosphine tris-sulfonate and [AuCl(tht)] (tht = tetrahydrothiophene). The spectroscopic room temperature properties showed that the compound was emissive (albeit requiring UV excitation) at 494 and 515 nm in the solid state and aqueous solution respectively, with a corresponding lifetime of *ca.* 2 μs for the latter. Interestingly, the complex can be incorporated into hydrogel microspheres based on poly(*N*-isopropylacrylamide) yielding stimuli-responsive, highly phosphorescent (525 nm) materials that should have genuine bioimaging applications, particularly if the excitation energy can be lowered.[54] Calculations have postulated that the excited state adopts a Jahn–Teller distortion approximating a T-shape and therefore the compliance of the medium to allow such a distortion can be invoked to rationalise the media-dependent emission properties of the complex.[55,56]

Supramolecular Au(I) architectures have been generated using 2-pyridineformamide thiosemicarbazone ligands, resulting in a

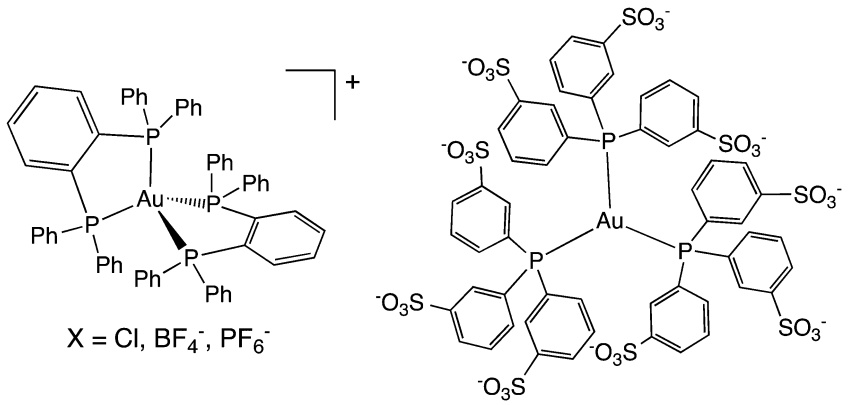


Fig. 5 Luminescent tetrahedral and trigonal planar Au(I) complexes.

luminescent species.[57] The absorption spectra are dominated by ligand-centred n–π* transitions to *ca.* 392 nm. Corresponding solid-state emission spectra were attributed to ligand-centred fluorescence in all cases, which were perturbed to varying degrees by the presence of Au(I) and the existence of any weak Au···Au interactions in the solid-state, as indicated by the X-ray crystallographic studies.

Related thiocarbamoyl-pyrazoline ligands have also been coordinated to Au(I) to give emissive complexes.[58] The ligands are neutral S donors, reacting with [AuCl(PPh$_3$)] to give two-coordinate linear geometry complexes. The electronic properties (CH_2Cl_2) showed absorption at 300–350 nm due to a LMCT transition together with coincident ligand-centred transitions; solid-state samples gave emission spectra, revealing peaks at *ca.* 415 nm (λ_{ex} = 320 nm). The emitting state is likely to comprise significant LMCT character, although in line with other studies, the possibility of metal-perturbed ligand-centred emission should not be ruled out.

At Cardiff, our group investigated a series of bio-inspired mercapto-pteridine ligands (Fig. 6) obtained *via* the condensation of 4,5-diamino-6-hydroxy-2-mercaptopyrimidine hemisulfate hydrate with a selection of functionalised diketones.[59] Pteridines, bicyclics comprised of a fused pyrimidine and pyrazine ring, are the core structures of key biochemical systems in nature, for example pterins and folic acid[60] and have also shown potent anti-cancer activity (*e.g.* methotrexate).[61] The ligands react with [AuCl(PR$_3$)] (R = Ph or Cy) to yield the expected two-coordinate complexes, wherein the mercapto-pteridine ligand coordinates as an anionic thiolate donor. The absorption spectra showed bands attributed to overlapping ligand-centred transitions as well as a S-to-Au LMCT contribution. The complexes were emissive in solution, displaying visible luminescence assigned to the coordinated pteridine fluorophore. Cytotoxic evaluation (MTT assay) of these complexes was conducted on MCF7 (breast adenocarcinoma), A549 (lung adenocarcinoma), PC3 (prostate adenocarcinoma) and LOVO (colon adenocarcinoma) revealing strong anti-proliferative effects that were comparable to cisplatin. For a given pteridine ligand, the complexes incorporating PPh$_3$ were most active.

Despite their ubiquitous deployment in transition metal coordination chemistry, the number of N-heterocycle complexes of Au(I) are relatively few. The simple heteroleptic species [Au(PPh$_3$)(C$_5$H$_5$N)]$^+$ was first reported by Schmidbaur as recently as 2004 (Fig. 7).[62,63] A range of homoleptic species [Au(Py)$_2$]$^+$ (where Py = a 4-substituted pyridine) were reported in 2008, with solid-state luminescent properties strongly dependent upon the nature of the intermolecular Au(I)···Au(I) interactions.[64] Our own studies have investigated a series of pyridine and quinoline appended phthalimide-derived ligands to form complexes of the type [Au(PPh$_3$)(L)](PF$_6$) (Fig. 7) (where L = pyridine or quinoline donor).[65] The emission data ($CHCl_3$) revealed metal-perturbed ligand-centred fluorescence in all cases.

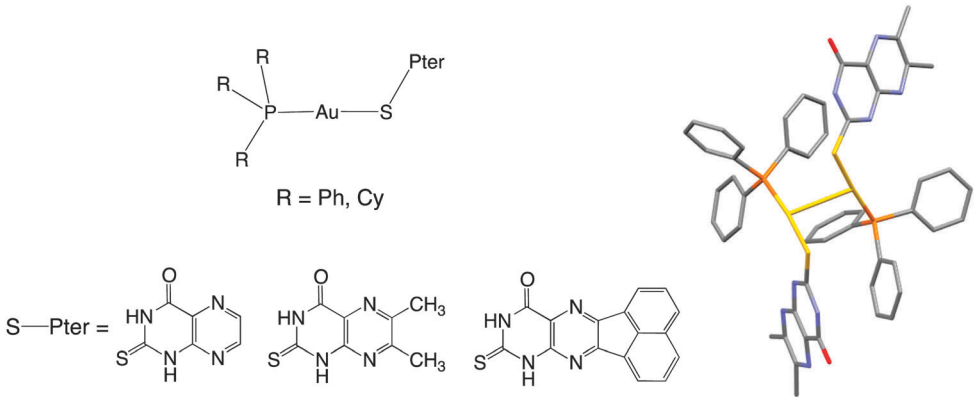


Fig. 6 Left: mercapto-pteridine complexes of Au(I). Right: crystal structure of a Au(I) complex.

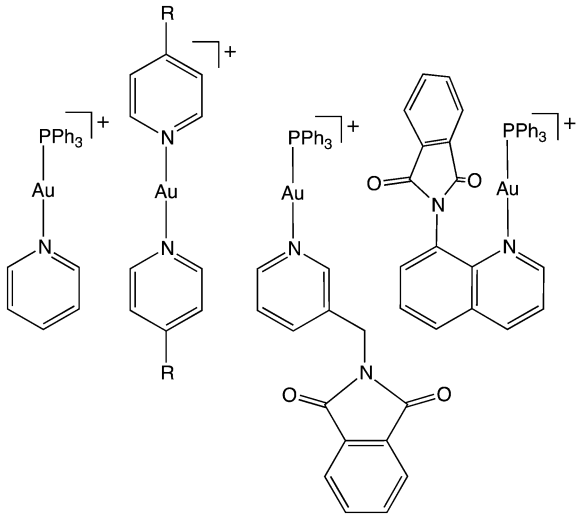


Fig. 7 Examples of Au(I) complexes of nitrogen heterocycle ligands.

When reacted with Au(I), brominated azadipyrromethene ligands yield luminescent complexes that absorb visible light.[66] A linear two-coordinate geometry at Au(I) was achieved *via* the binding of a single pyrrole nitrogen and an ancillary PMe_2Ph ligand. The photophysical properties of the complexes (2-MeTHF at room temperature) were complemented by DFT calculations, suggesting that dual emission observed at *ca.* 375 nm and 670 nm was due to ligand-centred fluorescence.

The development of organometallic Au(I) species has afforded opportunities in the pursuit of luminescent complexes. Isocyanide Au(I) complexes have been reported using a coordinative tetrafluorophenyl donor that is conjugated to a perylene fluorophore (Fig. 8).[67] X-ray crystallography confirmed the integrity of the Au–C interaction revealing a two-coordinate linear geometry. The complexes were stable in $CHCl_3$ solution and the absorption spectra dominated by the perylene-based transitions, characterised by distinct vibronic features at 350–475 nm. The emission from the complexes was attributed to the perylene unit in all cases, short lifetimes typical of perylene-centred fluorescence and with notable quantum yields (up to 96%), suggesting that heavy atom assisted quenching was not evident.

Fluorinated aryl moieties can promote 'metalloligand' properties based on Au(I), yielding thermodynamically stable targets for the design of new architectures.[68] [AuCl(tht)] reacts with LiC_5F_4N to give the anionic complex $[Au(C_5F_4N)_2]^-$, thereby generating a 'metalloligand'. A range of related species using a variety of fluorinated aryl units were subsequently used as building blocks for more complex multimetallic species.[69] No supporting photophysical studies were reported.

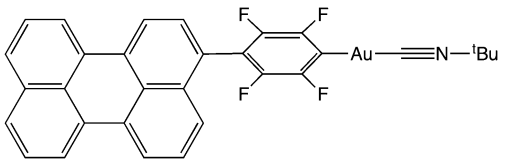


Fig. 8 A fluorescent, perylene-functionalised Au(I) complex.

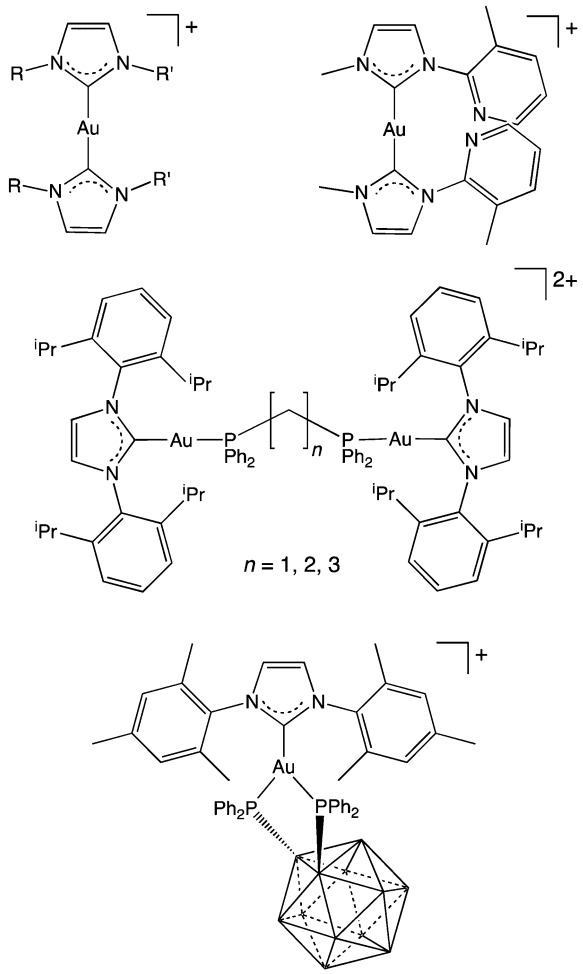


Fig. 9 Examples of Au(I) complexes incorporating NHC ligands.

The use of N-heterocyclic carbenes (NHCs) as ligands for Au(I) (Fig. 9) has rapidly developed over the past decade. In the context of this review, pioneering work by the groups of Baker and Berners-Price has investigated the biological activity of NHC-containing Au(I) compounds. A prime motivation for this development has been the use of NHCs as viable alternatives to more common phosphine ligands.[70,71] Structural control over the precursor imidazolium salts allows relatively easy control over the steric and electronic influences as well as the lipophilicity, the latter a key consideration for biological applications. NHC complexes of Au(I) have shown anti-tumour activity, TrxR inhibition[72] and more focused studies have proposed that mitochondria are targeted. Mechanistically, the interaction of complexes with protein targets can permeabilize the mitochondrial membrane.[73] Homoleptic cationic Au(I) NHC complexes (top, Fig. 9) of the form $[Au(NHC)_2]^+$, with varying lipophilicities controlled by different alkyl groups on the NHC ligand, have also been investigated as anti-mitochondrial agents, with the most lipophilic species inducing the greatest mitochondrial swelling and permeability.[74] Complexes incorporating benzimidazolylidene NHCs have also shown promising anti-proliferative effects.[75]

Investigation of the potential of NHC Au(I) complexes as anti-cancer drug candidates has led to a comparison of mono-NHC

and bis-NHC Au(I) species.[76] The complexes were highly stable in buffered aqueous solutions at physiological pH, and although they did not bind to the model proteins cytochrome *c* and lysozyme, metalation was observed for Atox-1 (a copper chaperone protein). Despite the obvious structural differences, similar cytotoxic potency was observed against human ovarian carcinoma cells.

A series of emissive NHC Au(I) complexes with remarkable quantum yields (up to 99% in the solid state) have been reported.[77] The three-coordinate species incorporate a NHC ligand and a diphosphine carborane (Fig. 9), giving rise to a distorted trigonal planar geometry. The electronic properties (de-aerated CH_2Cl_2) revealed a dominant ligand-based absorption band at 310 nm and corresponding emission 470–520 nm (λ_{em} was dependent upon the NHC substituents). The bathochromic shift in polar solvent suggests an excited state of CT character; the lifetime data confirmed a phosphorescence emission in all cases (*ca.* 10–22 μs). Complementary TDDFT calculations were invaluable in assigning a CT transition from the *nido*-carborane ligand to the metal–ligand fragment (*i.e.* $L_{car}ML_{NHC}CT$) involving the NHC moiety.

Cytotoxic Au(I) NHC complexes have been synthesised from the transmetallation of the corresponding Ag(I) complex of 2-pyridin-2-yl-2*H*-imidazo[1,5-*a*]pyridin-4-ylium.[78] The biological activity of the cationic $[Au(L)_2]PF_6$ complex was assessed (MTT assay) against four different cancer cell lines, and demonstrated comparable IC-50 values to cisplatin. Supporting fluorescence microscopy imaging work with stained (using 4,6-diamidino-2-phenylindole dihydrochloride) cells indicated fragmented nuclei and other indicators of apoptosis.

Dyson and Laguna have shown that water-soluble alkynyl-derived Au(I) complexes can be synthesized through the use of either 3,7-diacetyl-1,3,7-triaza-5-phosphabicyclo-[3.3.1]nonane (DAPTA) or 1,3,5-triaza-7-phosphaadamantane (PTA) as ancillary phosphine ligands (both are less toxic than PEt_3).[79] Complexes of the general form $[Au(C{\equiv}CR')(PR_3)]$ incorporated a wide variety of alkyl- and aryl-substituted alkynes (for example, where R′ = benzyl, pyridyl, thiazolyl) and were assessed spectroscopically, structurally and from a cytotoxic perspective. Solid-state luminescence was observed in all cases and was attributed to π–π*(C≡C) or σ(Au–P)–π*(C≡C) excited states and therefore dependent on the specific nature of the coordinated alkyne. Biological evaluation of the complexes was investigated using human ovarian cancer cells, with comparison against cisplatin and auranofin. Under biological conditions, the alkyne ligands were prone to substitution reactions with cysteines; incubation with DNA showed no notable interactions or induced damage. Epifluorescence microscopy was utilized in an attempt to identify the specific intracellular localization of the Au(I) complexes, although the limited emission from the complexes merely confirmed that uptake was efficient.

Complexes based on coumarin-functionalised alkynyl ligands (Fig. 10), [Au(PTA/DAPTA)(coum)] and $[Au(coum)_2]^-$ (where coum = 4-(prop-2-in-1-yloxy)-1-benzopyran-2-one or 7-(prop-2-in-1-yloxy)-1-benzopyran-2-one),[80] possess luminescence properties (λ_{em} = 350–380 nm) dominated by coumarin-based excited states, and are therefore not well suited to biological imaging applications.

The development of an azide ligated Au(I) synthon, $[Au(N_3)(PPh_3)]$,[81,82] to facilitate 'gold-click' chemistry has led to metalated triazolyl ligands adorned with a range of functionality (Fig. 11).[83] Reaction of $[Au(N_3)(PR_3)]$ (R = Ph, Cy) with alkynyl-functionalised coumarins yielded triazolyl-coordinated species with a pendant coumarin fluorophore. From a photophysical perspective, the scope of this synthetic approach is vast, since a range of fluorescent alkynyl derivatives can be imagined that address biocompatibility.

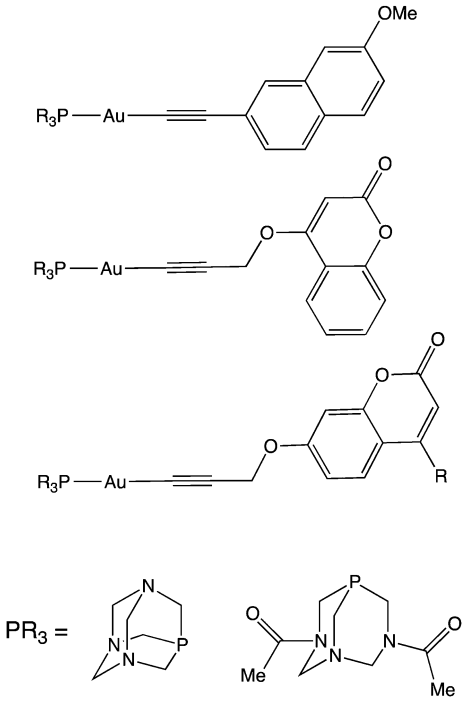


Fig. 10 Water-soluble, fluorescent heteroleptic alkyne/phosphine Au(I) complexes.

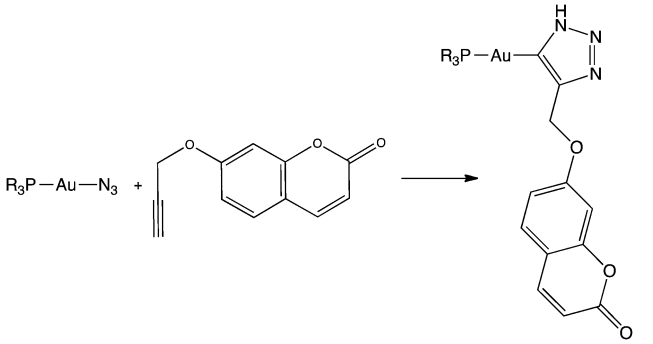


Fig. 11 An example of 'click' chemistry with a gold azide complex.

4. Luminescent homometallic Au(I)-based arrays

The propensity of gold complexes to aggregate *via* metal–metal attractions is well known. The ability to utilise and potentially exploit these interactions in the design of supramolecular architectures has driven significant progress in the last few years.

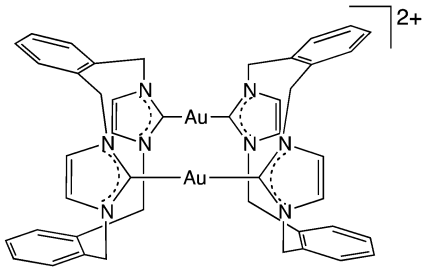


Fig. 12 Example of a bridging cyclophane NHC-based Au(I) complex.

In tandem with the opportunities for structural control, the photophysical properties of Au(I) compounds that possess aurophilic interactions are often distinct and complex. The strength of the aurophilic interaction can perturb or even modulate the excited states leading to tunable behaviour that can be exploited in the design of chemosensor platforms.[84]

The synthesis of dimetallic Au(I) complexes is a simple strategy for investigating the possibility of intramolecular aurophilic interactions. Two different studies have investigated the use of linked NHCs to generate dimetallic Au(I) complexes. Berners-Price and collaborators have reported a series of papers describing the synthesis and properties of bridging cyclophane ligands (Fig. 12) that yield dimetallic, luminescent Au(I) complexes.

The conformation of the complexes ensures that short Au(I)···Au(I) contacts (<3 Å) are observed; this distance can be modulated as a function of the bridging unit within the bis-NHC ligand. These complexes have been investigated in a variety of contexts, including some early pioneering studies looking at the biological action[85] as well as sensing opportunities.[70] Structural studies using both single crystal X-ray diffraction, XANES and EXAFS have revealed the existence of anion binding resulting from electrostatically driven interactions with the two-coordinate Au(I) atoms.[86] For this class of Au(I) complex the emission arises from metal-perturbed, ligand-centred excited states, yielding relatively high energy excitation (λ_{ex} = 313 nm) and emission (λ_{em} = 396 nm) profiles.

Tetra-gold clusters stabilised by NHC ligands have been synthesised from $[Au(SEt_2)_2]Cl$ and the corresponding Ag(I) NHC complex.[87] In the solid state the $[Au_4L_2](PF_6)_2$ species possess Au(I)···Au(I) contacts of 3.292(1) and 3.276(1) Å, whilst the luminescence properties (λ_{em} = 431 nm) were characterised as ligand-centred.

Work at Cardiff (with Dervisi and Fallis) has looked at related NHC species in the development of metallamacrocyclic Au(I) architectures (Fig. 13).[88] Isomannide was utilised as the bridging unit, yielding a rigid backbone for linking the NHC moieties. The resultant dimetallic Au(I) complexes display two-coordinate, approximately linear geometry, possessed a long Au(I)···Au(I) distance (>6 Å) and were chiral, as evidenced through circular dichroism measurements. The luminescence properties from these complexes suggest an excited state which is dominated by ligand-centred character, albeit significantly perturbed by the coordinated Au(I).

The correlation between Au(I)···Au(I) distance and the observed photophysical properties of complexes has been investigated using

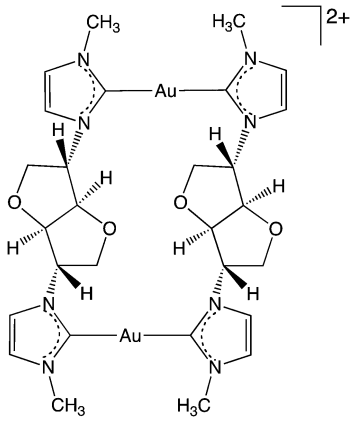


Fig. 13 A metallamacrocycle based on NHC Au(I) complex dimers.

4-pyridyl-ethynyl ligands.[89] Au(I) alkynyl complexes often possess intense alkynyl-centred (*i.e.* $\pi \rightarrow \pi^*$) absorptions in the low-energy part of the UV region, as well as possible CT transitions involving Au(I). For the dimetallic species, each Au(I) was coordinated by a bridging ditertiary phosphine and a 4-pyridyl-ethynyl ligand coordinated *via* the alkyne (Fig. 13); the size and geometric character of the bridging unit influencing the optical properties. In the case of the 2,2′-bis(diphenylphosphanyl)propane ligand an absorption band was observed at *ca.* 310 nm and assigned to a CT $\sigma^*_{Au-Au} \rightarrow \pi^*$ transition resulting from an aurophilic interaction in solution. Supporting studies using NMR spectroscopy confirmed the presence of π–π stacking that cooperatively supports the aurophilic interactions.[90] In the solid-state the luminescence properties of the complexes display a clear trend between the Au(I)···Au(I) distance (be it intra- or intermolecular) and the emission quantum yields and lifetimes. The variation in the radiative rate constant (k_r) implies a modulation of spin–orbit coupling that allows deactivation from the excited state, which may contain an element of σ^*_{Au-Au}–π* character.

Laguna and Tunik have reported a series of dimetallic Au(I) complexes incorporating alkyne and/or oligophenylene bridged diphosphines.[91] The complexes were isolated in the general form [(AuX)$_2$(P^P)] (where X = Cl, C_6F_5) *via* reaction with [Au(tht)X]. Structural studies confirmed the two-coordinate arrangement of ligands, with intermolecular Au(I)···Au(I) interactions supported by π–π stacking of the aryl units. The absorption properties were confined to the UV region and attributed to intra-ligand transitions in all cases. Room temperature emission spectra of solid-state samples suggest a short-lived singlet emission (λ_{em} = 380–480 nm) which was ligand-centred and perturbed by the coordinated Au(I).

Phenylene spacer dithiolate ligands have been used to bridge two $[Au(PPh_2R)]^+$ (R = phenylene or pyridine) moieties, giving luminescent complexes in the solid state due to a possible mixture of ILCT–LL′CT transitions.[92]

2,7-Disubstituted fluorene chromophores have been appended with alkyne donors to yield rigid, dimetallic Au(I) complexes (Fig. 14).[93] Biological assessments of the ligands and complexes *in vitro* and *in vivo* revealed that the dimetallic fluorenone Au(I) complex was particularly active, attributed to the generation of

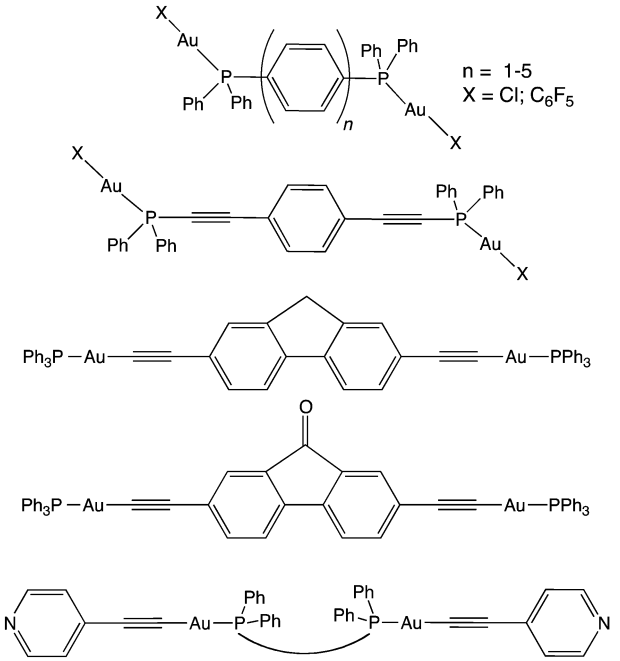


Fig. 14 Examples of bridged dimetallic Au(I) complexes.

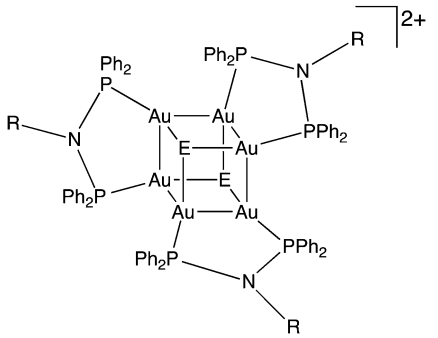


Fig. 15 Example of a hexanuclear Au(I) cluster (E = S, Se).

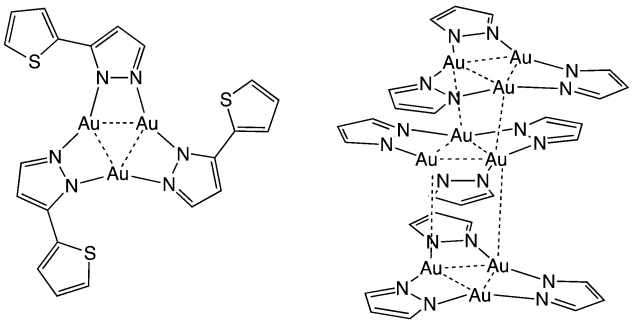


Fig. 16 Trimetallic Au(I) array (left) with stacking character (right).

intracellular reactive oxygen species. Complex uptake with Hep3B cells was assessed using ICP-MS, but no supporting studies using CFM are detailed, despite the reported visible luminescence from these species.[94]

Higher nuclearity Au(I)-containing clusters possess intriguing photoluminescent properties. Yam and co-workers have reported an aesthetically beautiful Au_{18} thiacrown-like architecture structurally supported by Au(I)···Au(I) interactions, peripheral tridentate phosphine and μ_3-sulfido ligands.[95] The Au(I)···Au(I) distances lie in the range 3.0145–3.3295 Å and the solution state absorption properties were dominated by two intense bands at 318 and 346 nm, assigned as LMCT modified by aurophilic interactions. The Au_{18} complex was luminescent, giving an intraligand-based phosphorescence at *ca.* 500 nm. The scope for this class of compound in the exploration of host–guest chemistry and potentially biological imaging is vast.

Following on from this work, Yam has also described a series of hexanuclear and decanuclear Au(I) sulfido and selenido complexes (Fig. 15), supported by bridging diphosphino amine ligands;[96] the structures reveal short intramolecular Au(I)···Au(I) distances <3.3 Å. The emission properties of the Au_6 and Au_{10} clusters, obtained in both solution and solid-state, were described as either a green (metal-perturbed IL), and/or orange (LMMCT) phosphorescence. The selenido derivatives generally induced a bathochromic shift in the luminescence properties.

White-light emission has been demonstrated using a Au(I) cluster based upon the ligating properties of 3-(2-thienyl)-pyrazole (Fig. 16).[97] The trimetallic monomer cluster [{Au(L)}$_3$] was prepared through reaction of the ligand and [AuCl(tht)]. In the solid-state the compound crystallizes in two dominant forms that each show stacked structures supported by different intermolecular Au(I)···Au(I) interactions. These structural differences manifest themselves in the distinct photoluminescent properties of each form, giving either orange-red or white light emission. In solution, increasing the monomer concentration to 10^{-3} M resulted in aggregation and an emission at 558 nm assigned to an excimeric triplet state.

Koshevoy and Chou have described intense emission from discrete Au_{10} clusters constructed from [AuCl(tht)] and functionalised alkynyl ligands; a derivatised series of related compounds were synthesised by treating the Au_{10} clusters with a di-gold diphosphine complex yielding heteroleptic octametallic cationic variants.[98] Both classes of compounds revealed strong triplet emission in both solution and solid-state measurements with remarkable quantum yields reported to unity (100%).

In brief, heterometallic aggregates that contain Au(I) and other group 11 metal ions are well known,[99] but often lack the required stability in solution for biological application. However, metallophilic interactions can modulate the luminescent properties of heterometallic assemblies that contain Au(I), as shown in a series of complexes reported by Gimeno.[100] Although currently underdeveloped, it is noteworthy that Au(I) can be combined with other emissive metallo-species to yield heterometallic complexes with potentially advantageous optical properties[8] that circumvent the limitations of discrete Au(I) entities. For example, the luminescent properties of Au(I)–Re(I) dimers bridged by either 4-ethynylpyridine[101] or an ethynylphenanthroline[102] ligand yield complexes dominated by the ^{3}MLCT character of the Re(I) tricarbonyl unit. A similar observation was noted in a trimetallic Re(I)–Au(I) species using 1,2-dithiolene units where the phosphorescent emission from the Re(I) tricarbonyl moiety

dominated the emission properties.[103] Very recently, luminescent lanthanide–Au(I) coordination polymers have been reported utilising dicyanoaurate building blocks.[104] Tetrametallic Au(I)–Yb(III) d–f hybrids have also been developed from 5,5′-diethynyl-2,2′-bipyridine, revealing efficient sensitisation of the near-IR emitting Yb(III) in dichloromethane solution.[105]

5. Bioimaging Au(I) complexes in cells

A detailed understanding and insight into the mechanisms of biological action, including the possibility to target specific sites in cells, ultimately informs the rational design of new therapeutics.[106] However, understanding the cellular uptake and intracellular distribution of Au(I) complexes is challenging. Although confocal fluorescence microscopy (CFM) is a convenient and non-invasive optical technique it obviously requires (highly) emissive, biocompatible fluorophores; all of the biologically active Au(I) complexes identified earlier (*e.g.* auromalate auranofin and its structural cousins) do not possess the requisite solution state luminescence attributes to allow such applicability. Therefore, at present, the development in cellular imaging of Au(I) complexes can be embodied in two strategies: (i) the use of analytical techniques that allow elemental isotopic (*e.g.* ^{197}Au and ^{31}P) composition to be mapped; and (ii) the functionalization of Au(I) complexes with fluorescent labels, typically using well known organic fluorophores, to facilitate CFM. Recalling earlier discussion of the dissociation of ligands from Au(I), the significant caveat for the latter method is the assumption that the fluorophore label remains coordinated to Au(I). Ideally, the emission of the free fluorophore should therefore be distinguishable from that of the complex; the application of fluorescence lifetime imaging microscopy (FLIM) would clearly be advantageous in such scenarios.

CFM can offer improved resolution, but tends to be more qualitative (FLIM can provide quantitative information) than for other techniques such as inductively coupled plasma mass spectrometry (ICP-MS, a potentially destructive technique often compromised by relatively poor spatial resolution) and atomic absorption spectroscopy[107] (AAS). Synchrotron radiation-induced X-ray fluorescence microscopy (SR-XRF) can also provide the mapping of metal ions within cell sections, and simultaneously analyse for several elements with a resolution *ca.* 300 nm.[108] A combination of both elemental mapping and optical methods clearly present a powerful approach for Au(I)-based agents.

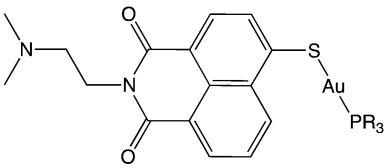
In this context, Berners-Price has described the application of nano-scale secondary ion mass spectrometry (NanoSIMS)[109] and energy filtered transmission electron microscopy (EF-TEM), which combine a high sensitivity to gold and exceptional resolution (*ca.* 50 nm) of subcellular ultrastructure.[110] Human breast adenocarcinoma cells were treated with a high concentration (0.1 mM) of [Au(d2-pype)$_2$]Cl and NanoSIMS ion maps (^{12}C, ^{14}N$^-$, ^{31}P$^-$, ^{34}S$^-$, ^{197}Au$^-$) revealed cell elongation and nucleic acid modifications. Conventional TEM revealed significant distortions of the mitochondria with a sharp increase in the electron density of these organelles, indicative of Au(I) accumulation. ^{197}Au maps depicted aggregates in mostly non-DNA structures, whilst at very high concentrations of the complex, Au(I) was found associated with sulfur-rich regions of the nucleus and cytoplasm, supporting a mode of action based upon the inhibition of thiol proteins, such as Trx.

Ott has investigated a range of non-emissive [AuCl(PR$_3$)] complexes applied to cell lines (5.0 μM aqueous solutions for 6 hours) using ICP-MS and AAS. The lowest cellular uptake was observed for the least lipophilic complex [AuCl(PMe$_3$)]; [AuCl(PEt$_3$)] and [AuCl(P^{t}Bu$_3$)] had slightly higher uptakes with [AuCl(PPh$_3$)] demonstrating the most significant uptake. Biophysical parameters of the HT-29 cells allowed the respective cellular molar concentrations to be determined, which were comparable to cisplatin, but below the uptake of auranofin (109 μM). The low levels of nuclear uptake across the series of compounds suggest that this class of complex does not target DNA.

To facilitate the use of CFM, Ott subsequently developed a series of linear Au(I) complexes incorporating an ancillary phosphine (with varying alkyl/aryl groups) and a thiolated fluorophoric ligand (Fig. 17), giving [Au(PR$_3$)(S-Nap)] (where S-Nap = 4-mercapto-1,8-naphthalic anhydride or *N*-(*N*′,*N*′-dimethylaminoethyl)-1,8-naphthalimide-4-sulfide).[111] Spectroscopic studies showed no influence of the ancillary P ligand, and a bathochromic shift in fluorescence emission (438 to 545 nm) characteristic of intramolecular charge transfer (ICT). CFM imaging of MCF-7 cells was achieved with [Au(*N*-(*N*′,*N*′-dimethylaminoethyl)-1,8-naphthalimide-4-sulfide)(PPh$_3$)] showing that the complex localized in cell nuclei. Supporting cytotoxicity studies showed IC$_{50}$ values of 1.1–3.7 μM for MCF-7 cells, which were comparable to auranofin (1.1 μM) and cisplatin (2.0 μM); the free 1,8-naphthalimide ligands were also cytotoxic (IC$_{50}$ 1.9–4.6 μM).[112] Biodistribution studies (CFM and AAS) showed uptake into cell organelles and nuclei of cancer cells together with inhibition of TrxR.[113]

Water-soluble cyclophane-bridged NHC complexes of Au(I) have found applicability to CFM.[114] The emission properties of the dimetallic Au(I) complexes (λ_{ex} 350 nm; λ_{em} 496 nm) were biocompatible and cell imaging with RAW264.8 cells revealed good uptake, lysosomal localization and a moderate cytotoxicity (IC$_{50}$ 52 μM).

Au(I) alkyne complexes are gaining significant interest as future candidates for gold-based drugs. Ott has recently described a range of alkyne coordinated Au(I) complexes (Fig. 18) that selectively target TrxR; complexes incorporating either anisole or benzyl ether units (highlighted in blue) were most active against TrxR.[115] Importantly, the activity of the



R = Me, Et, ^{t}Bu, Ph

Fig. 17 A naphthalimide-derived Au(I) complex.

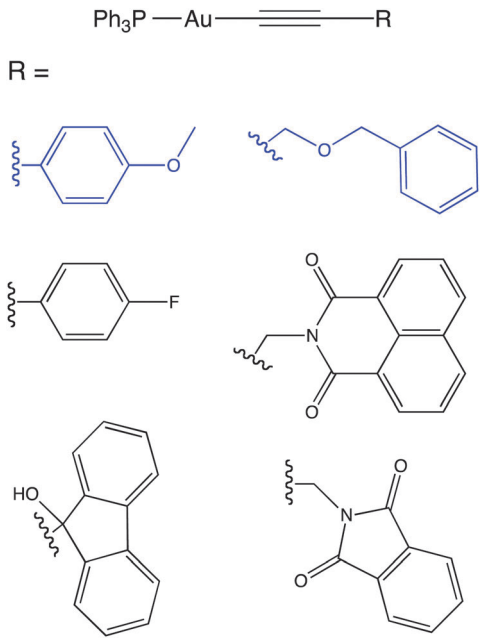


Fig. 18 A range of bioactive alkyne-functionalised Au(I) complexes.

complexes was attributed to the intact metal-containing species.

At Cardiff we developed a series of alkynyl-functionalised anthraquinone (AQ) ligands and their corresponding mono- and dimetallic Au(I) complexes (Fig. 19).[116] The work was motivated by the known biological activity of functionalized AQ species, in particular those naturally occurring products such as aloe emodin, as well as therapeutics like doxorubicin and mitoxantrone.[117] From a synthetic perspective, commercially available hydroxy-AQ precursors were reacted with propargyl bromide to yield the corresponding alkynyl adorned AQ ligands. Subsequent reaction with [AuCl(PPh$_3$)] led to a range of linear mono- and di-metallic Au(I) complexes. The absorption properties of the complexes were dominated by ligand-centred transitions in all cases, with the AQ chromophore dominating in the visible part of the spectrum. The precise absorption wavelength of the AQ chromophore was strongly influenced by the position of substitution at the AQ core, and in these cases possessed significant CT character due to donor–acceptor properties (alkoxy-to-quinone). Lifetimes were characteristic of ligand-based fluorescence (<5 ns). A comparison of the cytotoxicity (MTT assay) against several cancer cell lines showed that the complexes were far more toxic than the free ligands. CFM was undertaken using a selection of free ligands and complexes (λ_{ex} = 405 nm) all showing good uptake ($>80\%$). For example, the 1,4-AQ Au(I) complex showed no nuclear uptake, with general cytoplasmic staining (Fig. 20) and some areas of intense fluorescence, which could not be attributed to any specific organelle localisation.

In summary, there is a fascinating breadth of Au(I) complexes that possess biocompatible photophysical properties, based upon mono- and polymetallic structures. Predicting and tuning the luminescent properties of such species can be challenging. Coupling Au(I) with known organic fluorophores has been successfully utilised in cell imaging, but the combination with phosphorescent metal-based species could provide useful avenues in the development of new imaging probes for confocal fluorescence microscopy. It is clear from biological studies that the activity of Au(I) complexes invariably originates from the substitution of ligands at the metal centre and the affinity of Au(I) for sulfur and selenium in biologically important substrates. This presents some unique challenges when considering the fate of cytotoxic Au(I) complexes and their applicability to biological imaging; the development of alkyne coordination complexes may provide a promising option in this context. The combination of both analytical and spectroscopic imaging techniques can yield an increasingly detailed picture of the intracellular distribution of gold-containing species, and should enable the targeted design of biologically active Au-based agents in the future.

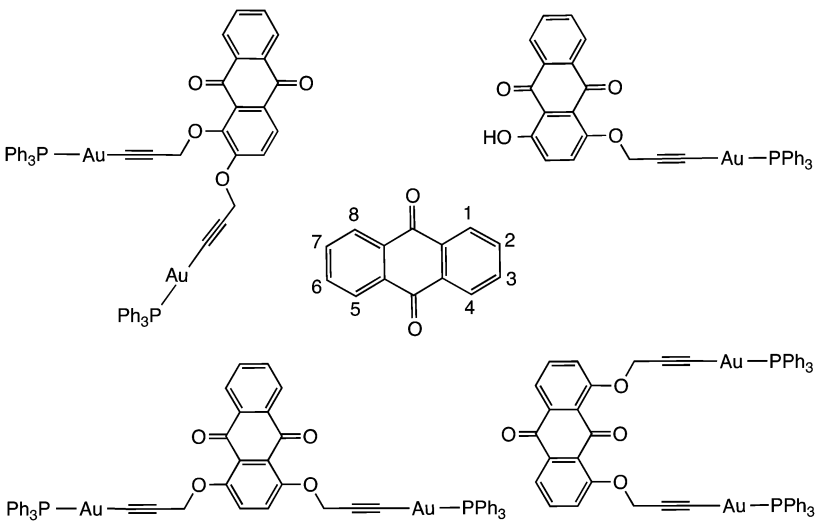


Fig. 19 Various anthraquinone-functionalised Au(I) complexes.

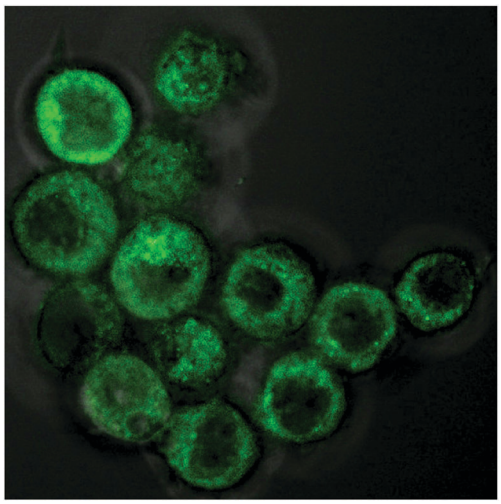


Fig. 20 Images of MCF-7 cells incubated with an AQ-derived Au(I) complex (100 μg ml^{-1} 4 °C, 30 min). Excited at 405 nm; acquired at 530–580 nm.[116]

Acknowledgements

The authors thank Cardiff University for support.

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