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Phosphinoamine coinage metal complexes with a coumarin fluorophore: synthesis, characterization, and *in vitro* (photo)cytotoxicity

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Herein, we report the synthesis and characterization of coinage metal complexes coordinated to a coumarin-functionalized (bis(4-(*tert*-butyl)phenyl)) phosphinoamine ligand ($\mathbf{L^1}$). Treatment of the ligand with CuCl led to the formation of an unexpected tetranuclear compound [$\mathbf{L^1}$CuCl]$_4$, while reaction with [Au(tht)$_2$SbF$_6$] or [Au(tht)Cl] (tht = tetrahydrothiophene) in an equimolar ratio resulted in [$\mathbf{L^1}_2$Au]SbF$_6$ or [$\mathbf{L^1}$AuCl]. Reaction of the latter compound with 1-thio-β-D-glucose tetraacetate (Glc) led to [$\mathbf{L^1}$Au(Glc)]. Owing to the presence of the fluorophore, the resulting metal complexes exhibited strong emissive properties, with the Au^{I} complexes demonstrating quantum yields exceeding 80%. The emission is mainly contributed by the coumarin moiety. As a result, we further investigated these compounds for their cytotoxicity, photocytotoxicity, and potential in cellular imaging applications. Despite the known general cytotoxicity of Cu^{I}, the new coinage metal complexes show low cytotoxicity and are useful for cell imaging.

Introduction

In recent years, there has been growing interest in using luminescent small-molecule materials as bioimaging agents for probing the structure and function of biological systems with minimal disruption to living cells or organelles.[1–3] Among these, gold-based compounds have emerged as particularly promising candidates.[4–7] Research has highlighted several advantages associated with gold complexes in this context. One notable benefit is their high photoluminescence quantum yield;[8,9] for instance, studies by Bodio and Goze demonstrated that removing a gold atom from the complex significantly reduces photoluminescence (PL) efficiency.[10] Additionally, these compounds often possess long-lived excited states, ranging from hundreds of nanoseconds to several microseconds,[11–13] making them effective for suppressing background autofluorescence in biological environments.[14,15] Another appealing feature is the tunability of their excitation and emission wavelengths across the visible spectrum, which can be achieved through structural modifications of the ligand framework.[16–19]

Furthermore, the mechanisms of action of Au^{I} compounds have been extensively studied.[20] Au^{I} complexes predominantly target enzymes that are not localized in the cell nuclei.[21] Among these, thioredoxin reductases, which have thiols and selonol functional group, are among the most thoroughly investigated enzymes.[22,23] The high affinity of Au^{I} centers for soft nucleophiles, particularly thiol and selenol groups, underlies their selective inhibition of these redox-active enzymes.[24]

Gold phosphine complexes, in particular, have attracted attention for biomedical applications due to the strong binding affinity of phosphines to Au^{I} ions and their lipophilic nature, which aids in crossing cellular membranes.[25] A well-known example is Auranofin, a gold(I) phosphine complex that has received clinical approval for the treatment of rheumatoid arthritis.[26] In recent times, attaching a fluorophore such as BODIPY and porphyrin has become a common method in the design of therapeutic metal complexes (Scheme 1).[27–34] We have also previously shown that attaching an organic dye can strongly influence the photophysical properties of the metal complexes.[8,35–39] Building on this approach, we have used 7-amino-4-methylcoumarin (also referred to as coumarin 120) as an organic fluorophore to synthesize and characterize phosphinoamine ligand and its coinage metal complexes with potential applications in optical imaging. Despite the known general cytotoxicity of Cu^{I},[40,41] we include Cu^{I} complexes in our library of coinage metal complexes. Furthermore, the complexes were studied for their efficiency towards *in vitro* cytotoxicity and photocytotoxicity.

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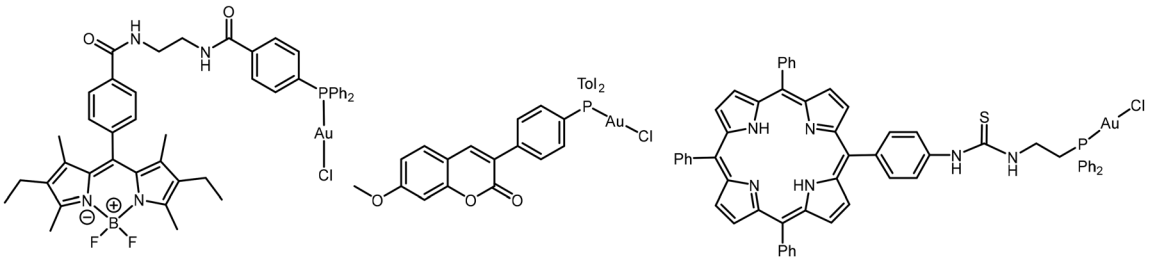


Scheme 1 Previously reported gold(I) complexes attached to a fluorophore *via* phosphine groups.[27–29]

Results and discussion

Synthesis and characterisation

In this work, the synthesis of a series of photoluminescent coinage metal complexes using a coumarin-based (bis(4-(*tert*-butyl)phenyl)) phosphinoamine ligand $\mathbf{L^1}$ was targeted. The complexes were studied for their photophysical properties and investigated for their cytotoxicity towards human cervix carcinoma (HeLa) cells. Phosphinoamine ligand $\mathbf{L^1}$ with 7-amino-4-methylcoumarin in the ligand backbone was synthesized according to a previously reported procedure.[39] The *tert*-butyl groups in the backbone were introduced due to solubility reasons. The equimolar reaction of the ligand $\mathbf{L^1}$ and CuCl led to the formation of the unexpected tetranuclear Cu^I complex $[\mathbf{L^1}CuCl]_4$ (**1**) (Scheme 2) in a 52% yield. The molecular structure of the complex was confirmed by single crystal X-ray diffraction (SCXRD) studies (Fig. 1). The compound crystallizes in the triclinic space group $P\bar{1}$ and exhibits a distorted Cu_4Cl_4 cubane-like core, with Cu and Cl atoms occupying opposite vertices. A similar cubane-like core has also been reported for silver complexes synthesized using NHC (N-heterocyclic carbene)-phosphine hybrid ligands.[42–44]

The distance between copper(I) ions located on opposite sides is 3.01 Å, consistent with other copper clusters described in the literature.[45,46] Each copper(I) ion is coordinated to a phosphine ligand and three chloride anions, resulting in a distorted tetrahedral geometry for the copper cations. The P–N bond lengths in the metal complex are approximately 1.7 Å, similar to those observed in the free ligand $\mathbf{L^1}$.[39] The $^{31}P\{^1H\}$ NMR spectrum shows a singlet at δ 27.0 ppm, which is downfield shifted compared to the free ligand (δ 24.4 ppm).

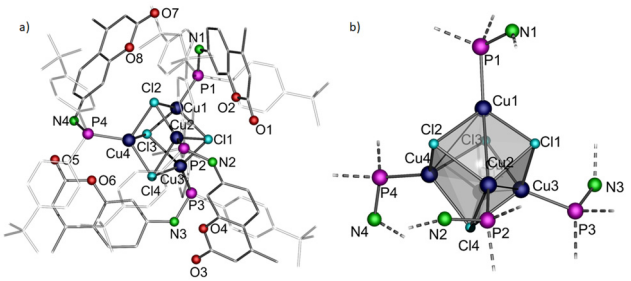
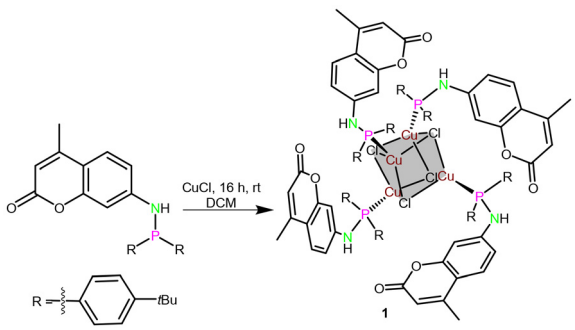


Fig. 1 Molecular structure of copper complex **1** in the solid state (left) and simplified view of the cubane-shaped core structure of **1** without the coumarin and *para*-(*tert*-butyl)phenyl rings (right). Hydrogen atoms and non-coordinating solvents are removed for clarity. Selected bond distances (Å) and angles (°): Cu1–Cu2 3.0073(4), Cu3–Cu4 3.0062(4), Cu1–Cl1 2.5975(5), Cu1–Cl2 2.3150(5), Cu1–Cl3 2.3440(5), Cu2–Cl1 2.2914(5), Cu2–Cl2 2.5576(5), Cu2–Cl4 2.4122(5), Cu3–Cl1 2.4010(5), Cu3–Cl3 2.3032(5), Cu3–Cl4 2.5220(5), Cu4–Cl2 2.3527(5), Cu4–Cl3 2.6445(5), Cu4–Cl4 2.3042(5), Cu1–P1 2.1600 (5), Cu2–P2 2.1638(6), Cu3–P3 2.1617(5), Cu4–P4 2.1615(5), N1–P1 1.706(2), N2–P2 1.704(2), N3–P3 1.705(2), N4–P4 1.704(2); P1–Cu1–Cl1 108.57(2), P1–Cu1–Cl2 125.62(2), P1–Cu1–Cl3 122.62(2), Cl1–Cu1–Cl2 103.07(2), Cl2–Cu1–Cl3 99.33(2), Cl3–Cu1–Cl1 90.95(2), N1–P1–Cu1 114.81(6).[48]

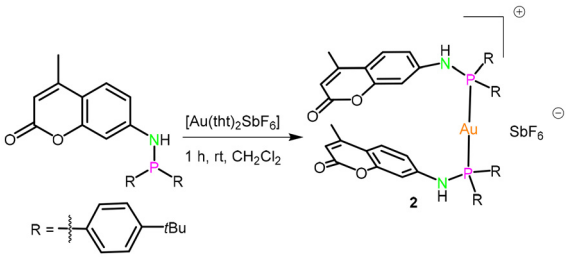
Although the copper(I) complex exhibits luminescence, its quantum yield was measured to be only 40% (as discussed below). Probes with high PL efficiency provide stronger imaging signals at lower dye concentrations, reducing the risk of cytotoxicity and interference with biological pathways.[47]

Therefore, to enhance quantum efficiency, several gold(I) complexes were synthesized.

The gold(I) complex $[\mathbf{L^1}_2Au]SbF_6$ (**2**) was obtained by reacting two equivalents of ligand $\mathbf{L^1}$ with one equivalent of $[Au(tht)_2SbF_6]$ in DCM (dichlormethane) (Scheme 3). Colorless single crystals of complex **2** were isolated in 82% yield by layering a THF solution with n-pentane. The compound crystallizes in the monoclinic space group $P2_1/n$, with half a molecule in the asymmetric unit. The molecular structure in the solid state is shown in Fig. 2. The gold(I) cation is coordinated to two phosphorus atoms and adopts an almost linear geometry, with a P–Au–P′ angle of 171.63(8)°. The charge of the Au^I ion is compensated by an SbF_6 counter anion. The molecular structure in the solid state shows that the two coumarin moieties in



Scheme 2 Synthesis of phosphinoamine coordinated tetranuclear Cu^I complex **1**.



Scheme 3 Synthesis of cationic Au^{I} complex **2**.

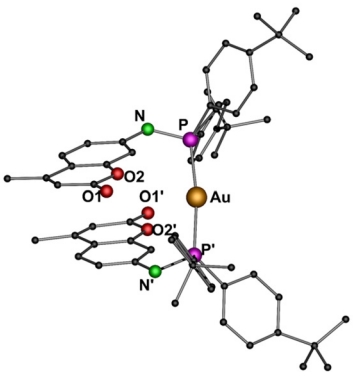
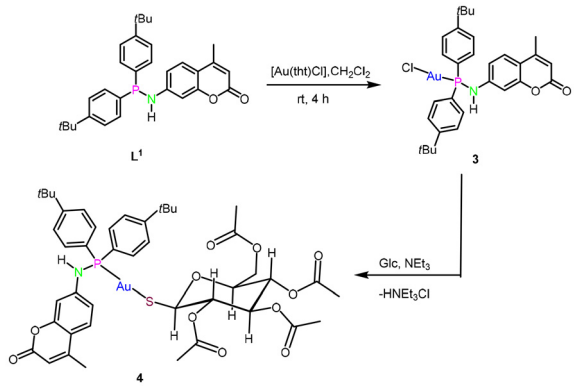


Fig. 2 Molecular structure of the cationic part of gold(I) complex **2** in the solid state. Hydrogen atoms, non-coordinating solvents and the SbF_6^- anion are removed for clarity. Selected bond distances (Å) and angles (°): Au–P 2.305(2), N–P 1.676(5); P–Au–P 171.63(8).[48]

the complex are arranged in a head-to-tail stacking pattern. The Au–P distance is 2.305(2) Å, while the N–P bond length is 1.676(5) Å, slightly shorter than in the free ligand (1.7099(10) Å).

In solution, complex **2** exhibits a singlet at δ 71.9 ppm in the $^{31}P\{^{1}H\}$ NMR spectrum, which is downfield shifted relative to the ligand (δ 24.4 ppm). The cation was identified in the HRESI-MS spectrum at m/z = 1139.4238, confirming the formation of the expected product. The Au^{I} complexes exhibit comparatively larger downfield shifts than the Cu^{I} complex **1**, due to the relativistic effects and strong π-accepting nature of Au^{I}.

It is already reported in the literature that the cationic and neutral gold(I) compounds show different cytotoxicity behaviours.[49,50] Therefore, in addition to synthesizing the cationic complex, the preparation of two neutral gold(I) complexes, ligated by the coumarin-based phosphinoamine ligand **L^1**, was also pursued. To achieve this, ligand **L^1** was reacted with [Au(tht)Cl] in an equimolar ratio in DCM to produce [**L^1**AuCl] (**3**), following our previously reported procedure (Scheme 4).[39] Inspired by the substitution pattern of Auranofin we treated the chloride–gold complex **3** with the *in situ* generated thiolate of 1-thio-β-D-glucose tetraacetate (hereafter referred to as Glc) to obtain [**L^1**Au(Glc)] (**4**) (Scheme 4). The phosphorus resonance of complex **4** appears as a singlet at δ 64.2 ppm in the $^{31}P\{^{1}H\}$ NMR spectrum, which is downfield



Scheme 4 Synthesis of Au^{I} complexes **3** and **4**.

shifted compared to the chloride-gold complex **3** (δ 57.2 ppm). Among the gold complexes, the downfield shift of the phosphorus NMR resonances correlates directly with the π-accepting ability of the ancillary ligands.[51,52] The chemical formula of the complex was ascertained by the appearance of the molecular ion peak at m/z = 1032.2770 in the HRESI-MS spectrum.

Photophysical properties

The metal complexes were further investigated for their optical properties. The absorption spectra of the ligand **L^1** and complex **3** in DCM are reported in our previous studies,[39] and the spectra of complexes **1**, **2** and **4** are displayed in Fig. 3a. The spectra of all the compounds feature a strong absorption band at ~330 nm, mainly contributed by the attached coumarin moiety. UV-Vis spectra of the complexes were also recorded in DMEM solution (Fig. 3b). The complexes exhibit a red-shift in the absorption band when dissolved in a mixture of DMEM and DMSO compared to DCM, resulting in the onset of absorption shifting into the visible region.

The metal complexes **1–4** were also investigated for their photophysical properties in DMSO solutions, and their PL spectra are displayed in Fig. 4.

All the complexes feature blue fluorescence with the emission band centered at ~425 nm, which is mainly from the attached dye. Cu^{I} complex **1** has a quantum yield (ϕ_{PL}) of 40%,

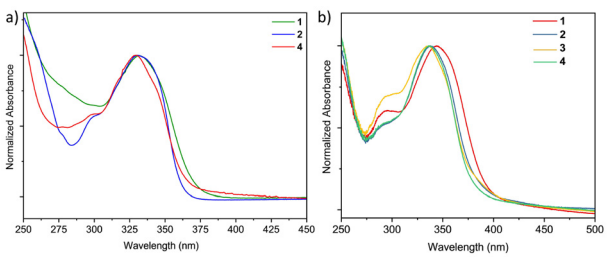


Fig. 3 UV-Vis spectra of (a) complexes **1**, **2** and **4** in DCM and (b) complexes **1–4** in a mixture of DMEM (Dulbecco's modified Eagle's medium, [+] 4.5 g L^{-1} D-Glucose, L-Glutamin, [+] Pyruvat, Gibco™) and DMSO (dimethylsulfoxide) in a 15 : 1 ratio.

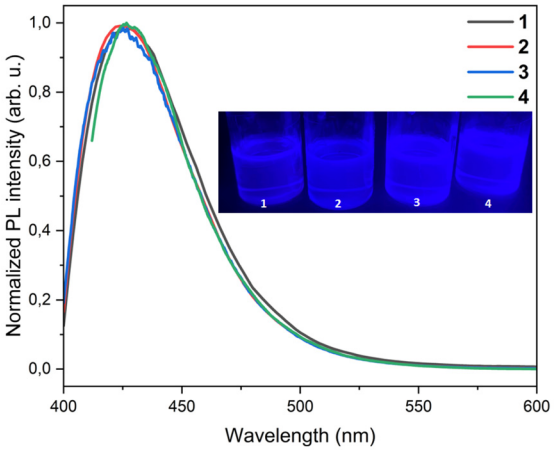


Fig. 4 Emission spectra of the complexes **1–4** (100 μM) in DMSO, λ_{exc} = 365 nm. Inset: photographs of DMSO solutions of complexes **1–4** when excited with 365 nm light.[48]

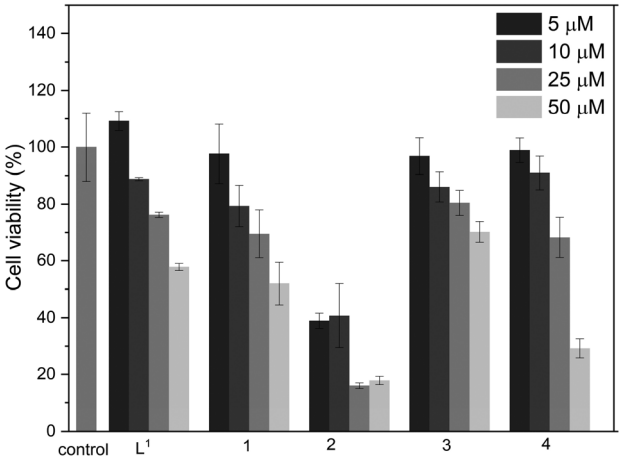


Fig. 5 Cytotoxicity assays (MTT) of the ligand $\mathbf{L^1}$ and the metal complexes (**1–4**) in HeLa tumor cell line. Cells were incubated with different concentrations of the ligand and the metal complexes (5–50 μM) for 72 h at 37 °C. Control: untreated cells. Data were averaged, and the standard deviation was calculated with the multiple determinations of each substance and concentration. Depicted are the mean values and standard deviation from n = 8 experiments.[48]

whereas the ϕ_{PL} of Au^I complexes **2–4** were measured to be 84%, 93%, 91%, respectively. The metal complexes exhibit a significant increase in the ϕ_{PL} compared to the ligand $\mathbf{L^1}$ (29%). Although Cu^I is an inert d^{10} metal like Au^I complex, the ϕ_{PL} of **1** is significantly lower than that of Au^I compounds. This is because Cu^I is prone to excited-state distortion, transitioning from a tetrahedral to a square planar geometry, which facilitates non-radiative deactivation of the absorbed light.[35,53]

Cytotoxicity studies

The complexes, along with the ligand, were further studied for their cytotoxicity in HeLa cells by means of 3-(4,5-dimethylthiazol-2-yl)-2,5-di-phenyltetrazoliumbromide (MTT) based proliferation assay (Fig. 5). Ligand $\mathbf{L^1}$, Au^I complex **3** are the least cytotoxic towards the HeLa cells, followed by Cu^I complex **1**. LD_{50} values were not attained for these compounds even at a 50 μM concentration, which is a remarkable result regarding the known cytotoxicity of Cu^I.[40,41] The cationic complex **2** showed higher toxicity even at low concentrations. Similar cytotoxicity behavior was previously observed for analogous cation Au^I complex and was previously attributed to the ability of delocalized cations to selectively target the mitochondria of cancer cells.[23,25,54] Au^I complex **4** showed comparatively higher toxicity. Overall, the complexes demonstrated reduced cytotoxic efficacy, with LD_{50} values exceeding 75 μM for compounds **1** and **3** (Fig. 7), LD_{50} values of 37 μM for compound **4**, and below 5 μM for compound **2**, relative to previously reported Au^I complexes featuring alternative ancillary ligands.[55–57] This attenuated potency is consistent with prior observations for coumarin-substituted Au^I complexes.[10,29,58,59]

Literature reports have shown that the coordination of a coumarin-phosphine ligand to a gold(I) center results in enhanced fluorescence intensity.[28] A similar observation was made for the ligand $\mathbf{L^1}$ (ϕ_{PL} = 29%) upon complexation with both Cu^I (ϕ_{PL} = 40%) and Au^I ions (ϕ_{PL} >80%).

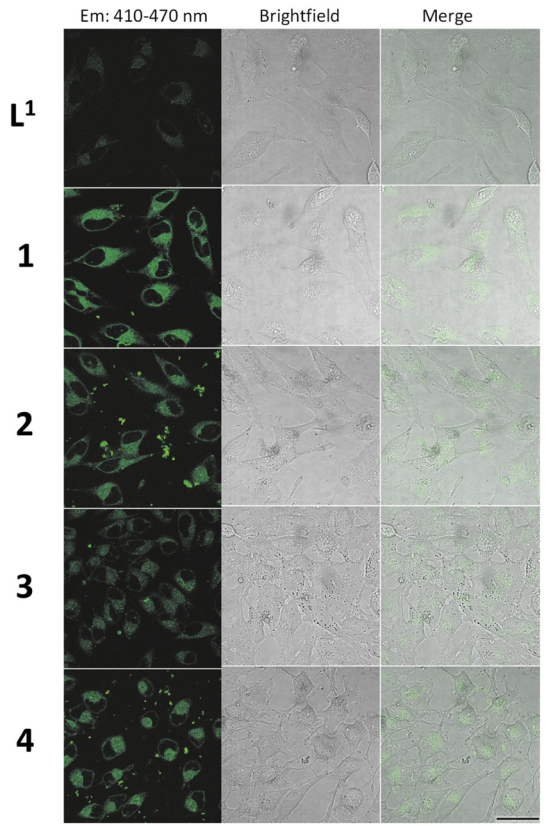


Fig. 6 Live confocal microscopy images of HeLa cells after 5 h of treatment with 25 μM of the ligand $\mathbf{L^1}$ and metal complexes **1–4**. Fluorescent emission was set to 410–470 nm. Left: Green colour shows the intracellular localization of the fluorescent compounds, which is absent in the control image (untreated cells, Fig. S18); Centre: Brightfield images of the HeLa cells; Right: Overlay images. Scale bar = 40 μm.[48]

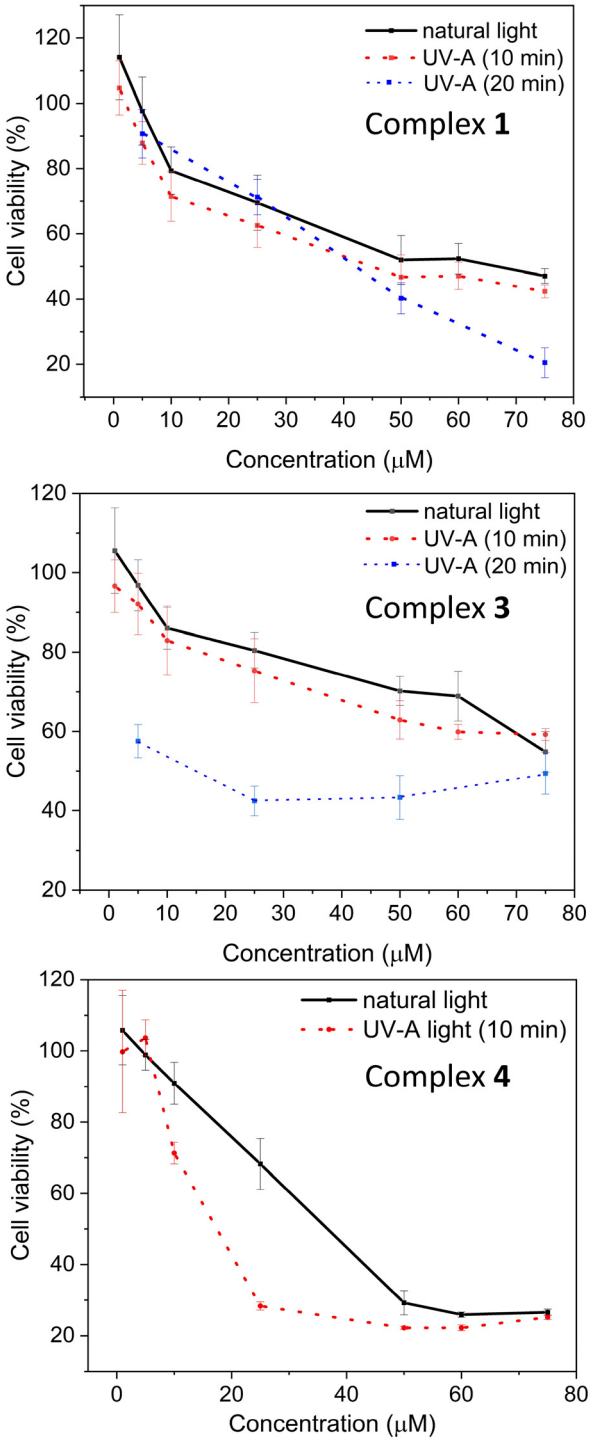


Fig. 7 Photocytotoxicity of the metal complexes (**1**, **3** and **4**) in the HeLa tumor cell line. Cells were treated with different concentrations of the metal complexes (1–75 μM), followed by 365 nm photo-irradiation and incubation for 72 h at 37 °C. The natural light and 365 nm photo-irradiated cells are shown by a solid line and dotted line, respectively. Data were averaged, and the standard deviation was calculated with the multiple determinations of each substance and concentration. Depicted are the mean values and standard deviation from n = 6 experiments.

This characteristic is especially interesting for investigating the stability and intracellular localization of metal-based fluorophores using confocal microscopy. To assess the cellular uptake of ligand $\mathbf{L^1}$ and its metal complexes (**1–4**), live-cell imaging experiments were conducted (Fig. 6). All complexes, prepared *in vitro* and transported into the cell, accumulated in the cytoplasm of HeLa cells following treatment with 25 μM of each compound for 5 h, compared to the ligand, as confirmed by the fluorescence intensity. The cells treated with the phosphineamine ligand $\mathbf{L^1}$ alone, gave a very weak fluorescent signal, also localized in the cytoplasm. The control is shown in Fig. S18. The weak fluorescence observed even after 5 hours of incubation suggests that the compound remains stable *in vitro* and does not undergo undesired protonation or oxidation, processes that typically result in strong fluorescence.[10,60] These observations are in line with previously reported studies.[10,60] In spite of the low ϕ_{PL} of Cu^I complex, a bright fluorescence signal was observed, indicating a greater cellular uptake of complex **1**. In contrast, weak emission was observed for complex **3**, indicating a lower cellular uptake, which might be a plausible reason for the very low cytotoxicity. Cells treated with complex **4** showed a change in morphology, suggesting a potential induction of apoptosis.[3]

Since the complexes **1**, **3** and **4** showed poor cytotoxicity, which is particularly remarkable with respect to the cytotoxicity of Cu^I, we wanted to explore their *in vitro* photocytotoxicity behaviour.[61–64] HeLa cells were treated with the complexes and exposed to UV-A light (365 nm), followed by an incubation period of 72 h at 37 °C (Fig. 7).

All the complexes (**1**, **3** and **4**) showed enhanced cytotoxicity when irradiated with UV-A light, but to a different extent. LD_{50} values are similar for Cu^I complex **1** before and after irradiation for 10 min and 20 min (41–44 μM). Au^I complex **3** did not reach the LD_{50} value when the cells were exposed to UV-A light only for 10 min. However, a strong cytotoxicity of Au^I complex **3** was observed when the cells were photoirradiated for 20 min, with an LD_{50} value of 15 μM. Thereby, the cytotoxicity cannot be enhanced only by Cu^I but also by Au^I. Complex **4** showed greater photocytotoxicity when compared to the other complexes. LD_{50} value dropped to 37 μM from 18 μM within 10 min of irradiation by UV-A light. However, we also like to mention that further studies are needed to understand the mechanism of action of these complexes upon photo-irradiation. These results also indicate that Au^I complexes hold promise as candidates for applications in photodynamic therapy, particularly given the limited number of studies focused on Au^I-based compounds.[65]

Conclusions

In conclusion, we have reported the synthesis of a Cu^I complex and three Au^I complexes using a coumarin-substituted phosphinoamine ligand. The reaction of the ligand with CuCl led to the formation of an unexpected tetranuclear compound. All the complexes were characterized by standard analytical tech-

niques. Owing to the presence of coumarin dye, all the metal complexes were emissive. The emission is mainly contributed by the coumarin moiety. All the Au^{I} complexes were emissive with high quantum yields. The cytotoxicity of the complexes was evaluated. Compared to auranofin with IC50 values in the nM range,[66] the metal complexes **1–4** show significantly reduced cytotoxicity in the μM range, but they show emission that can be used to image their localization in cells. However, their toxicity increased significantly upon photo-irradiation, an effect that has been rarely explored in the context of Au^{I} complexes. Despite the known general cytotoxicity of Cu^{I}, the new coinage metal complexes show low cytotoxicity and are useful for cell imaging.

Conflicts of interest

There are no conflicts to declare.

Data availability

Supplementary information: Synthesis and characterization, NMR spectra, IR spectra, mass spectra, X-ray crystallography, photoluminescence data, cytototoxicity studies, and live cell imaging. See DOI: **https://doi.org/10.1039/d5dt01532d**.

The support the findings of this study are available in Radar4Chem with the identifier: **https://doi.org/10.22000/y7jpsvnmm42jkuuz**.

CCDC 2467347 and 2467348 contain the supplementary crystallographic data for this paper.[67a,b]

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