Highly active group 11 metal complexes with α-hydrazidophosphonate ligands

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α-Hydrazidophosphonates are interesting scaffolds that could combined the biological properties of hydrazones and phosphonyl species, and their coordination properties remains unknown. The coordination chemistry of these ligands towards group 11 metals has been studied. A series of novel gold(I), silver(I) and copper(I) complexes with α-hydrazidophosphonate ligands have been prepared and characterised. The coordination geometries obtained vary from the linear to the trigonal planar for gold(I) to distorted trigonal planar or tetrahedral for silver(I) and copper(I). Structural characterisation of two silver derivatives shows the ligands in an O^N^O tridentate fashion, with dissimilar bond lengths. These compounds were screened for the *in vitro* cytotoxic activity against two tumour human cell lines such as HeLa (cervical carcinoma) and A549 (lung carcinoma). The IC_{50} values reveal an excellent cytotoxic activity of the metal complexes compared with the α-hydrazidophosphonate ligands alone and *cisplatin*.

Introduction

Phosphonyl derivatives have aroused a great interest because of their important biological properties.[1] Between this broad range of activity, it is worth mentioning their potential as herbicides,[2] antibiotics,[3] insecticides,[4] fungicides,[4] anti-viral agents,[5] and as enzyme inhibitors,[6] including their potential use against the HIV proteases.[7] Among the different developed methods for the preparation of phosphonate compounds, the nucleophilic addition of dialkylphosphites to C=O or C=N (Pudovik reaction)[8] has been used as one of the most powerful tool in the synthesis of α-hydroxy-[9] or α-aminophosphonates[10] as direct precursors of phosphonic acid derivatives (Figure 1).[11,12]

We have previously developed a straightforward synthetic strategy for the preparation of α-hydrazidophosphonates starting from the corresponding hydrazones.[13] Hydrazones and their metal complexes are molecules which have recently shown to bear biological properties.[14] Consequently, the final α-hydrazidophosphonates could combined the properties of hydrazones and phosphonyl species and could display interesting medicinal applications. In addition, no coordination chemistry of these molecules as ligands has been reported up to date, in spite of their similarity with both the phosphonate and hydrazide ligands and their great potential as bidentate or tridentate chelate ligands.

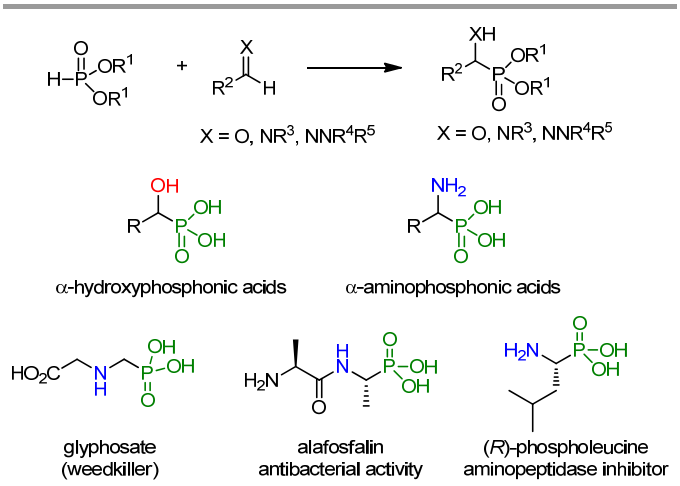


Fig. 1. Biologically active phosphonyl derivatives.

During the last decades, and since the discovery of *cisplatin* as a potent antitumour agent, many research groups have focused their efforts on the rational design of new metal-based anticancer agents for their use in cancer chemotherapy.[15] All these attempts have been centred on the search for new metal complexes, as promising clinical candidates, able to overcome the drawbacks of current clinical drugs including toxicity, resistance and other pharmacological deficiencies. Among this plethora of evaluated metals *in vitro* and *in vivo*, are group 11 metal derivatives (Figure 2). Gold complexes are by far the most studied because of their high cell growth inhibition capacity as a potential antitumour drug.[16] Interestingly, our group have previously reported the synthesis and functionalisation of gold-based complexes with very good cytotoxic activity.[17]

In contrast, although silver(I) complexes have been extensively used as therapeutic compounds during centuries mainly as antiseptic,[18] antimicrobial[19] and as anti-inflammatory agents,[20] they have only recently received special attention for their anti-tumour activity.[21] Copper complexes have been investigated on the basis that being an endogenous metal may

be more selective towards cancer cells, although they can also be toxic because of its redox activity and affinity for binding sites in proteins and enzymes.[22] However, Cu(I) has been less explored for this aim compared with its oxidized form Cu(II), since their activity is mainly due to its redox capacity (Cu(II)/Cu(I)).[22]

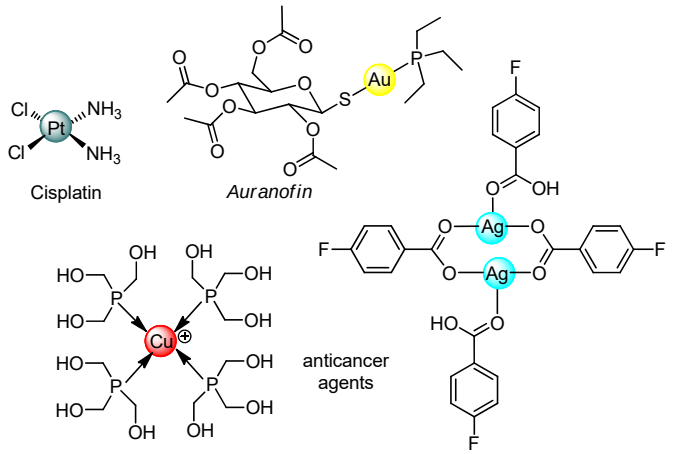


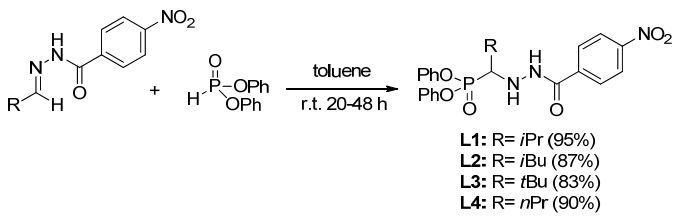
Fig. 2. Biologically active metal complexes.

Based on this background and with the growing interest for searching new anticancer agents, encouraged us to join the promising properties of phosphonate derivatives with the interesting biological activities of group 11 metal complexes to evaluate the antitumour capacity of the resulting organometallic species, since it is well known that the biological properties can be significantly affected by the coordinating ligands.

To the best of our knowledge, this is the first time that α-hydrazidophosphonate derivatives have been considered as organic ligands in metal coordination chemistry. These group 11 compounds have been explored in their cytotoxic activity towards two human cell lines HeLa (cervical cancer) and A549 (lung cancer) with excellent results.

Results and discussion

Based on our experience in the synthesis of α-hydrazidophosphonates[13] and group 11 metal derivatives[23] with demonstrated biological properties,[17] we decided to bring together both species in a single complex to explore the synergic activity that may exhibit the resulting organometallic species. α-Hydrazidophosphonates **L1-L4** were firstly synthesised following our previously reported procedure, depicted in Scheme 1. This easy method allows access to a great variety of this kind of structures with very good yields.

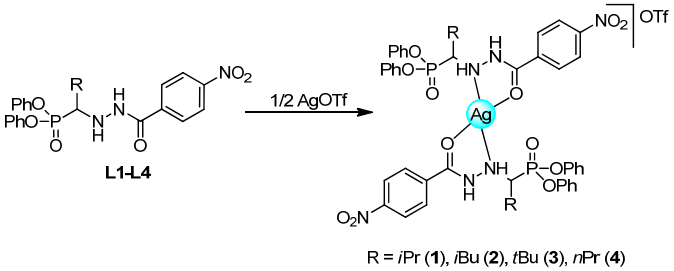


Scheme 1. Synthesis of ligands **L1-L4** by uncatalysed hydrophosphonylation of hydrazides with diphenylphosphite.[13]

The coordination properties of the α-hydrazidophosphonate species **L1-L4** towards group 11 metals have been explored by the first time, and complexes **1-14** have been synthesised. All the compounds have been characterised by means of IR, elemental analysis and NMR spectroscopy. Assignments of the ^{1}H NMR and ^{13}C{^{1}H} NMR signals were made on the basis of 2D COSY and HSQC spectra. Complete spectroscopic information of the complexes has been collected in the Experimental Section of this article.

Synthesis of Ag(I) metal complexes 1-8

Firstly, homoleptic Ag(I) derivatives **1-4** have been prepared by reaction of **L1-L4** with AgOTf in a 2:1 molar ratio as shown in Scheme 2.



Scheme 2. Formation of [AgL$_2$]OTf complexes **1-4**.

Since Ag can form complexes with coordination index between 2 and 4, in this case, and based on the IR and NMR spectra, we propose the formation of the tetrahedral derivatives **1-4**. On these, each ligand would bond the metal atom as an N^O chelate, through the O atom of the carbonyl group and the iminic NH of the hydrazide. Similar bis(chelate) N^O silver complexes have been obtained with other ligands such as the 8-hydroxyquinoline.[24] The IR spectra show a shift in the C=O and in the iminic NH stretching bands relative to the ligands alone. Thus, as an example the ligand **L1** presents two absorptions at 3275 and 3245 cm^{-1} for the NH groups and in complex **1** a broad absorption at 3227 appears; the corresponding carbonyl absorption displaces from 1652 in the free ligand to 1655 cm^{-1} in **1**. Similar values are found for the rest of the complexes. The ^{31}P{^{1}H} NMR spectra show one resonance for the equivalent phosphorus atoms at 20.2 (**1**), 20.0 (**2**), 20.6 (**3**) and 20.0 (**4**) shifted downfield compared with the free ligands.

The effect of the metal over the electronic properties of the ligands is observed in the ^{1}H NMR spectra of complex **1** in comparison with that of the ligand alone (see Figure 3). Coordination of the metal to the ligand produces a downfield shift for the protons of the isopropyl group and the NH but curiously a highfield displacement of the protons of the nitrophenyl ring.

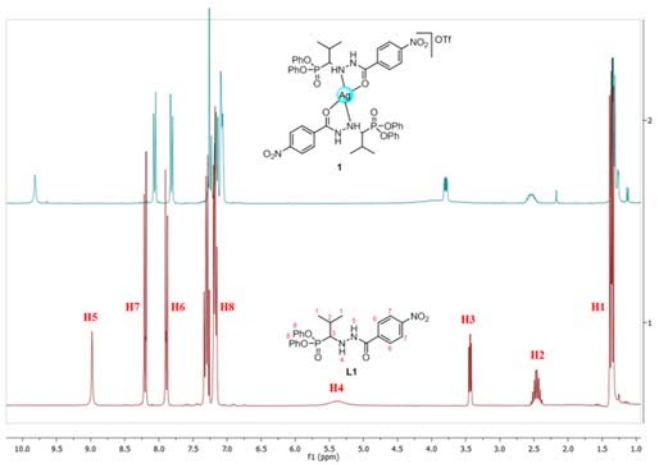
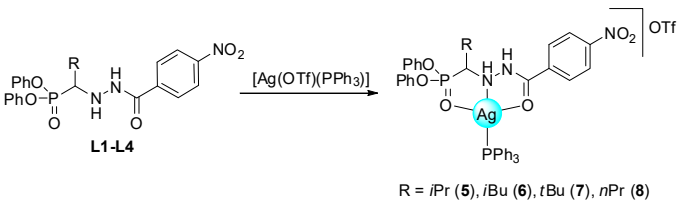


Fig. 3. ^{1}H NMR spectra of **L1** and complex **1** performed in $CDCl_3$ at r.t. (400 MHz).

Moreover, in the mass spectra for the ESI+ experiments the peaks for the molecular cations $[M–OTf]^+$ appear at m/z = 1045 for complexes **1** and **4**, and m/z = 1075 for complexes **2** and **3**. This is in agreement with the general proposed formula $[AgL_2]^+$. All these techniques point out the presence of a silver atom coordinated to two ligands through the most nucleophilic iminic nitrogen and carbonyl oxygen atom in a tetrahedral fashion.

The reaction of the ligands **L1**-**L4** with $[Ag(OTf)(PPh_3)]$ in a 1:1 molar ratio has been performed to afford the Ag(I) compounds **5**-**8** as depicted in Scheme 3.



Scheme 3. Formation of $[AgL(PPh_3)]OTf$ complexes **5**-**8**.

The ligands are coordinated to the silver centres as tridentate O^N^O chelates and to the phosphorus atom of the triphenylphosphine moiety, giving rise to tetrahedral complexes **5-8** (Scheme 3). This type of coordination has been also supported by the shifting found on the IR, and at ^{31}P and ^{1}H NMR spectra for these complexes (see experimental section for a complete characterisation of all these complexes). The $^{31}P\{^{1}H\}$ NMR spectra show two resonances for the two different phosphorus atoms, one sharp singlet arising at the phosphonate and a broad singlet for the triphenylphosphine bind to silver, as a consequence of the fast dissociation of phosphorus ligands in silver complexes. In the spectra of complexes **5** and **6** carried out at low temperature is possible to observe that the broad resonance splits into two doublets because of the coupling of the phosphorus atom with the two silver isotopomers, ^{109}Ag and ^{107}Ag.

Crystal structures determination

Crystals of the Ag(I) complexes **5** and **8** have been obtained by slow diffusion of hexane into a solution of **5** or **8** in CH_2Cl_2 and they have been determined by X-ray diffraction studies, supporting our abovementioned kind of coordination depicted in Scheme 3. Compound **5** crystallises in the monoclinic space group $P2_1/c$ with one molecule by asymmetric unit (Figure 4).

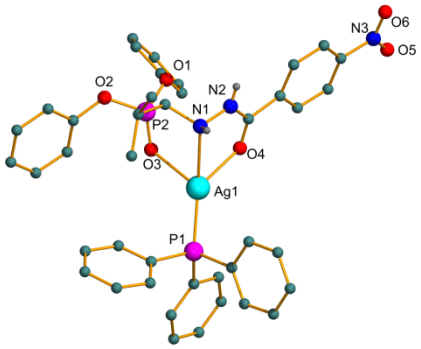


Fig. 4. Diagram of the cation of complex **5**. Aromatic hydrogen atoms are omitted for clarity. Selected bond lengths [Å] and angles [°] for complex **5**: Ag(1)-O(4) 2.326(2), Ag(1)-P(1) 2.3533(10), Ag(1)-O(3) 2.445(2), Ag(1)-N(1) 2.490(3), P(2)-O(3) 1.469(2), P(2)-O(1) 1.573(2), P(2)-O(2) 1.580(3), O(1)-C(31) 1.420(4), O(2)-C(41) 1.408(4), C(50)-N(1) 1.490(4), N(1)-N(2) 1.411(4), N(2)-C(54) 1.336(4), C(54)-O(4) 1.237(4); O(4)-Ag(1)-P(1) 137.79(7), O(4)-Ag(1)-O(3) 84.10(9), P(1)-Ag(1)-O(3) 126.92(6), O(4)-Ag(1)-N(1) 69.11(8), P(1)-Ag(1)-N(1) 139.69(7), O(3)-Ag(1)-N(1) 74.57(9).

The Ag atom shows slightly distorted tetrahedron coordination, since Ag is bound to three donating atoms. The angles of this ligand as a tridentate chelate with the silver centre are O(4)-Ag(1)-O(3) 84.10(9)°, O(4)-Ag(1)-N(1) 69.11(8)°, O(3)-Ag(1)-N(1) 74.57(9)° and O(4)-Ag(1)-P(1) 137.79(7)°. The Ag-O distances vary and with the oxygen atom, in the carbonyl group is 2.326(2) Å, whereas a weaker bond of 2.445(2) Å is found with the oxygen atom from the phosphonate moiety. Additionally, there is a Ag-N(1) distance of 2.490(3) Å with the hydrazide nitrogen and the Ag-P(1) of 2.3533(10), which is a strong bond. Although there are several structures in which the silver atom is bound to two oxygen, one nitrogen and one phosphorus atoms,[25] the tridentate O^N^O coordination mode to a unique ligand is unusual.

The structure of complex **8** is shown in Figure 5. It crystallises in the triclinic P-1 space group with two independent molecules. The two molecules are asymmetric in the bond lengths of the ligand to the silver centre. In one molecule the Ag atom is tetrahedrically coordinated to the phosphine and to the three donor atoms of the ligand with distances Ag(1)-O(4) 2.348(5), Ag(1)-N(1) 2.447(5) and Ag(1)-O(3) 2.471(5), which are similar to those found in complex **5**. However in the second molecule the bond lengths are shorter to the carbonyl oxygen and the iminic nitrogen, Ag(2)-O(10) 2.321(5) and Ag(2)-N(4) 2.404(6), and there is a long Ag(2)-O(9) distance of 2.646 Å with the oxygen of the phosphonyl group. The geometry around the silver centre Ag(2) can be considered as distorted trigonal planar with a narrow O(10)-Ag(2)-N(4) angle of 71.65(18)°, since the silver centre and the three donor atoms are in the same plane.

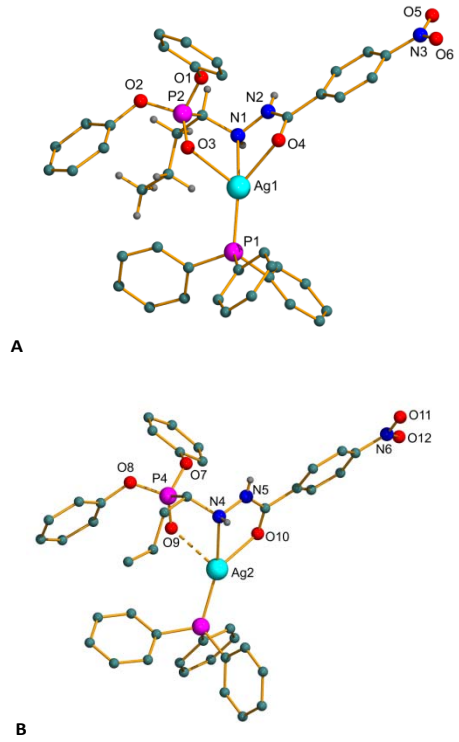
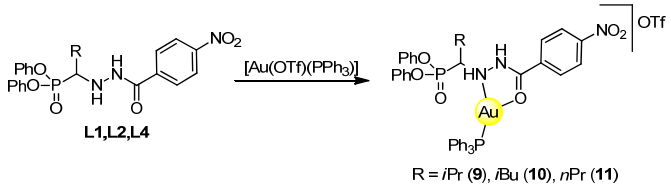


Fig. 5. Diagrams of the two independent cations of complex **8**. Aromatic hydrogen atoms are omitted for clarity. Selected bond lengths [Å] and angles [°] for complex **8**: *Molecule A:* Ag(1)-O(4) 2.348(5), Ag(1)-P(1) 2.352(2), Ag(1)-N(1) 2.447(5), Ag(1)-O(3) 2.471(5), P(2)-O(3) 1.467(5), N(1)-N(2) 1.430(8), O(4)-C(47) 1.235(8); O(4)-Ag(1)-P(1) 137.97(13), O(4)-Ag(1)-N(1) 69.68(17), P(1)-Ag(1)-N(1) 144.18(15), O(4)-Ag(1)-O(3) 86.12(17), P(1)-Ag(1)-O(3) 119.64(12), N(1)-Ag(1)-O(3) 76.08(17). *Molecule B:* Ag(2)-O(10) 2.321(5), Ag(2)-P(3) 2.345(2), Ag(2)-N(4) 2.404(6), P(4)-O(9) 1.468(5), N(4)-N(5) 1.426(8), O(10)-Ag(2)-P(3) 136.57(13), O(10)-Ag(2)-N(4) 71.65(18), P(3)-Ag(2)-N(4) 150.40(15).

Synthesis of Au(I) metal complexes 9-12.

The capacity of Au(I) to coordinate α-hydrazidophosphonates **L1**, **L2** and **L4** was also explored. Thus, Au(I) compounds **9-11** have been prepared by reaction of the corresponding ligands with [Au(OTf)(PPh_3)] in a molar ratio 1:1 as shown in Scheme 4.

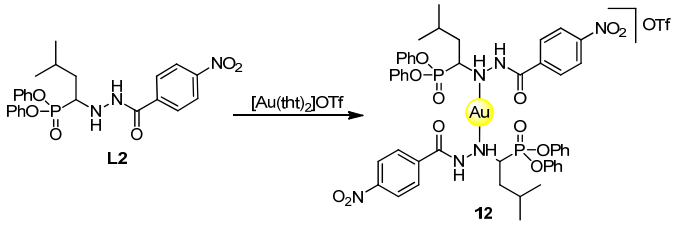


Scheme 4. Formation of [AuL(PPh_3)]OTf complexes **9**-**11**.

Although, the gold(I) prefers a lineal coordination and its affinity through donating oxygen atoms is low, in these cases a variation in the frequency of the carbonyl group in the IR spectra is observed, as for example from 1652 cm^{-1} in free ligand **L1** to 1163 cm^{-1} in complex **9**. Consequently, a tridentate coordination is proposed for complexes **9-11**, where gold atom would be bound to the P atom of the triphenylphosphine, to the iminic NH group of the hydrazide and to the oxygen atom of the carbonyl group. Taking in consideration the geometry of the ligands, we hypothesised that a chelating coordination would be favoured in these three cases. A similar geometry has been previously reported in a 8-hydroxyquinolinate gold(I) derivative with an N^O chelate ligand.[26]

It is worth noting that it is possible to find the molecular cations $[M–OTf]^+$ of complexes **9-11** in the mass spectra for the ESI+ experiments. That is m/z = 928 for complexes **9** and **11**, and m/z = 942 for complex **10** $[AuL(PPh_3)]^+$ (see experimental section for more details).

The preparation of new gold complexes with $[Au(tht)_2]OTf$ (tht = tetrahydrothiophene) in a molar ration 2:1 was also tried. However, the final products of these reactions were really unstable. The NMR analysis of the resulting reaction crudes proved the presence of a tht molecule, which would support a low capacity by the hydrazide ligands to displace the tht groups. Interestingly, only with **L3** we were able to get the corresponding linear complex **12** as described in Scheme 5.



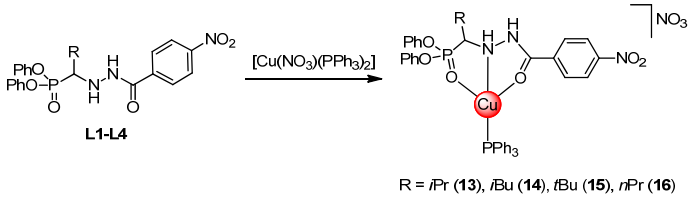
Scheme 5. Formation of $[Au(L2)_2]OTf$ complex **12**.

The ligand could be coordinated to the metal centre through the iminic NH group of the hydrazide, giving rise to a linear complex (Scheme 5). This is mainly supported by the shifting found on the ^1H NMR spectrum for the final complex, where only the NH involved in the coordination is strongly highfield shifted. Undoubtedly, in this complex could also be some weak contacts between the oxygen atoms and the gold centre but we do not propose in the drawing because no shift for the carbonyl group is observed in the infrared spectrum. Linear gold(I) derivatives with the gold centre coordinated to two NH group have been previously reported in the case of aliphatic amines.[27]

In the mass spectrum (ESI+) the molecular cation $[Au(L2)_2]^+$ is found at m/z = 1163. This value also supports the formation of the proposed complex.

Synthesis of Cu(I) metal complexes 13-16

Other interesting metal for its biological properties is copper. In this sense, the ability of Cu(I) to coordinate **L1**-**L4** was also investigated. Thus, Cu(I) compounds **13-16** have been prepared by reaction of the corresponding α-hydrazidophosphonates **L1-L4** with $[Cu(NO_3)(PPh_3)_2]$ in a molar ratio 1:1 as shown in Scheme 6.



Scheme 6. Formation of $[CuL(PPh_3)]NO_3$ complexes **13**-**16**.

The coordination is proposed to be similar to the silver complexes on the base of the IR, ^{31}P and ^{1}H NMR spectra (see experimental section). Some copper(I) complexes have been previously described in which coordination to a phosphine and to a tridentate O^N^O ligands has been achieved.[28] Thus, a chemical shift is observed in the ^{1}H NMR spectra in the resonances of the iminic protons, as for example from 5.35 in ligand **L1** to 3.44 ppm in complex **13**. Similarlarly, the ^{31}P NMR spectra presents two different resonances for the phosphorous of the phosphonate ligand and the tryphenylphosphine bound to copper. Moreover, the fragments for the molecular cations $[M–NO_3]^+$ of all complexes **13-16** were found in the ESI+ mass spectra. Therefore, m/z = 794 was found for complexes **13** and **16**, and m/z = 808 for complexes **14** and **15**.

Biological evaluation

The *in vitro* cytotoxic activity of the silver **5-8** and copper **13-16** complexes, all of them bearing the α-hydrazidophosphonate and triphenylphosphine ligands, was tested against two tumour human cell lines, A549 (human lung carcinoma) and HeLa (human cervix epithelial carcinoma). They were chosen for two reasons: the presence of a lipophilic phosphine ligand, and because they are the most stable in solution. As measure of control, metal-free ligands **L1-L4** were tested for cytotoxicity against the two cell lines explored. Our IC_{50} values were compared with those of *cisplatin.*[29]

Compounds are not soluble in water, but they are soluble in DMSO and in the DMSO/water mixtures used in the cytotoxicity tests, which contain a small amount of DMSO (≤ 0.1 %). We did not observe any precipitation of the complexes while performing the tests. The colourless (Ag(I) Cu(I)) DMSO solutions are very stable at room temperature for weeks.

Cells were exposed to each compound for 24 h. By using the colorimetric mitochondrial function-based MTT viability assay the IC_{50} values were calculated from dose–response curves obtained by nonlinear regression analysis. IC_{50} values are concentrations of a drug required to inhibit tumour cell proliferation by 50 %, compared to the control viability. Controls were performed using cells grown in medium with 0.1 % DMSO. IC_{50} values at 24 h are listed in Table 1.

Table 1. IC_{50} (24 h) values of complexes and ligands against HeLa and A549 tumour cells (μM).

		HeLa	**A549**
		IC_{50} (μM)	IC_{50} (μM)
Cisplatin		55 ± 9 (DMSO)	114.2±11(H_2O)
L	**L1**	>50	>50
	L2	>50	>50
	L3	>50	>50
	L4	>50	>50
$[Ag(L)(PPh_3)]OTf$	**5**	2.76 ± 0.01	3.05 ± 0.05
	6	2.49 ± 0.49	8.60 ± 0.25
	7	2.47 ± 0.41	11.22 ± 0.53
	8	5.27 ± 0.79	9.70 ± 0.52
$[Cu(L)(PPh_3)_2]NO_3$	**13**	3.93 ± 0.81	5.02 ± 0.97
	14	1.60 ± 0.47	8.01 ± 0.75
	15	1.49 ± 0.01	>50
	16	0.84 ± 0.47	9.08 ± 1.76

As reported in Table 1, the tested ligands (**L1**-**L4**) showed no cytotoxic activity (IC_{50} > 50 μM). In contrast, silver(I) and copper(I) complexes were found to be extraordinarily effective as cytotoxic agents *in vitro* against the growth of the cancer cell lines tested. In general, they shown a higher activity against HeLa cells (IC_{50} values range between 0.84 and 5.27 μM) compared with A549 tumour cells (IC_{50} values range between 3.05 and 11.22 μM, and surprisingly one of the complexes (**15**) presented a value > 50 μM) being copper complex **16** the most potent agent against HeLa cells with IC_{50} value of 0.84 μM, and silver complex **5** against A549 cells with IC_{50} value of 3.05 μM. There is not a clear correlation between the ligand used and the activity since all of them show excellent values in the low micromolar range, much lower than the corresponding values of *cisplatin*. These values obtained for the silver and copper complexes are among the lowest found for any silver or copper derivatives, taking into account the experimental conditions (measured at 24 h). These outstanding activities of these complexes are worth for further studies giving the low toxicity of the metals and the possibility of new biological targets.

EXPERIMENTAL SECTION

General Procedures. Purification of reaction products was carried out either filtration. The synthesis of the copper complexes **13-16** were carried out under Ar atmosphere, in dried and degassed solvents prior to use. The starting material $[Ag(OTf)(PPh_3)]$[30] was prepared according to published procedures. $[Au(OTf)(PPh_3)]$ was obtained by reaction of $[AuCl(PPh_3)]$[31] with Ag(OTf) in dichloromethane and used *in situ*. $[Au(tht)_2]OTf$ is also used *in situ* starting from [AuCl(tht)][32] and [AgOTf(tht)] in solution of dichloromethane. All other reagents were commercially available and used without further purification. ESI ionisation method and mass analyser type MicroTof-Q were used for the ESI measurements. ^{1}H, $^{31}P\{^{1}H\}$, and $^{13}C\{^{1}H\}$ NMR, including 2D experiments, were recorded at room temperature on a BRUKER AVANCE 400 spectrometer (^{1}H, 400 MHz, ^{13}C, 100.6 MHz) or on a BRUKER AVANCE II 300 spectrometer (^{1}H, 300 MHz, ^{13}C, 75.5 MHz), with chemical shifts (δ, ppm) reported relative to the solvent peaks of the deuterated solvent. Infrared spectra were recorded in the range 4000–250 cm^{-1} on a Perkin-Elmer Spectrum 100 FTIR spectrometer.

Synthesis and characterisation of $[Ag(L1)_2]OTf$ (1). To an acetone solution (30 mL) of **L1** (93.8 mg, 0.2 mmol), Ag(OTf) (25.7 mg, 0.1 mmol) was added at room temperature. After the addition, the reaction mixture was stirred for 1 h. The volume was reduced under vacuum to 5 mL, and addition of hexane (10 mL) afforded compound **1** as a yellow solid, after

filtration, with a 79 % yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.82 (s, 2H, *NH*); 8.06 (br d, 4H, *H-1*, $^{3}J_{HH}$ = 8.8 Hz); 7.81 (br d, 4H, *H-2*, $^{3}J_{HH}$ = 8.8 Hz); 7.26-7.06 (m, 20H, *Ph*); 3.93 (br s, 2H, *NH*CH); 3.79 (dd, 2H, *CH*NH, $^{2}J_{PH}$ = 9.2 Hz, $^{3}J_{HH}$ = 4.7 Hz); 2.55 (m, 2H, *CH*$(CH_3)_2$); 1.35 (d, 6H, CH_3, $^{3}J_{HH}$ = 7 Hz); 1.32 (d, 6H, CH_3, $^{3}J_{HH}$ = 6.9 Hz). ^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ = 20.2 (s, 2P, *P=O*). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 166.3 (s, 2C, *CO*); 150.1 (s, 2C, C_{ipso} *CO*); 149.9 (d, 2C, C_{ipso}*Ph,* $^{2}J_{CP}$ = 10.5 Hz); 149.6 (d, 2C, C_{ipso}*Ph*, $^{2}J_{CP}$ = 10.3 Hz); 136.9 (s, 2C, C_{para} NO_2); 130.1 (br s, 4C, C_{meta} O*Ph*); 130.0 (br s, 4C, C_{meta} O*Ph*); 128.7 (s, 4C, C_{H-2} CO*Ph*NO_2); 125.9 (br d, 2C, C_{para} O*Ph*); 125.8 (br d, 2C, C_{para} O*Ph*); 123.8 (s, 4C, C_{H-1} CO*Ph*NO_2); 120.4 (d, 4C, C_{ortho} O*Ph,* $^{3}J_{CP}$ = 4.3 Hz); 120.3 (d, 4C, C_{ortho} O*Ph,* $^{3}J_{CP}$ = 4.3 Hz); 64.6 (d, 2C, OP*CH*(C_3H_7)NH, $^{1}J_{CP}$ = 156.6 Hz); 28.6 (s, 2C, *CH*$(CH_3)_2$); 20.2 (d, 2C, CH_3, $^{3}J_{CP}$ = 9.4 Hz); 19.2 (d, 2C, CH_3, $^{3}J_{CP}$ = 4.9 Hz). IR (cm^{-1}): υ(*NH*) = 3237; υ(*HAr*) = 3076; υ(*H alkanes*) = 2967; υ(*CO*NH) = 1655; υ(*C=CAr*) =1590, 1524, 757; υ(NO_2) = 1488, 1346; υ(*P=O*) = 1159; υ(*ArOP*) = 1224-1205; υ(*CP*) = 936. MS (ESI+): m/z (%) = 1045.2, $[(C_{23}H_{24}O_6N_3P)_2Ag]^+$, 97.98 %.

Synthesis and characterisation of [Ag(L2)$_2$]OTf (2). To an acetone solution (30 mL) of **L2** (96.6 mg, 0.2 mmol), Ag(OTf) (25.7 mg, 0.1 mmol) was added at room temperature. After the addition, the reaction mixture was stirred for 1 h. The volume was reduced under vacuum to 5 mL, and addition of hexane (10 mL) afforded compound **2** as a yellow solid, after filtration, with an 80 % yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.33 (s, 2H, *NH*); 8.12 (br d, 4H, *H-1*, $^{3}J_{HH}$ = 8.9); 7.87 (br d, 4H, *H-2*, $^{3}J_{HH}$ = 8.9); 7.28-7.07 (m, 20H, *Ph*); 3.99 (m, 2H,P*CH*NH,); 2.10 (m, 2H, CH_2*CH*$(CH_3)_2$); 1.93 (m, 4H, CH*CH*$_2$CH); 1.02 (m, 12H, CH_3). **^{31}**P{^{1}H} NMR (162 MHz, $CDCl_3$): δ = 20.0 ppm (s, 1P, *P=O*). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 166.1 (s, 2C, *CO*); 150.2 (s, 2C, C_{ipso} *CO*); 149.9 (d, 2C, C_{ipso}*Ph,* $^{2}J_{CP}$ = 10.4 Hz); 149.7 (d, 2C, C_{ipso}*Ph,* $^{2}J_{CP}$ = 10.4 Hz); 136.7 (s, 2C, C_{para} NO_2), 130.2 (s, 4C, C_{meta} O*Ph*); 130.1 (s, 4C, C_{meta} O*Ph*); 128.7 (s, 2C, C_{H-2} CO*Ph*NO_2); 126.0 (s, 2C, C_{para} O*Ph*); 123.8 (s, 2C, C_{H-1} CO*Ph*NO_2); 120.4 (d, 4C, C_{ortho} O*Ph,* $^{3}J_{CP}$ = 4.3 Hz); 120.3 (d, 4C, C_{ortho} O*Ph,* $^{3}J_{CP}$ = 4.3 Hz); 57.2 (d, 2C, OP*C*HNH, $^{1}J_{CP}$ = 159.9 Hz); 37.0 (d, 2C, CH*CH*$_2$CH, $^{2}J_{CP}$ = 1.5 Hz); 25.3 (d, 2C, CH_2*CH*$(CH_3)_2$, $^{3}J_{CP}$ = 10.2 Hz); 23.0 (br s, 2C, CH_3); 22.0 (br s, 2C, CH_3). IR (cm^{-1}): υ(*NH*) = 3246; υ(*HAr*) = 3072; υ(*H alkanes*) = 2960; υ(*CO*NH) = 1656; υ(*C=CAr*) = 1599, 1525, 758; υ(NO_2) = 1488, 1346; υ(*P=O*) = 1159; υ(*ArOP*) = 1236-1204; υ(*CP*) = 935. MS (ESI+): m/z (%) **=** 1073.9, $[(C_{24}H_{26}O_6N_3P)_2Ag]^+$, 43.98 %.

Synthesis and characterisation of [Ag(L3)$_2$]OTf (3). To an acetone solution (30 mL) of **L3** (96.6 mg, 0.2 mmol), Ag(OTf) (25.7 mg, 0.1 mmol) was added at room temperature. After the addition, the reaction mixture was stirred for 1 h. The volume was reduced under vacuum to 5 mL, and addition of hexane (10 mL) afforded compound **3** as a yellow solid, after filtration, with a 60 % yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.42 (s, 2H, *NH*); 8.19 (br d, 4H, *H-1*, $^{3}J_{HH}$ = 8.8 Hz); 7.87 (br d, 4H, *H-2*, $^{3}J_{HH}$ = 8.7 Hz); 7.29-7.14 (m, 20H, *Ph*); 3.52 (d, 2H, *CH*NH, $^{2}J_{PH}$ = 7.9 Hz); 1.40 (s, 18H, CH_3). ^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ = 20.6 (s, 1P, *P=O*). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 163.8 (s, 2C, *CO*); 150.1 (s, 4C, C_{ipso}*OPh*), 148.1 (s, 2C, C_{ipso} *CO*); 138.0 (s, 2C, C_{para} NO_2); 130.1 (br d, 4C, C_{meta} O*Ph*); 130.0 (br d, 4C, C_{meta} O*Ph*); 128.4 (s, 4C, C_{H-2} CO*Ph*NO_2); 125.7 (s, 2C, C_{para} O*Ph*); 125.6 (s, 2C, C_{para} O*Ph*); 124.0 (s, 4C, C_{H-1} CO*Ph*NO_2); 120.7 (d, 4C, C_{ortho} O*Ph*, $^{3}J_{CP}$ = 4.1 Hz); 120.6 (d, 4C, C_{ortho} O*Ph*, $^{3}J_{CP}$ = 4.2 Hz); 69.3 (d, 2C, OP*CH*NH, $^{1}J_{CP}$ = 159.7 Hz); 34.5 (s, 2C, CH*C*$(CH_3)_3$); 28.3 (d, 6C, CH_3, $^{3}J_{CP}$ = 6.3 Hz). IR (cm^{-1}): υ(*NH*) = 3274; υ(*NH*) = 3246; υ(*HAr*) = 3104; υ(*H alkanes*) = 2971-2929; υ(*CO*NH) = 1637; υ(*C=CAr*) = 1590, 1513, 753; υ(NO_2) = 1488, 1343; υ(*P=O*) = 1154; υ(*ArOP*) = 1231-1204; υ(*CP*) = 934. MS (ESI+): m/z (%) **=** 1073.3, $[(C_{24}H_{26}O_6N_3P)Ag]^+$, 2.23 %.

Synthesis and characterisation of [Ag(L4)$_2$]OTf (4). To an acetone solution (30 mL) of **L4** (93.8 mg, 0.2 mmol), Ag(OTf) (25.7 mg, 0.1 mmol) was added at room temperature. After the addition, the reaction mixture was stirred for 1 h. The volume was reduced under vacuum to 5 mL, and addition of hexane (10 mL) afforded compound **4** as a yellow solid, after filtration, with a 46 % yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.81 (s, 2H, *NH*); 8.13 (m, 4H, *H-1*); 7.86 (m, 4H, *H-2*); 7.27-7.08 (m, 20H, *Ph*); 3.88 (m, 2H, *CH*NH); 2.03 (m, 4H, CH$CH_2$$CH_2$$CH_3$); 1.73 (m, 4H, $CHCH_2$$CH_2$$CH_3$); 1.00 (t, 6H, CH_3, $^{1}J_{HH}$ = 7.3 Hz). ^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ = 20.0 (s, 1P, *P=O*). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 165.7 (s, 2C, *CO*); 150.1 (s, 2C, C_{ipso} *CO*); 150.0 (d, 2C, C_{ipso}*OPh,* $^{2}J_{CP}$ = 9.1Hz); 149.7 (d, 2C, C_{ipso}*OPh,* $^{2}J_{CP}$ = 10.3 Hz); 136.9 (s, 2C, C_{para} NO_2); 130.1 (s, 4C, C_{meta} O*Ph*); 130.0 (s, 4C, C_{meta} O*Ph*); 128.6 (s, 4C, C_{H-2} CO*Ph*NO_2); 125.9 (br s, 4C, C_{para} O*Ph*); 123.8 (s, 4C, C_{H-1} CO*Ph*NO_2); 120.5 (d, 4C, C_{ortho} O*Ph*, $^{3}J_{CP}$ = 4.3 Hz); 120.3 (d, 4C, C_{ortho} O*Ph*, $^{3}J_{CP}$ = 4.3Hz); 58.76 (d, 2C, OP*CH*NH, $^{1}J_{CP}$ = 160.4 Hz); 30.21 (d, 2C, CH$CH_2$$CH_2$$CH_3$, $^{2}J_{CP}$ = 3.42); 19.75 (d, 2C, $CHCH_2$$CH_2$$CH_3$, $^{3}J_{CP}$ = 12.3 Hz); 13.95 (s, 2C, CH_3). IR (cm^{-1}): υ(*NH*) = 3288; υ(*NH*) = 3249; υ(*HAr*) = 3057; υ(*H alkanes*) = 2962-2918; υ(*CO*NH) = 1651; υ(*C=CAr*) = 1598, 1521, 764; υ(NO_2) = 1487, 1339; υ(*P=O*) = 1159; υ(*ArOP*) = 1241-1206; υ(*CP*) = 935. MS (ESI+): m/z (%) **=** 1045.2, $[(C_{23}H_{24}O_6N_3P)_2Ag]^+$, 0.03 %.

Synthesis and characterisation of [Ag(L1)(PPh$_3$)]OTf (5). To a dichloromethane solution (30 mL) of **L1** (46.9 mg, 0.1 mmol), [Ag(OTf)(PPh_3)] (51.9 mg, 0.1 mmol) was added at room temperature. After the addition, the reaction mixture was stirred for 1 h. The volume was reduced under vacuum to 5 mL, and addition of hexane (10 mL) afforded compound **5** as a white solid, after filtration, with a 80 % yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.03 (s, 1H, *NH*); 8.13 (br d, 2H, *H-1*, $^{3}J_{HH}$ = 8.8 Hz); 7.82 (br d, 2H, *H-2*, $^{3}J_{HH}$ = 8.8 Hz); 7.35-7.08 (m, 25H, *Ph*); 5.39 (br s, 1H, *NH*CH); 3.41 (m, 1H, *CH*NH); 2.38 (m, 1H, *CH*$(CH_3)_2$); 1.28 (d, 3H, CH_3, $^{3}J_{HH}$ = 6.9 Hz); 1.23 (d, 3H, CH_3, $^{3}J_{HH}$ = 6.8 Hz). ^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ = 19.7 (s, 1P, *P=O*); 13.2 (m, PPh_3). ^{31}P{^{1}H} NMR (121 MHz, $(CD_3)_2CO$, -88˚C): δ = 19.7 (s, 1P, *P=O*); 8.8 (2 d, 1P, Ag-P, $J_{109Ag-P}$ = 366.4 Hz , $J_{107Ag-P}$ = 316.86 Hz). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 164.3 (s, 2C, *CO*); 150.3 (d, 2C, C_{ipso}*Ph,* $^{2}J_{CP}$ = 10.0 Hz); 150.0 (m, 2C, C_{ipso}*Ph*, $^{2}J_{CP}$ = 10.0 Hz); 149.9 (s, 2C, C_{ipso} *CO*); 137.9 (s, 1C, C_{para} NO_2); 134.0 (br d, 6C, C_{orto} PPh_3, $^{2}J_{CP}$ = 13.9 Hz); 131.0 (s, 3C, $C_{para}$$PPh_3$); 130.7 (d, 3C, $C_{ipso}$$PPh_3$, $^{1}J_{CP}$ = 34.0 Hz); 130.1 (s, 4C, C_{meta} O*Ph*); 130.0 (s, 4C, C_{meta} O*Ph*); 129.3 (d, 6C, C_{meta} PPh_3, $^{3}J_{CP}$ = 5.1 Hz); 128.4 (s, 2C, C_{H-2} CO*Ph*NO_2); 125.7 (s, 2C, C_{para} O*Ph*); 125.6 (s, 2C, C_{para} O*Ph*); 124.0 (s, 2C, C_{H-1} CO*Ph*NO_2); 120.7 (“t”, 8C, C_{ortho} O*Ph,* $^{3}J_{CP}$ = 4.2 Hz); 65.3 (d, 2C, OP*CH*(C_3H_7)NH, $^{1}J_{CP}$ = 161.7 Hz); 28.7 (d, 2C, *CH*$(CH_3)_2$ $^{2}J_{CP}$ = 2.2 Hz); 20.8 (d, 2C, CH_3, $^{3}J_{CP}$ = 8.4 Hz); 19.4 (d, 2C, CH_3, $^{3}J_{CP}$ = 7.3Hz). IR (cm^{-1}): υ(*NH*) = 3235; υ(*HAr*) = 3060; υ(*H alkanes*) = 2961; υ(*CO*NH) = 1663; υ(*C=CAr*) = 1589, 1522, 748; υ(NO_2) =

1487, 1343; υ(*P=O*) = 1158 ; υ(*ArOP*) = 1222-1207; υ(*CP*) = 929. MS (ESI+): m/z (%) = 831.1, 838.2 $[C_{41}H_{39}O_6N_3P_2Ag]^+$, 16.4 %.

Synthesis and characterisation of [Ag(L2)(PPh$_3$)]OTf (6). To a dichloromethane solution (30 mL) of **L2** (48.3 mg, 0.1 mmol), [Ag(OTf)(PPh$_3$)] (51.9 mg, 0.1 mmol) was added at room temperature. After the addition, the reaction mixture was stirred for 1 h. The volume was reduced under vacuum to 5 mL, and addition of hexane (10 mL) afforded compound **6** as a white solid, after filtration, with a 71 % yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.90 (s, 1H, *NH*); 8.26 (m, 2H, *H-1*); 7.94 (m, 2H, *H-2*); 7.46-7.16 (m, 25H, *Ph*), 5.35 (br s, 1H, *NH*CH); 3.68 (m, 1H,P*CH*NH,); 2.13 (m, 1H, $CH_2CH(CH_3)_2$); 1.88 (m, 2H, CHCH_2CH); 1.07 (m, 6H, CH_3). ^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ = 19.6 (s, 1P, *P=O*); 11.0 (s, 1P, $AgPPh_3$). ^{31}P{^{1}H} NMR (121 MHz, $(CD_3)_2CO$, -88 ˚C): δ = 20.1 (s, 1P, *P=O*); 8.2 (2 d, 1P, Ag-P, $J_{109Ag\text{-}P}$ = 367.0 Hz, $J_{107Ag\text{-}P}$ = 318.0Hz). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 162.3 (s, 1C, *CO*); 150.2 (m, 3C, *C$_{ipso}$ OPh, C$_{ipso}$ CO*, *C$_{ipso}$ OPh*); 137.9 (s, 1C, *C$_{para}$ NO$_2$*), 134.0 (br d, 6C, *C$_{ortho}$ PPh$_3$*, $^2J_{CP}$ = 11.6 Hz); 131.0 (s, 3C, *C$_{para}$ PPh$_3$*); 130.6 (d, 3C, C$_{ipso}$ *PPh$_3$*, $^1J_{CP}$ = 12.6 Hz); 130.1 (br s, 2C, *C$_{meta}$ OPh*); 129.8 (br s, 2C, *C$_{meta}$ OPh*); 129.2 (br s, 6C, C$_{meta}$ *PPh$_3$*); 128.4 (s, 1C, *C$_{H\text{-}2}$* CO*Ph*NO$_2$); 125.7 (s, 1C, *C$_{para}$* O*Ph*); 125.6 (s, 1C, *C$_{para}$* O*Ph*); 124.0 (s, 2C, *C$_{H\text{-}1}$* CO*Ph*NO$_2$); 120.7 (m, 4C, *C$_{ortho}$* O*Ph*); 57.6 (d, 1C, OPCHNH, $^1J_{CP}$ = 166.6 Hz); 37.1 (d, 1C, CHCH_2CH, $^2J_{CP}$ = 3.6 Hz); 25.0 (d, 1C, $CH_2CH(CH_3)_2$, $^3J_{CP}$ = 12.1 Hz); 23.5 (br s, 1C, CH_3); 21.8 (br s, 1C, CH_3). IR (cm^{-1}): υ(*NH*) = 3292; υ(*NH*) = 3248; υ(*HAr*) = 3076; υ(*H alkanes*) = 2958; υ(*CO*NH) = 1653; υ(*C=CAr*) = 1598, 1520, 764; υ(*NO$_2$*) = 1487, 1338; υ(*P=O*) = 1186; υ(*ArOP*) = 1239-1205; υ(*CP*) = 935. MS (ESI+): m/z (%) = 852.1, $[C_{42}H_{41}O_6N_3P_2Ag]^+$, 19.9 %.

Synthesis and characterisation of [Ag(L3)(PPh$_3$)]OTf (7). To a dichloromethane solution (30 mL) of **L3** (48.3 mg, 0.1 mmol), [Ag(OTf)(PPh$_3$)] (51.9 mg, 0.1 mmol) was added at room temperature. After the addition, the reaction mixture was stirred for 1 h. The volume was reduced under vacuum to 5 mL, and addition of hexane (10 mL) afforded compound **7** as a white solid, after filtration, with a 20 % yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.06 (s, 1H, *NH*); 8.24 (br d, 2H, *H-1*, $^3J_{HH}$ = 8.9 Hz); 7.91 (br d, 2H, *H-2*, $^3J_{HH}$ = 8.8 Hz); 7.47-7.17 (m, 25H, *Ph*), 5.48 (m, 1H, *NH*CH); 3.38 (d, 1H, *CH*NH, $^2J_{PH}$ = 4.7 Hz); 1.40 (s, 6H, CH_3). ^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ = 20.37 (s, 1P, *P=O*); 11.29 (s, 1P, $AgPPh_3$). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 163.6 (s, 1C, *CO*); 150.2 (d, 2C, *C$_{ipso}$Ph,* $^2J_{CP}$ = 10.4 Hz); 150.1 (d, 2C, *C$_{ipso}$ Ph,* $^2J_{CP}$ = 10.3 Hz); 149.9 (s, 1C, *C$_{ipso}$ CO*); 138.1 (s, 1C, *C$_{para}$ NO$_2$*); 134.1 (br s, 6C, *C$_{ortho}$ PPh$_3$*); 131.0 (s, 3C, *C$_{para}$ PPh$_3$*); 130.1 (s, 2C, C$_{meta}$ *OPh*); 130.0 (s, 2C, C$_{meta}$ *OPh*); 129.3 (s, 6C, *C$_{meta}$PPh$_3$*); 128.3 (s, 3C, *C$_{H\text{-}2}$* CO*Ph*NO$_2$; 125.7 (s, 1C, *C$_{para}$* O*Ph*); 125.6 (s, 1C, *C$_{para}$* O*Ph*); 124.0 (s, 1C, *C$_{H\text{-}1}$* CO*Ph*NO$_2$); 120.7 (d, 2C, *C$_{ortho}$* O*Ph*, $^3J_{CP}$ = 4.3 Hz); 120.7 (d, 2C, *C$_{ortho}$* O*Ph*, $^3J_{CP}$ = 4.2 Hz); 69.4 (d, 1C, OP*CH*NH, $^1J_{CP}$ = 160.2 Hz); 34.4 (d, 1C, CH*C*$(CH_3)_3$, $^2J_{CP}$ = 1.2 Hz); 28.2 (d, 3C, CH_3, $^3J_{CP}$ = 6.5Hz). IR (cm^{-1}): υ(*NH*) = 3273; υ(*HAr*) = 3057; υ(*H alkanes*) = 2928; υ(*CO*NH) = 1647; υ(*C=CAr*) = 1590, 1523, 743; υ(*NO$_2$*) = 1488, 1343; υ(*P=O*) = 1157; υ(*ArOP*) = 1241-1208; υ(*CP*) = 931. MS (ESI+): m/z (%) = 852.2, $[C_{42}H_{41}O_6N_3P_2Ag]^+$, 6.43 %.

Synthesis and characterisation of [Ag(L4)(PPh$_3$)]OTf (8). To a dichloromethane solution (30 mL) of **L4** (46.9 mg, 0.1 mmol), [Ag(OTf)(PPh$_3$)] (51.9 mg, 0.1 mmol) was added at room temperature. After the addition, the reaction mixture was stirred for 1 h. The volume was reduced under vacuum to 5 mL, and addition of hexane (10 mL) afforded compound **8** as a white solid, after filtration, with a 70 % yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.96 (s, 1H, *NH*); 8.25 (m, 2H, *H-1*); 7.93 (m, 2H, *H-2*); 7.45-7.17 (m, 25H, *Ph*); 3.65 (m, 1H, *CH*NH); 2.07-1.92 (m, 2H, CH$CH_2CH_2CH_3$); 1.82-1.70 (m, 2H, $CHCH_2CH_2CH_3$); 1.04 (t, 3H, CH_3, $^1J_{HH}$ = 7.3 Hz). ^{31}P{^{1}H} NMR (162MHz, $CDCl_3$): δ = 19.4 (s, 1P, *P=O*); 11.2 (m, 1P, $AgPPh_3$). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 164.3 (s, 1C, *CO*); 150.5 (m, 3C, *C$_{ipso}$OPh*, *C$_{ipso}$OPh, C$_{ipso}$ CO*); 137.8 (s, 1C, *C$_{para}$ NO$_2$*); 134.0 (br d, 6C, *C$_{ortho}$ PPh$_3$*, $^2J_{CP}$ = 13.8 Hz); 131.0 (s, 1C, *C$_{para}$* PPh_3); 130.6 (br d, 3C, C$_{ipso}$ *PPh$_3$*); 130.1 (br d, 6C, *C$_{meta}$ OPPh$_3$*); 130.0 (br d, 6C, *C$_{meta}$ OPPh$_3$*); 129.3 (br s, 6C, *C$_{meta}$* PPh_3); 128.5 (br s, 1C *C$_{H\text{-}2}$* CO*Ph*NO$_2$); 125.7 (br d, 2C, *C$_{para}$ OPPh$_3$*); 125.6 (br d, 2C, *C$_{para}$ OPPh$_3$*); 124.0 (s, 1C, *C$_{H\text{-}1}$* CO*Ph*NO$_2$); 120.7 (m, 4C, *C$_{ortho}$* O*Ph*); 59.2 (d, 1C, OP*CH*NH, $^1J_{CP}$ = 166.2 Hz); 30.4 (d, 1C, CH$CH_2CH_2CH_3$, $^2J_{CP}$ = 3.23 Hz); 19.8 (d, 1C, $CHCH_2CH_2CH_3$, $^3J_{CP}$ = 11.9 Hz); 14.02 (s, 1C, CH_3). IR (cm^{-1}): υ(*NH*) = 3233; υ(*HAr*) = 3072; υ(*H alkanes*) = 2965; υ(*CO*NH) = 1655; υ(*C=CAr*) = 1599, 1524, 758; υ(*NO$_2$*) = 1488, 1346; υ(*P=O*) = 1159; υ(*ArOP*) = 1237-1203; υ(*CP*) = 934. MS (ESI+): m/z (%) = 838.2, $[C_{41}H_{39}O_6N_3P_2Ag]^+$, 30.26 %.

Synthesis and characterisation of [Au(L1)(PPh$_3$)]OTf (9). A solution of [Au(OTf)(PPh$_3$)] (0.11 mmol) prepared *in situ* and **L1** (46.9 mg, 0.1 mmol) was stirred in DCM (30 mL) for 1 h at room temperature. The volume was reduced to 5 mL, and addition of hexane (10 mL) afforded compounds **9** as a white solid, after filtration, with a 37 % yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.71 (s, 1H, *NH*); 8.25 (m, 2H, *H-1*); 7.98 (m, 2H, *H-2*); 7.59-7.14 (m, 25H, *Ph*); 6.30 (br s, 1H, *NH*CH); 3.71 (dd, 1H, *CH*NH, $^2J_{PH}$ = 7.4 Hz, $^3J_{HH}$ = 5.9 Hz); 2.58 (m, 1H, *CH*$(CH_3)_2$); 1.42 (d, 3H, CH_3, $^3J_{HH}$ = 6.9 Hz); 1.36 (d, 3H, CH_3, $^3J_{HH}$ = 6.9 Hz). ^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ = 29.0 (s, 1P, Au(PPh_3)); 17.7 (s, 1P, *P=O*). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 164.1 (s, 1C, *CO*); 150.2 (m, 3C, *C$_{ipso}$Ph, C$_{ipso}$Ph, C$_{ipso}$ CO*); 133.5 (s, 1C, *C$_{para}$ NO$_2$*); 134.2 (m, 4C, *C$_{ortho}$ PPh$_3$*); 130.3-129.6 (m, 13C, *C$_{meta}$ OPh, C$_{meta}$ PPh$_3$, C$_{para}$ PPh$_3$*); 128.5 (s, 2C, *C$_{H\text{-}2}$* CO*Ph*NO$_2$); 125.7 (s, 2C, *C$_{para}$ OPh*); 125.6 (s, 2C, *C$_{para}$ OPh*); 123.9 (s, 2C, *C$_{H\text{-}1}$* CO*Ph*NO$_2$); 120.6 (m, 4C, *C$_{ortho}$* O*Ph*); 65.9 (d, 1C, OP*CH*(C_3H_7)NH, $^1J_{CP}$ = 157.5 Hz); 28.6 (d, 1C, *CH*$(CH_3)_2$ $^2J_{CP}$ = 1.6 Hz); 20.4 (d, 1C, CH_3, $^3J_{CP}$ = 7.6 Hz); 19.6 (d, 1C, CH_3, $^3J_{CP}$ = 6.6 Hz). IR (cm^{-1}): υ(*NH*) = 3235; υ(*HAr*) = 3060; υ(*H alkanes*) = 2961; υ(*CO*NH) = 1663; υ(*C=CAr*) = 1589, 1522, 748; υ(*NO$_2$*) = 1522 or 1487, 1343; υ(*P=O*) = 1158; υ(*ArOP*) = 1222-1207; υ(*CP*) = 929. MS (ESI+): m/z (%) = 928.2, $[C_{41}H_{39}O_6N_3P_2Au]^+$, 25.27 %.

Synthesis and characterisation of [Au(L2)(PPh$_3$)]OTf (10). A solution of [Au(OTf)(PPh$_3$)] (0.11 mmol) prepared *in situ* and **L2** (48.3 mg, 0.1 mmol) was stirred in DCM (30 mL) for 1 h at room temperature. The volume was reduced to 5 mL, and addition of hexane (10 mL) afforded compounds **10** as a yellow solid, after filtration, with a 42 % yield. δ = 8.87 (br s, 1H, *NH*CO); 8.23 (m, 2H, *H-1*); 7.93 (m, 2H, *H-2*); 7.59-7.13 (m, 25H, *Ph*); 5.25 (br s, 1H, *NH*CH); 3.68 (m, 1H, PNH*CH*); 2.14 (m, 1H, $CH_2CH(CH_3)$); 1.87 (m, 2H, CHCH_2CH); 1.06 (m, 6H, CH_3).

^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ = 31.0 (s, 1P, *Au(PPh$_3$)*; 19.7 (s, 1P, *P=O*). ^{13}C{^{1}H} NMR (ppm) (101 MHz, CD_2Cl_2): δ = 164.5 (s, 1C, *CO*) ; 150.8 (m, 3C, *C$_{ipso}$ OPh, C$_{ipso}$ OPh*, C$_{ipso}$ CO); 138.7 (s,

1C, C_{para} NO_2); 134.4-121.1 (m, 32C, *Ph*); 57.9 (d, 1C, OP*CH*(C_3H_7)NH, $^1J_{CP}$ = 165.7 Hz); 37.5 (d, 1C, CHCH_2CH, $^2J_{CP}$=3.4 Hz); 25.3 (d, 1C, $(CH_3)_2CHCH_2$, $^3J_{CP}$= 12.3 Hz); 23.68 (s, 1C, CH_3); 21.86 (s, 1C, CH_3). IR (cm^{-1}): υ(*NH*) = 3247; υ(*HAr*) = 3057; υ(*H alkanes*) = 2957; υ(*CO*NH) = 1653; υ(*C=CAr*) = 1589, 1519, 747; υ(NO_2) = 1487, 1343; υ(*P=O*) = 1159; υ(*ArOP*) = 1243-1207; υ(*CP*) = 932. MS (ESI): m/z (%) = 941.96, $[C_{42}H_{39}O_6N_3P_2Au]^+$, 7.72 %.

Synthesis and characterisation of [Au(L3)(PPh$_3$)]OTf (11). A solution of [Au(OTf)(PPh_3)] (0.11 mmol) prepared *in situ* and **L3** (48.3 mg, 0.1 mmol) was stirred in DCM (30 mL) for 1 h at room temperature. The volume was reduced to 5 mL, and addition of hexane (10 mL) afforded compounds **11** as a yellow solid, after filtration, with a 54 % yield. ^{1}H NMR (400 MHz, CD_2Cl_2): δ= 8.95 (s br, 1H, *NH*); 8.25 (m, 2H, *H-1*); 7.90 (m, 2H, *H-2*); 7.67-7.18 (m, 25H, *Ph*); 5.49 (br s, 1H, *NH*CH); 3.34 (br d, 1H, *CH*NH); 1.38 (s, 9H, CH_3). ^{31}P{^{1}H} NMR (162 MHz, CD_2Cl_2): δ= 31.4 (s, 1P, *AuPPh$_3$*); 20.2 (s, 1P, *P=O*). ^{13}C NMR (ppm) (101 MHz, CD_2Cl_2): δ = 132.7 (s, 1C, C_{para} NO_2); 134.4-130.0 (m, 22C, *PPh$_3$*, C_{meta} OPh); 128.7 (s, 2C, $C_{H\text{-}2}$ CO*Ph*NO_2); 125.9 (m, 2C, C_{para} *OPh*); 124.4 (s, 2C, $C_{H\text{-}1}$ CO*Ph*NO_2); 121.2 (m, 4C, C_{ortho} *OPh*); 69.7 (d, 1C, *CH*NH, $^1J_{C\text{-}P}$= 158.8Hz); 28.4 (d, 3C, CH_3, $^3J_{C\text{-}P}$= 6.5Hz). IR (cm^{-1}): υ(*NH*) = 3274; υ(*NH*) = 3247; υ(*HAr*) = 3104; υ(*H alkanes*) = 2973-2928; υ(*CO*NH) = 1637; υ(*C=CAr*) = 1594, 1512, 753; υ(NO_2) = 1490, 1343; υ(*P=O*) = 1154; υ(*ArOP*) = 1232-1206; υ(*CP*) = 935.

Synthesis and characterisation of [Au(L2)$_2$]OTf (12). A solution of [Au(tht)$_2$]OTf (0.55 mmol) prepared *in situ* and **L2** (48.3 mg, 0.1 mmol) was stirred in DCM (30 mL) for 1 h at room temperature. The volume was reduced to 5 mL, and addition of hexane (10 mL) afforded compounds **12** as a pale yellow solid, after filtration, with a 28 % yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.96 (br s, 2H, *NH*); 8.23 (m, 4H, *H-1*); 7.93 (m, 4H, *H-2*); 7.33-7.15 (m, 20H, *Ph*); 3.69 (m, 2H, P*CH*NH); 3.19 (br s, 2H, *NH*CH); 2.14 (m, 2H, $CH_2CH(CH_3)_2$); 1.88 (m, 4H, CHCH_2CH); 1.07 (m, 12H, CH_3). ^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ = 18.6 (s, 1P, *P=O*). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 150.1 (m, 4C, C_{ipso}*Ph*); 145.0 (s, 2C, C_{ipso} *CO*); 138.0 (s, 2C, C_{para} NO_2); 130.1 (s, 4C, C_{meta} *OPh*); 130.0 (s, 4C, C_{meta} *OPh*); 128.4 (s, 4C, $C_{H\text{-}2}$ CO*Ph*NO_2); 125.8 (s, 2C, C_{para} *OPh*); 125.7 (s, 2C, C_{para} *OPh*); 124.0 (s, 4C, $C_{H\text{-}1}$ CO*Ph*NO_2); 120.8 (m, 4C, C_{ortho} O*Ph*, $^3J_{C\text{-}P}$= 3.9Hz); 120.7 (m, 4C, C_{ortho} O*Ph*, $^3J_{C\text{-}P}$= 4.0Hz); 29.9 (s, 2C, CHCH_2CH); 25.0 (d, 2C, $CH_2CH(CH_3)_2$, $^3J_{CP}$ = 13.0 Hz); 23.6 (s, 2C, CH_3); 21.8 (s, 2C, CH_3). IR (cm^{-1}): υ(*NH*) = 3291; υ(*NH*) = 3247; υ(*HAr*) = 3113; υ(*H alkanes*) = 2954; υ(*CO*NH) = 1652; υ(*C=CAr*) = 1597, 1519, 748; υ(NO_2) = 1488, 1338; υ(*P=O*) = 1160; υ(*ArOP*) = 1237-1204; υ(*CP*) = 933. MS (ESI+): m/z (%) = 1163, $[(C_{24}H_{26}O_6N_3P)_2Au]^+$, 7 %.

Synthesis and characterisation of [Cu(L1)(PPh$_3$)]NO$_3$ (13). To a dichloromethane solution (30 mL) of **L1** (46.9 mg, 0.1 mmol), [Cu(NO_3)(PPh_3)$_2$] (64.9 mg, 0.1 mmol) was added at room temperature. After the addition, the reaction mixture was stirred for 30 min. The volume was reduced under vacuum to 5 mL, and addition of hexane (10 mL) afforded compound **13** as a pale yellow solid, after filtration, with a 90 % yield. ^{1}H NMR (ppm) (400 MHz, CD_2Cl_2): δ= 8.75 (s br, 1H, *NH*); 8.24 (m, 2H, *H-1*); 7.89 (m, 2H, *H-2*); 7.40-7.17 (m, 25H, *Ph*); 5.41 (br s, 1H, *NH*CH); 3.44 (m, 1H, *CH*NH); 2.45 (m, 1H, *CH*(CH_3)); 1.36 (d, 3H, CH_3, $^3J_{H\text{-}H}$= 6.8 Hz); 1.32 (d, 3H, CH_3, $^3J_{H\text{-}H}$= 6.8 Hz).^{31}P NMR (ppm) (162 MHz, CD_2Cl_2): δ= 19.7 (s, 1P, *P=O*); -0.5 (s, 1P, *PPh$_3$*).^{13}C NMR (ppm) (101 MHz, CD_2Cl_2): δ= 164.4 (s, 1C, *CO*); 150.9 (s, 1C, C_{ipso} *CO*); 138.8 (s, 1C, C_{para} NO_2); 134.1 (s br, 6C, C_{ortho} *PPh$_3$*); 132.2 (d, 3C, C_{ipso} *PPh$_3$*, $^1J_{C\text{-}P}$= 30.8 Hz); 130.9 (s br, 3C, C_{para} *PPh$_3$*); 130.4 (s, 2C, C_{meta} *OPh*); 130.3 (s, 2C, C_{meta} *OPh*); 129.4 (br s, 6C, C_{meta} *PPh$_3$*); 128.7 (s, 2C, $C_{H\text{-}2}$ *CO*PhNO$_2$); 126.0 (s, 1C, C_{para} *OPh*); 125.9 (s, 1C, C_{para} *OPh*); 124.4 (s, 2C; $C_{H\text{-}1}$ COPhNO$_2$); 120.2 (m, 4C, C_{ortho} *OPh*); 65.7 (d, 1C, *CH*NH, $^1J_{C\text{-}P}$ = 160.8Hz); 29.0 (d, 1C, *CH*(CH_3) $^2J_{C\text{-}P}$ = 2.1Hz); 21.0 (d, 1C, CH_3, $^3J_{C\text{-}P}$ = 8.3Hz); 19.6 (d, 1C, CH_3, $^3J_{C\text{-}P}$ = 7.5Hz). IR (cm^{-1}): υ(*NH*) = 3276; υ(*H alkanes*) = 2969; υ(*CO*NH) = 1653; υ(*C=CAr*) = 1594, 1517, 759; υ(NO_2) = 1488, 1347; υ(*P=O*) = 1162 ; υ(*ArOP*) = 1282-1217; υ(*CP*) = 930. MS (ESI+): m/z (%) = 794.2, $[C_{41}H_{39}O_6N_3P_2Cu]^+$, 2.5 %.

Synthesis and characterisation of [Cu(L2)(PPh$_3$)]NO$_3$ (14). To a dichloromethane solution (30 mL) of **L2** (48.3 mg, 0.1 mmol), [Cu(NO_3)(PPh_3)$_2$] (64.9 mg, 0.1 mmol) was added at room temperature. After the addition, the reaction mixture was stirred for 30 min. The volume was reduced under vacuum to 5 mL, and addition of hexane (10 mL) afforded compound **14** as a yellow solid, after filtration, with an 86 % yield. ^{1}H NMR (ppm) (400 MHz, CD_2Cl_2): δ = 8.77 (s br, 1H, *NH*); 8.25 (m, 2H, *H-1*); 7.91 (m, 2H, *H-2*); 7.43-7.19 (m, 25H, *Ph*); 5.32 (s br, 1H, *NH*CH); 3.66 (m, 1H, *CH*NH); 2.12 (m, 1H, *CH*(CH_3)); 1.87 (m, 2H, CHCH_2CH); 1.06(br t, 6H, CH_3). ^{31}P NMR (ppm) (162 MHz, CD_2Cl_2): δ = 19.8 (s, 1P, *P=O*); -0.9 (s, 1P, *PPh$_3$*). ^{13}C NMR (ppm) (101 MHz, CD_2Cl_2): δ = 164.5 (s, 1C, *CO*); 151.0 (s, 1C, C_{ipso} *OPh*); 150.4 (s, 1C, C_{ipso} *CO*); 138.7 (s, 1C, C_{para} NO_2); 134.1 (d, 6C, C_{orto} *PPh$_3$*, $^3J_{C\text{-}P}$ = 9.1 Hz); 132.2 (d, 3C, C_{ipso} *PPh$_3$*, $^1J_{C\text{-}P}$ = 30.8 Hz); 130.9 (s, 3C, C_{para} *PPh$_3$*); 130.4 (s, 2C, C_{meta} *OPh*); 130.3 (s, 2C, C_{meta} *OPh*); 129.4 (s, 6C, C_{meta} *PPh$_3$*); 128.7 (s, 2C, $C_{H\text{-}2}$ CO*Ph*NO_2); 126.1 (s, 1C, C_{para} *OPh*); 125.9 (s, 1C, C_{para} *OPh*); 124.4 (s, 2C, $C_{H\text{-}1}$ CO*Ph*NO_2); 120.2 (d, 2C, C_{orto} *OPh,* $^4J_{C\text{-}P}$ = 4.1 Hz); 120.1 (d, 2C, C_{orto} *OPh,* $^4J_{C\text{-}P}$ = 94.2 Hz) 58.0 (d, 1C, *CH*NH, $^1J_{C\text{-}P}$ = 166.2Hz); 37.40 (d, 1C, CHCH_2CH, $^2J_{C\text{-}P}$= 3.7Hz); 25.3 (d, 1C, $CHCH_2CH(CH_3)_2$, $^3J_{C\text{-}P}$ = 12.4Hz); 23.7 (s, 1C, CH_3); 21.8 (d, 1C, CH_3). IR (cm^{-1}): υ(*NH*) = 3294; υ(*NH*) = 3248; υ(*CO*NH) = 1653; υ(*C=CAr*) = 1597, 1520, 764; υ(NO_2) = 1488, 1338; υ(*P=O*) = 1160; υ(*ArOP*) = 1238-1205; υ(*CP*) = 935. MS (ESI+): m/z (%) = 808, $[C_{42}H_{41}N_3O_6P_2Cu]^+$, 46 %.

Synthesis and characterisation of [Cu(L3)(PPh$_3$)]NO$_3$ (15). To a dichloromethane solution (30 mL) of **L3** (84.3 mg, 0.1 mmol), [Cu(NO_3)(PPh_3)$_2$] (64.9 mg, 0.1 mmol) was added at room temperature. After the addition, the reaction mixture was stirred for 30 min. The volume was reduced under vacuum to 5 mL, and addition of hexane (10 mL) afforded compound **15** as a pale yellow solid, after filtration, with a 90 % yield. ^{1}H NMR (ppm) (400 MHz, CD_2Cl_2): δ = 8.90 (br s, 1H, *NH*); 8.25 (m, 2H, *H-1*); 7.90 (m, 2H, *H-2*); 7.43-7.18 (m, 25H, *Ph*); 5.46 (s br, 1H, *NH*CH); 3.35 (d, 1H, *CH*NH, $^2J_{H\text{-}P}$ = 5.2Hz); 1.38 (s, 9H, CH_3). ^{31}P NMR (ppm) (162 MHz, CD_2Cl_2): δ = 20.4 (s, 1P, *P=O*); -0.4 (s, 1P, *PPh$_3$*). ^{13}C NMR (ppm) (101 MHz, CD_2Cl_2): δ = 163.7 (s, 1C, *CO*); 150.9 (s, 1C, C_{ipso} *OPh*); 150.3 (s, 1C, C_{ipso} CO); 138.9 (s, 1C, C_{para} NO_2); 134.1 (d, 6C, C_{ortho} *PPh$_3$,* $^2J_{C\text{-}P}$ = 12.0 Hz); 132.2 (d, 3C, C_{ipso} *PPh$_3$*, $^1J_{C\text{-}P}$ = 32.4 Hz); 130.9 (s, 3C, C_{para} *PPh$_3$*); 130.4 (s, 2C, C_{meta} *OPh*); 130.3 (s, 2C, C_{meta} *OPh*); 129.4 (br s, 6C, C_{meta} *PPh$_3$*); 128.7 (s, 2C, $C_{H\text{-}2}$ CO*Ph*NO_2); 126.0 (s, 1C, C_{para} *OPh*); 125.9 (s,

2C, C_{para} *OPh*); 124.4 (s, 2C; C_{H-1} CO*Ph*NO_2); 121.2 (d, 2C, C_{orto} *OPh*, $^3J_{C-P}$ = 4.2Hz); 121.1 (d, 2C, C_{ortho} *OPh*, $^3J_{C-P}$ = 4.1Hz); 69.7 (d, 1C, *CH*NH, $^1J_{C-P}$ = 158.8Hz); 34.7 (s, 1C, CH*C*$(CH_3)_3$); 28.4 (d, 3C, CH_3, $^3J_{C-P}$ = 6.5Hz). IR (cm^{-1}): υ(*NH*) = 3275; υ(*NH*) = 3245; υ(*HAr*) = 3068; υ(*H alkanes*) = 2903; υ(*CO*NH) = 1638; υ(*C=CAr*) = 1595, 1513, 753; υ(NO_2) = 1491, 1344; υ(*P=O*) = 1154; υ(*ArOP*) = 1232-1206; υ(*CP*) = 937. MS (ESI+): m/z (%) = 808, $[C_{42}H_{41}N_3O_6P_2Cu]^+$, 46 %.

Synthesis and characterisation of [Cu(L4)(PPh$_3$)]NO$_3$ (16). To a dichloromethane solution (30 mL) of **L4** (46.9 mg, 0.1 mmol), $[Cu(NO_3)(PPh_3)_2]$ (64.9 mg, 0.1 mmol) was added at room temperature. After the addition, the reaction mixture was stirred for 30 min. The volume was reduced under vacuum to 5 mL, and addition of hexane (10 mL) afforded compound **16** as a pale yellow solid, after filtration, with an 82 % yield. ^{1}H NMR (ppm) (400 MHz, CD_2Cl_2): δ = 8.65 (s br, 1H, *NH*); 8.19 (m, 2H, *H-1*); 7.83 (m, 2H, *H-2*); 7.43-7.12 (m, 25H, *Ph*); 5.46 (s br, 1H, *NH*CH); 3.54 (m, 1H, *CH*NH); 1.89-1.61 (m, 4H, CH_2); 0.97 (t, 3H, CH_3, $^3J_{H-H}$= 7.3 Hz). ^{31}P NMR (ppm) (162 MHz, CD_2Cl_2): δ = 19.6 (s, 1P, *P=O*); -0.4 (s, 1P, PPh_3). ^{13}C NMR (ppm) (101 MHz, CD_2Cl_2): δ = 134.2 (br s, 6C, C_{orto} PPh_3); 132.3 (d, 3C, C_{ipso} PPh_3, $^1J_{C-P}$= 32.0 Hz); 130.9 (s, 3C, C_{para} PPh_3); 130.4 (s, 2C, C_{meta} *OPh*); 130.3 (s, 2C, C_{meta} *OPh*); 129.4 (s, 6C, C_{meta} PPh_3); 128.8 (s, 2C, C_{H-2} CO*Ph*NO_2); 126.1 (s, 1C, C_{para} *OPh*); 125.9 (s, 1C, C_{para} *OPh*); 124.4 (s, 2C, C_{H-1} CO*Ph*NO_2); 121.2 (br s, 2C, C_{orto} *OPh*); 120.1 (br s, 2C, C_{orto} *OPh*); 30.7 (s, 1C, CH$CH_2$$CH_2CH_3$); 20.1 (s, 1C, $CHCH_2CH_2CH_3$); 14.2 (s, 1C, $CHCH_2CH_2CH_3$). IR (cm^{-1}): υ(*NH*) = 3249; υ(*HAr*) = 3046; υ(*H alkanes*) = 2898; υ(*CO*NH) = 1653; υ(*C=CAr*) = 1598, 1519, 758; υ(NO_2) = 1456, 1344; υ(*P=O*) = 1160; υ(*ArOP*) = 1274-1207; υ(*CP*) = 934. MS (ESI+): m/z (%) = 794.2, $[C_{41}H_{39}O_6N_3P_2Cu]^+$, 2 %.

Crystallography. Crystals were mounted in inert oil on glass fibres and transferred to the cold gas stream of an Xcalibur Oxford Diffraction diffractometer equipped with a low-temperature attachment. Data were collected using monochromatic Mo Kα radiation (λ = 0.71073 Å). Scan type ω. Absorption correction based on multiple scans was applied using spherical harmonics implemented in SCALE3 ABSPACK[33] scaling algorithm. The structures were solved by direct methods and refined on F^2 using the program SHELXL.[34] All non-hydrogen atoms were refined anisotropically. In all cases, hydrogen atoms were included in calculated positions and refined using a riding model. Refinements were carried out by full-matrix least-squares on F^2 for all data. CCDC reference numbers 1565044 for complex **5** and 1565045 for complex **8**.

Cell culture. HeLa (cervical cancer) and A549 (lung carcinoma) cells were maintained in high glucose DMEM (Dulbecco´s Modified Eagle´s Medium) supplemented with 5 % fetal bovine serum (FBS), 200 U/ml penicillin, 100 μg/ml streptomycin and 2 mM L-glutamine. Cultures were maintained in a humidified atmosphere of 95 % air/5 % CO_2 at 37 °C. Adherent cells were allowed to attach for 24 h prior to addition of compounds.

Cytotoxicity assay. The MTT assay was used to determine cell viability as an indicator for cells sensitivity to the complexes. Exponentially growing cells were detached from the plastic flask using trypsin-EDTA solution and seeded at a density of approximately 10^4 cells per well in 96-well flat-bottomed microplates and allowed to attach for 24 h prior to addition of compounds. The complexes were dissolved in DMSO and added to cells in concentrations ranging from 0.1 to 50 μM in quadruplicate. Cells were incubated with our compounds for 24 h at 37 °C. 10 μl of MTT (5 mg ml^{-1}) were added to each well and plates were incubated for 2 h at 37 °C. Finally, media was eliminated and DMSO (100 μl per well) was added to dissolve the formazan precipitates. The optical density was measured at 550 nm using a 96-well multiscanner autoreader (ELISA). The IC_{50} was calculated by nonlinear regression analysis using Prism software (GraphPad Software Inc). Each compound was analysed at least in three independent experiments.

CONCLUSIONS

Unprecedented α-hydrazidophosphonate group 11 metal complexes have been prepared. Several coordination modes of the ligands to group 11 metals have been proposed, which depends also upon the ancillary ligand, and some of them corroborated by X-ray diffraction. With the $MPPh_3^+$ fragment the coordination is tridentate chelate O^N^O with silver and copper, whereas an N^O binding mode is suggested for gold. The homoleptic silver and gold derivatives have been prepared and they are tetrahedral, N^O, for silver and linear for gold with bonding of the gold atom to the iminic nitrogen atoms. The cytotoxic activity of the more stable silver and copper complexes has been studied in two human tumour cell lines, HeLa (cervical carcinoma) and A549 (lung carcinoma). The IC_{50} values reveal an excellent cytotoxic activity of the metal complexes compared with the α-hydrazidophosphonate ligands alone and much higher than *cisplatin*. The values are in the low micromolar range and are among the lowest found in silver or copper complexes. These outstanding activities of these complexes are worth for further studies opening new avenues with low toxic metals and the possibility of new biological targets.

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Notes and references

1 C. M. Timperley (Ed.) *Best Synthetic Methods: Organophosphorus (V) Chemistry.* Elsevier Ltd.: London, 2015.

2 H.-W. He, H. Peng and X.-S. Tan (Eds.) *Environmentally Friendly Alkylphosphonate Herbicides*. Chemical Industry Press: Beijing and Springer-Verlag: Berlin Heidelberg, 2014.

3 G. Lukacs and M. Ohno (Eds.) in *Recent progress in the chemical synthesis of antibiotics*. Springer-Verlag: Berlin Heidelberg, 1990.

4 M. Balali-Mood and M. Abdollahi (Eds.) *Basic and Clinical Toxicology of Organophosphorus Compounds*. Springer-Verlag London, 2014.

5 J. Huang and R. Chen, *Heteroat. Chem.* 2000, **11**, 480–492.

6 P. Kafarski and B. Lejczak, *Phosphorus Sulfur Silicon Relat. Elem.* 1991, **63**, 193–215.

7 For recent examples, see: a) T. Cihlar, G.-X. He, X. Liu, J. M. Chen, M. Hatada, S. Swaminathan, M. J. McDermott, Z.-Y. Yang, A. S. Mulato, X. Chen, S. A. Leavitt, K. M. Stray and W. A. Lee, *J. Mol. Biol.*, 2006, **363**, 635–647; b) C. Callebaut, K. Stray, L. Tsai, M. Williams, Z.-Y. Yang, C. Cannizzaro, S. A. Leavitt, X. Liu, K. Wang, B. P. Murray, A. Mulato, M. Hatada, T. Priskich, N. Parkin, S. Swaminathan, W. Lee, G.-X. He, L. Xu and T. Cihlar, *Antimicrob. Agents Chemother.*, 2011, **55**, 1366–1376; c) K. G. Šašková, M. Kožíšek, K. Stray, D. de Jong, P. Řezáčová, J. Brynda, N. M. van Maarseveen, M. Nijhuis, T. Cihlář and J. Konvalinka, *J. Virol.*, 2014, **88**, 3586–3590.

8 A. N. Pudovik and I. V. Konovalova, *Synthesis*, 1979, 81–96.

9 a) O. I. Kolodiazhnyi, *Tetrahedron: Asymmetry*, 1998, **9**, 1279–1332; b) H. Gröger and B. Hammer, *Chem. Eur. J.*, 2000, 6, 943–948; c) T. P. Kee and T. D. Nixon, *Top. Curr. Chem.*, 2003, **223**, 45–65; d) S. Sobhani and Z. Tashrifi, *Tetrahedron*, 2010, **66**, 1429–1439.

10 a) J.-A. Ma, *Chem. Soc. Rev.*, 2006, **35**, 630–636; b) P. Merino, E. Marqués-López and R. P. Herrera, *Adv. Synth. Catal.*, 2008, **350**, 1195–1208; c) G. Keglevich and E. Bálint, *Molecules*, 2012, **17**, 12821–12835; d) K. V. Turcheniuk, V. P. Kukhar, G. Röschenthaler, J. L. Aceña, V. A. Soloshonok and A. E. Sorochinsky, *RSC Adv.*, 2013, **3**, 6693–6716; e) T. K. Olszewski, *Synthesis*, 2014, **46**, 403–429; f) R. P. Herrera, *Chem. Rec.,* 2017, DOI: 10.1002/tcr.201600129.

11 a) Ł. Albrecht, A. Albrecht, H. Krawczyk and K. A. Jørgensen, *Chem. Eur. J.*, 2010, **16**, 28–48; b) D. Zhao and R. Wang, *Chem. Soc. Rev.*, 2012, **41**, 2095–2108.

12 a) V. P. Kukhar and H. R. Hudson, (Eds.) in *Aminophosphonic and Aminophosphinic Acids: Chemistry and Biological Activity*. Wiley-VCH: Chichester, 2000; b) J. Huang and R. Chen, *Heteroatom Chem.*, 2000, **11**, 480–492; c) P. Kafarski and B. Lejczak, *Curr. Med. Chem.*, 2001, **1**, 301–312; d) Z. H. Kudzin, M. H. Kudzin, J. Drabowicz, C. V. Stevens, *Curr. Org. Chem.,* 2011, **15**, 2015–2071; e) C. S. Demmer, N. Krogsgaard-Larsen and L. Bunch, *Chem. Rev.*, 2011, **111**, 7981–8006.

13 R. P. Herrera, D. Roca-López and G. Navarro-Moros, *Eur. J. Org. Chem.*, 2010, 1450–1454.

14 a) S. Rollas and Ş. Güniz Küçükgüzel, *Molecules* 2007, ***12***, 1910–1939; b) M. Alagesan, N. S. P. Bhuvanesh and N. Dharmaraj, *Dalton Trans*., 2013, **42**, 7210–7223.

15 a) N. Chavain and C. Biot, *Curr. Med. Chem.*, 2010, **17**, 2729–2745; b) N. Muhammad and Z. Guo, *Curr. Opin. Chem. Biol.*, 2014, **19**, 144–153.

16 For selected reviews, see: a) E. R. T. Tiekink, *Crit. Rev. Oncol. Hematol.*, 2002, **42**, 225–248; b) I. Ott, *Coord. Chem. Rev.*, 2009, **153**, 1670–1681; c) S. Nobili, E. Mini, I. Landini, C. Gabbiani, A. Casini and L. Messori, *Med. Res. Rev.*, 2010, **30**, 550–580; d) C.-M. Che and R. W.-Y. Sun, *Chem. Commun.*, 2011, **47**, 9554–9560; e) A. Casini and L. Messori, *Curr. Top. Med. Chem.*, 2011, **11**, 2647–2660; e) B. Bertrand and A. Casini, *Dalton Trans.*, 2014, **43**, 4209–4219; f) T. Zou, C. T. Lum, C.-N. Lok, J.-J. Zhang and C.-M. Che, *Chem. Soc. Rev.*, 2015, **44**, 8786–8801.

17 For selected examples, see: a) M. C. Gimeno, H. Goitia, A. Laguna, M. E. Luque, M. D. Villacampa, C. Sepúlveda and M. Meireles, *J. Inorg. Biochem.*, 2011, **105**, 1373-1382; b) H. Goitia, Y. Nieto, M. D. Villacampa, C. Kasper, A. Laguna and M. C. Gimeno, *Organometallics*, 2013, **32**, 6069–6078; c) A. Gutiérrez, L. Gracia-Fleta, I. Marzo, C. Cativiela, A. Laguna and M. C. Gimeno, *Dalton Trans.*, 2014, **43**, 17054–17066; d) L. Ortego, F. Cardoso, S. Martins, M. F. Fillat, A. Laguna, M. Meireles, M. D. Villacampa and M. C. Gimeno, *J. Inorg. Biochem.*, 2014, **130**, 32–37; e) A. Gutiérrez, I. Marzo, C. Cativiela, A. Laguna and M. C. Gimeno, *Chem. Eur. J.*, 2015, **21**, 11088–11095; f) L. Ortego, M. Meireles, C. Kasper, A. Laguna, M. D. Villacampa and M. C. Gimeno, *J. Inorg. Biochem.*, 2016, **156**, 133–144.

18 G. McDonnell and A. D. Russell, *Clin. Microbiol. Rev.*, 1999, **12**, 147–179.

19 W. K. Jung, H. C. Koo, K. W. Kim, S. Shin, S. H. Kim and Y. H. Park, *Appl. Environ. Microbiol.*, 2008, **74**, 2171–2178.

20 B. S. Atiyeh, M. Costagliola, S. N. Hayek and S. A. Dibo, *Burns,* **2007**, *33*, 139–148.

21 a) C. N. Banti and S. K.Hadjikakou, *Metallonics*, 2013, **5**, 569–596; b) S. Medici, M. Peana, V. M. Nurchi, J. I. Lachowicz, G. Crisponi and M. A. Zoroddu, *Coord. Chem. Rev.*, 2015, **284**, 329–350

22 C. Santini, M. Pellei, V, Gandin, M. Porchia, F. Tisato and C. Marzano, *Chem. Rev.*, 2014, **114**, 815–862.

23 See for example: a) E. M. Barranco, O. Crespo, M. C. Gimeno, P. G. Jones, A. Laguna and C. Sarroca, *Dalton Trans.*, 2001, 2523–2529; b) O. Crespo, M. C. Gimeno, P. G. Jones and A. Laguna, *Inorg. Chem*., 1996, **35**, 1361–1366; c) O. Crespo, F. Canales, M. C. Gimeno, P. G. Jones and A. Laguna, *Organometallics*, 1999, **18**, 3142-–3148; d) O. Crespo, M. C. Gimeno, P. G. Jones and A. Laguna, *Inorg. Chem.*, 1994, **33**, 6128–6131.

24 K. Akhabari and A. Morsali, *Inorg. Chem.*, 2013, **52**, 2787-2789.

25 E. M. Barranco, M. C. Gimeno, A. Laguna and M. D. Villacampa, *Inorg. Chim. Acta*, 2005, **358**, 4177-5182.

26 L. G. Kuz'mina, N. V. Dvortsova, M. A. Porai-Koshits, E. I. Smyslova, K. I. Grandberg and E. G. Perevalova, *Metalloorg.Khim.(Russ.) (Organomet.Chem.(USSR))*, 1989, **2**, 1344-.

27 B. Ahrens, P. G. Jones and A. K. Fischer, *Eur. J. Inorg. Chem.* 1999, 1103-1110.

28 F. Hueso-Ureña, S. B. Jiménez-Pulido, M. P. Fernández-Liencres, M. Fernández-Gómez and M. N. Moreno-Carretero, *Dalton Trans.*, 2008, 6461–6466.

29 a) B. Bachowska, J. Kazmierczak-Baranska, M. Cieslak, B. Nawrot, D. Szczęsna, J. Skalik and P. Bałczewski, *ChemistryOpen*, 2012, **1**, 33–38; b) M. Frik, J. Fernández-Gallardo, O. Gonzalo, V. Mangas-Sanjuan, M. González-Álvarez, A. Serrano del Valle, C. Hu, I. González-Álvarez, M. Bermejo, I. Marzo and M. Contel, *J. Med. Chem.,* 2015, **58**, 5825–5841.

30 M. Bardají, O. Crespo, A. Laguna and A. K. Fischer, *Inorg. Chim. Acta*, 2000, **304**, 7–16.

31 R. Usón and A. Laguna, *Inorg. Synth.,* 1982, **21**, 71–74.

32 R. Usón, A. Laguna and M. Laguna, *Inorg. Synth.*, 1989, **26**, 85–91.

33 CysAlisPro, Version 1.171.35.11; Agilent Technologies. Multiscan absorption correction with SCALE3 ABSPACK scaling algorithm.

34 G. M. Sheldrick, SHELXL, *Acta Cryst.*, 2008, **A64**, 112–122.