Electronic Supporting Information for

Gold(I) complexes of water-soluble diphos-type ligands: Synthesis, anticancer activity, apoptosis and thioredoxin reductase inhibition.

Corinna Wetzel,[a] Peter C. Kunz,[a],* Matthias U. Kassack,[b] Alexandra Hamacher,[b] Philip Böhler[c], Wim Wätjen[c], Ingo Ott[d], Riccardo Rubbiani[d] and Bernhard Spingler[e]

[a] C. Wetzel, PD Dr. P. C. Kunz
Institut für Anorganische Chemie und Strukturchemie, Lehrstuhl I: Bioanorganische Chemie und Katalyse, Heinrich-Heine-Universität Düsseldorf, Universitätsstr. 1, D-40225 Düsseldorf, Germany, Fax: (+) 49 211 8112287, E-mail: peter.kunz@uni-duesseldorf.de

[b] Prof. Dr. M. U. Kassack, Dr. A. Hamacher
Universitätsstr. 1, D-40225 Düsseldorf, Germany, Heinrich-Heine-University Düsseldorf, D-40225 Düsseldorf, Germany

[c] PD Dr. W. Wätjen, P. Böhler
Institut für Toxikologie, Heinrich-Heine-University Düsseldorf, Universitätsstr. 1, D-40225 Düsseldorf, Germany

[d] Prof. Dr. I. Ott, R. Rubbiani
Institut für Pharmazeutische Chemie, Technische Universität Braunschweig, Beethovenstr. 55, D-38106 Braunschweig, Germany

[e] PD Dr. B. Spingler
Anorganisch-Chemisches Institut, Universität Zürich-Irchel, Winterthurerstr. 190, CH-8057 Zürich, Switzerland

1,2-Bis(chlorophenylphosphino)ethane: A solution of dppe (10g, 0.025 mol) in thf was added drop-wise at 0 °C to a suspension of freshly cut lithium (1.74g, 0.25 mol) in thf. The colour of the suspension turned to orange and the suspension was stirred for 1 h at 0 °C and afterwards heated to reflux for 3 h. The suspension was stirred over night at ambient temperature, the remaining lithium was removed, the dark red solution cooled to 0 °C and PCl_3 added (5.5 mL, 0.063 mol). The suspension was stirred for 1 h at 0 °C and over night at ambient temperature. The precipitate was removed by filtration over a plug of Celite and the filtrate concentrated in vacuo. Toluene was added and the resulting suspension again filtered though a plug of Celite. All volatiles were removed in vacuo to give the product as a sightly yellow oil. Yield: 2.73 g. $^{31}P\{^1H\}$-NMR (CD_2Cl_2): δ = 94. ^1H-NMR ($CDCl_3$): δ = 2.19 (t, J=8.06 Hz, 4H, $(CH_2)_2$), 7.40-7.66 (m, 10H, PhenylH´s). MALDI (CH_2Cl_2): *m/z* = 278.8 $[C_{14}H_{16}P_2O_2]^+$.

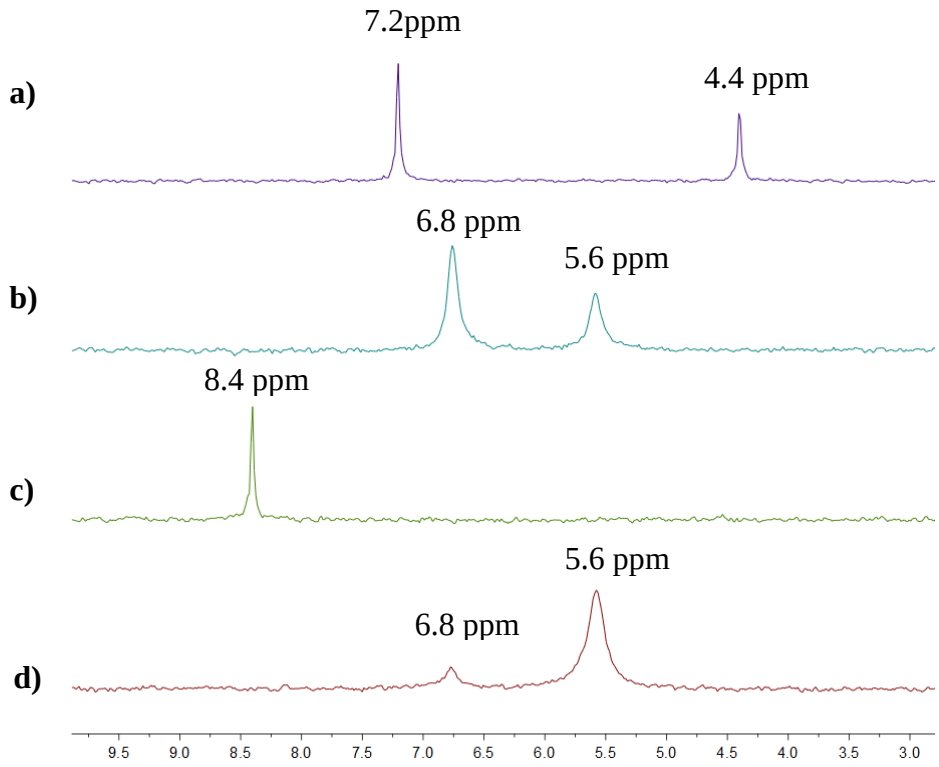

Figure ESI1. $^{31}P\{^1H\}$NMR-spectra of [(**3**)$(AuCl)_2$]. a) Taken from the reaction mixture, b) after isolation of [(**3**)$(AuCl)_2$], measured in dmso-d_6, c) fraction of [(**3**)$(AuCl)_2$] soluble in $CHCl_3$ measured in $CDCl_3$ and d) the residue not soluble in $CHCl_3$ measured in dmso-d_6.

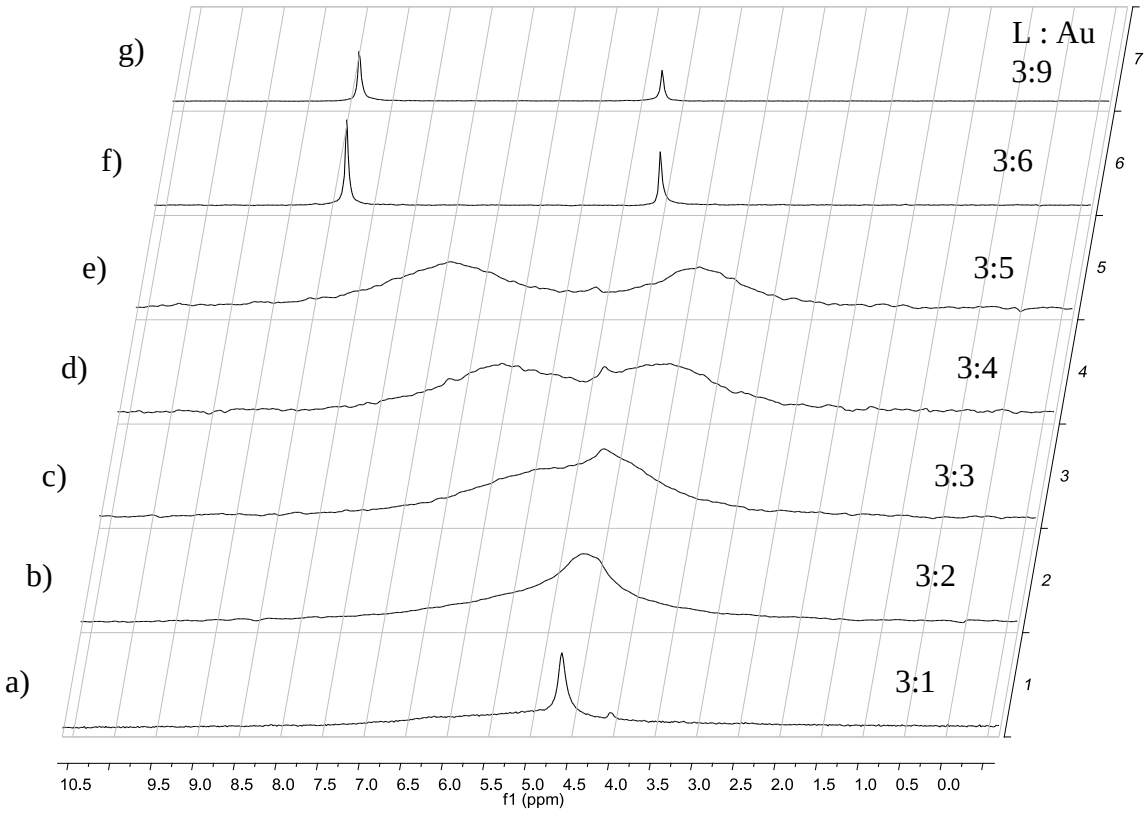

Figure ESI2. $^{31}P\{^{1}H\}$NMR-spectra of the NMR titration of **3** with [(tht)AuCl] in $CHCl_3$.

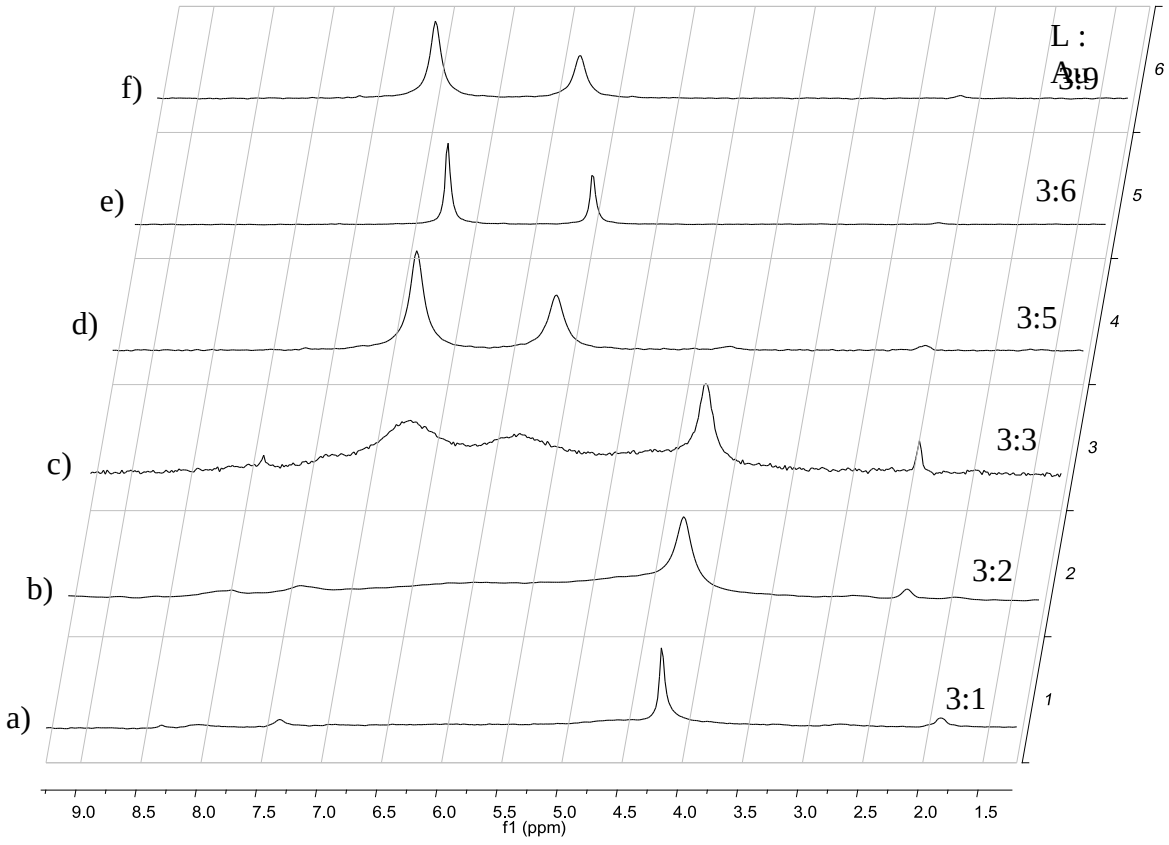

Figure ESI3. $^{31}P\{^{1}H\}$NMR-spectra of the NMR titration of **3** with [(tht)AuCl] in dmso-d_6.

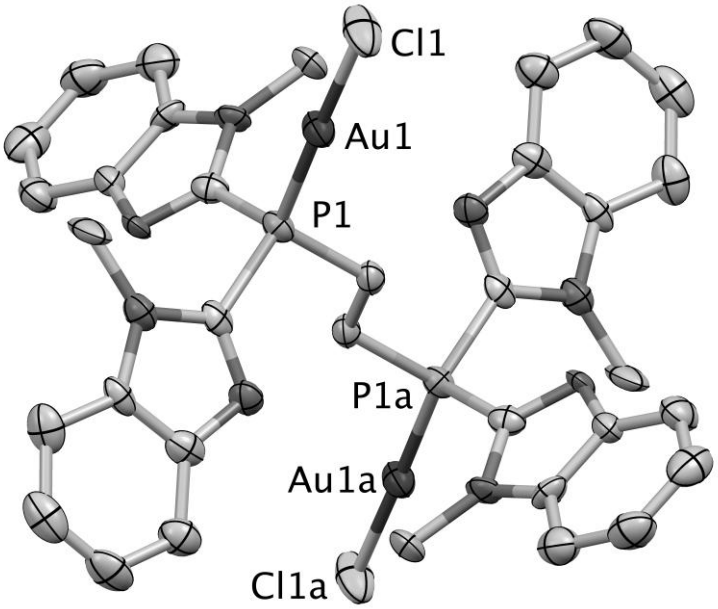

Figure ESI4. Molecular structure of [(**4**)$(AuCl)_2$]. Displacement ellipsoids are drawn at the 50 % level and H-atoms are omitted for clarity. Selected bond lengths [Å] and angles [°]: Au1–P1: 2.213(4), Au1–Cl1: 2.277(4), P1–Au1–Cl1: 178.62(13), P1–C1–C1a–P1a: 180.00.

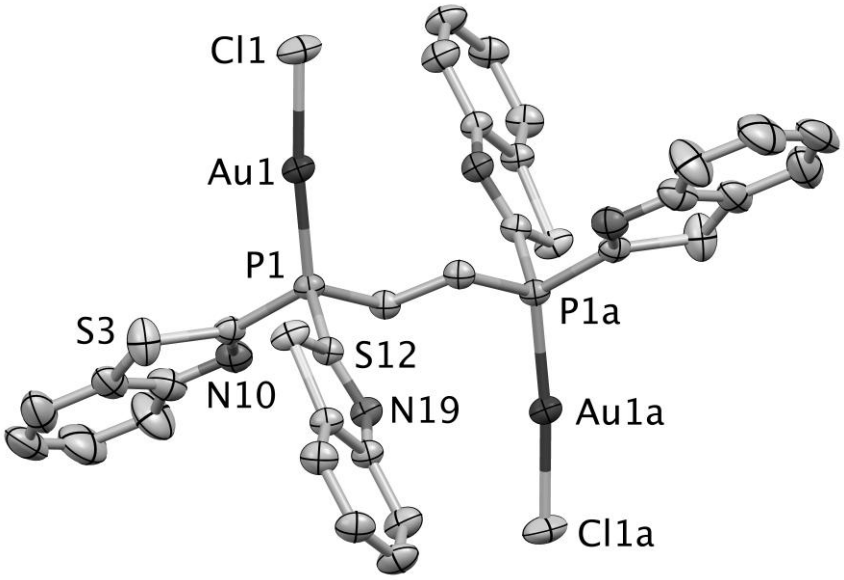

Figure ESI5. Molecular structure of [(**6**)$(AuCl)_2$]. Displacement ellipsoids are drawn at the 50 % level and H-atoms are omitted for clarity. Selected bond lengths [Å] and angles [°]: Au1–P1: 2.2143(10), Au1–Cl1: 2.2777(11), P1–Au1–Cl1: 174.05(4), P1–C–C–P1a: 180.00.

Table ESI1. X-ray data collection and refinement parameters for compounds [(**1**)$(AuCl)_2$], [(**3**)$(AuCl)_2$]•0.6EtOH•0.4CH_2Cl_2, [(**4**)$(AuCl)_2$], [(**6**)$(AuCl)_2$] and [(**3**)$_2$Au]PF_6.

	[(**1**)$(AuCl)_2$]	[(**3**)$(AuCl)_2$]·0.5EtOH ·0.4CH_2Cl_2	[(**4**)$(AuCl)_2$]	[(**6**)$(AuCl)_2$]·3(H_2O)	[(**3**)$_2$Au]PF_6
Empirical formula	$C_{18}H_{24}Au_2Cl_2N_8P_2$	$C_{23.5}H_{28.5}Au_2Cl_{2.8}N_4O_{0.5}P_2$	$C_{34}H_{32}Au_2Cl_2N_8P_2$	$C_{30}H_{26}Au_2Cl_2N_4O_3P_2S_4$	$C_{44}H_{48}AuF_6N_8P_5$
Formula weight	879.23	934.71	1079.45	1145.56	1154.72
Crystal system	Triclinic	Monoclinic	Triclinic	Triclinic	Triclinic
Space group	P-1	$P2_1$	P-1	P-1	P-1
a [Å]	7.7649(2)	10.94880(13)	9.6754(7)	8.0992(3)	11.5666(2)
b [Å]	9.3598(3)	12.37340(13)	11.3757(7)	9.9494(3)	12.5719(2)
c [Å]	9.7306(3)	11.42410(14)	12.1339(7)	11.4694(4)	16.9038(4)
α [°]	106.655(3)	90	103.894(5)	94.260(3)	77.1249(18)
β [°]	103.914(3)	97.4074(11)	108.377(6)	93.131(3)	81.4065(17)
γ [°]	100.648(3)	90	108.128(6)	97.282(3)	80.7994(15)
Volume [$Å^3$]	632.71(3)	1534.75(3)	1116.59(12)	912.32(5)	2348.83(8)
Z	1	2	1	1	2
Density (calc.) [Mg/m^3]	2.308	2.023	1.605	2.085	1.633
Absorp. coeff. [mm^{-1}]	11.941	9.935	6.783	8.532	3.368
Crystal size [mm^3]	0.19 x 0.14 x 0.03	0.64 x 0.09 x 0.02	0.15 x 0.07 x 0.02	0.17 x 0.10 x 0.04	0.24 x 0.14 x 0.04
Crystal description	colourless plate	colourless needle	colourless plate	colourless needle	colourless plate
Theta range for data collection [°]	2.30 to 30.51	2.76 to 30.51	2.20 to 27.10	2.54 to 33.14	2.61 to 30.51
Reflections collected	7398	46544	10910	15195	26468
Independent reflections	3836 [R(int) = 0.0277]	9360 [R(int) = 0.0674]	4930 [R(int) = 0.0586]	6962 [R(int) = 0.0279]	14316 [R(int) = 0.0382]
Reflections observed	3329	8417	2820	5537	9762
Completeness to theta	99.1 % to 30.51°	99.9 % to 30.51°	99.9 % to 27.10°	100.0 % to 33.14°	99.9 % to 30.51°
Max. and min. Transmission	0.7158 and 0.2646	0.8261 and 0.2292	0.8763 and 0.6921	0.7265 and 0.3943	0.8771 and 0.7495
Data / restraints / parameters	3836 / 0 / 147	9360 / 4 / 330	4930 / 0 / 219	6962 / 0 / 214	14316 / 1 / 616
Goodness-of-fit on F^2	1.052	1.034	0.947	1.029	0.904
Final R indices [I>2sigma(I)]	R1 = 0.0264, wR2 = 0.0693	R1 = 0.0324, wR2 = 0.0766	R1 = 0.0509, wR2 = 0.1401	R1 = 0.0331, wR2 = 0.0874	R1 = 0.0435, wR2 = 0.0743
Largest diff. peak and hole [$e.Å^{-3}$]	1.388 and -1.278	1.418 and -0.983	1.064 and -0.875	2.173 and -0.800	1.848 and -1.169

Table ESI2. pIC_{50} values (mean ± s.d.) of $[(L)_2Au]Cl$ and $[(L)(AuCl)_2]$ against human ovarian carcinoma cell lines sensitive (A2780 sens.) or resistant to cisplatin (A2780 cis.) (cisplatin as reference compound, n.a. = not available).

Ligand	$[(L)_2Au]X$		$[(L)(AuCl)_2]$	
	A2780 sens.	A2780 cis.	A2780 sens.	A2780 cis.
Cisplatin	5.88 ± 0.07	4.82 ± 0.04	5.88 ± 0.07	4.82 ± 0.04
1	4.54 ± 0.24	4.46 ± 0.22	4.52 ± 0.28	4.48 ± 0.18
2	4.67 ± 0.15	4.39 ± 0.15	4.62 ± 0.18	4.42 ± 0.21
3	6.40 ± 0.06	6.09 ± 0.13	6.24 ± 0.03	4.73 ± 0.11
4	n.a	n.a	5.63 ± 0.06	4.93 ± 0.07
5	6.35 ± 0.23	5.66 ± 0.89	5.58 ± 0.51	5.17 ± 0.05
6	n.a	n.a	5.21 ± 0.22	<4

Table ESI3. pIC_{50} values (µM, mean ± error) of $[(L)_2Au]^+$ against human leukaemia (K562) and rat hepatoma cell lines (H4IIE).

Compound	K 562	Hct116	H4IIE
Cisplatin	4.74 ± 0.05	1.54 ± 0.07	1.54 ± 0.02
$[(\mathbf{3})_2Au]PF_6$	< 4	1.33 ± 0.10	1.58 ± 0.06
$[(\mathbf{5})_2Au]Cl$	6.03 ± 0.05	1.04 ± 0.07	0.69 ± 0.07

Table ESI4. Inhibition of thioredoxin reductase (TrxR) and glutathione reductase (GR), mean ± error of the pIC_{50}-values of two separate experiments.

Compound	pIC_{50} (TrxR)/µM	pIC_{50} (GR)/µM
$[(\mathbf{1})_2Au]Cl$	6.86 ± 0.09	6.23 ± 0.06
$[(\mathbf{2})_2Au]Cl$	6.94 ± 0.02	5.95 ± 0.05
$[(\mathbf{3})_2Au]PF_6$	5.93 ± 0.11	5.37 ± 0.03
$[(\mathbf{5})_2Au]Cl$	6.85 ± 0.03	6.34 ± 0.05

Table ESI5. Relative activities of $[(L)_2Au]Cl$ and $[(L)(AuCl)_2]$ in relation to cisplatin ($IC_{50\ Cisplatin}$ / $IC_{50\ compound}$).

Ligand	$[(L)_2Au]X$		$[(L)(AuCl)_2]$	
	A2780 sens.	A2780 cis.	A2780 sens.	A2780 cis.
Cisplatin	1.000	1.000	1.000	1.000
1	0.046	0.387	0.044	0.407
2	0.061	0.325	0.055	0.354
3	**3.32**	**16.5**	**2.30**	0.713
4	n.a	n.a	0.564	1.14
5	**2.96**	**6.15**	0.502	**1.98**
6	n.a	n.a	0.202	n.a.