Synthesis and biological evaluation of gold(III) substituted tetraarylporphyrin chlorides as anticancer reagents

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Substituted gold(III) tetraarylporphyrins have been synthesised. The analogues TPPAuCl (TPP = tetraphenylporhyrin), MeOTPPAuCl, TMOPPAuCl, MeO_2CTPPAuCl, O_2NTPPAuCl and PyTPPAuCl were evaluated for their *in vitro* cytotoxic activity against the Sarcoma 180 mouse tumour cell line panel. Compound MeO_2CTPPAuCl exhibited good growth inhibitory properties against Sarcoma 180 and afforded IC_{50} values <3μM for 92.386% of the cell lines in the panel. Compounds MeOTPPAuCl and TPPAuCl were effective inhibitors of tumour cell growth, but generally less effective than MeO_2CTPPAuCl as cytotoxic agents.

Keywords: gold (III) substituted porphyrins, tetraaryl porphyrins, *in vitro* cytotoxicity

Considerable effort has been devoted to the search for new metal-containing anticancer drugs with preferential anticancer activity since the introduction of *cis*-diamminedichloroplatinum(II) (cisplatin) into clinical use.[1,2] However, although cisplatin and its analogues are better anticancer agents so far, the drug resistance and side effects of these agents still pose major problems in their clinical use.[3,4]

Considering that gold(III) possesses the same isoelectronic configuration (d^8) and structural (square planar) characteristics as platinum(II),[5–7] gold(III) complexes have been important in developing the field of metal-containing anticancer drug candidates recently.[8–11] Some studies showed that gold(III) compounds exhibit strong cytotoxic activity *in vitro* against tumour cells and have tumour-inhibiting properties *in vivo*.[12–15] However, it proved difficult to put many available gold(III) compounds into clinical use because these compounds exhibit poor solubility or are effective only at relatively high doses. Moreover, these compounds are usually unstable under physiological conditions, due to the reduction of gold(III) to gold(I). Based on the above reasons, the design and synthesis of gold(III) compounds with strongly chelating tetradentate ligands have been carried out. However, these gold(III) complexes have been found to be inactive towards cancer cells, presumably due to the over-stabilisation of gold(III) ions against reduction and demetalation. Messori and co-authors' report supported the above proposition in which a gold(III) complex of 1, 4, 8, 11-tetraazacyclotetradecane has poor cytotoxicity towards a series of cancer cells, and has IC_{50} values of >100 μM.[16] Consequently, a large number of modified tetradentate ligands have been synthesised which give chelate gold(III) complexes of sufficient stability in the physiological environment and they have been evaluated for *in vitro* anticancer properties. It has been found that low cisplatin cross resistance has been observed in gold complexes.[17–28] In particular, Che and co-workers prepared a series of gold(III) porphyrin compounds which behave as organic lipophilic cations with a planar structure, and are stable against demetallation under physiological conditions. Further *in vitro* and *in vivo* studies revealed that gold(III) porphyrin is a promising anticancer agent for the treatment of colon and liver cancer,[29–36] because the porphyrin ligand in these compounds can greatly stabilise the gold(III) centre, drastically reduce its redox reactivity and oxidising character, and carry the metal to the cellular targets. The use of gold(III) porphyrin complexes may provide an advantage for clinical application.

Researches on the mechanism of action of metal complexes indicate that the cytotoxic effects of metal complexes are the consequence of binding to DNA. The goal is to cause DNA damage specifically in cancer cells, leading to cell death. It is known that cisplatin exerts its anticancer effect through preferentially binding to quinine N-7 of cellular DNA.[37] Preliminary results about the action mechanism of gold(III) complexes suggest that gold(III) complexes directly interact with DNA as the basis for their cytotoxic effects.[38,39] But *in vivo* and *in vitro* binding assays showed that gold(III) porphyrin acted on DNA noncovalently, which was different to cisplatin. Che and co-workers' report showed that gold(III) porphyrin mediated mitochondrial transmembrane potential depletion, leading to cytochrome c release, nucleus translocation of apoptosis-inducing factor, and generation of reactive oxygen species.[30,32] However, their recent results addressed gold(III) porphyrin-induced phosphoproteome alterations and modulation of cell death by the mitogen-activated protein kinase family proteins. These results suggested that gold(III) porphyrin is a promising anticancer agent directed toward the mitochondria.[40]

Che and co-workers' studies demonstrated that a gold(III) modified porphyrin complex (5-hydroxyphenyl-10,15,20-triphenylporphyrinatogold(III) chloride), with improved aqueous stability, showed 100- to 3,000-fold higher cytotoxicity than platinum-based cisplatin and IC_{50} values in the nanomolar range in a panel of human breast cancer cell lines.[41] Thus the development of new modified porphyrin ligands chelating to gold(III) remains an active research area.

We therefore synthesised some new modified porphyrin ligands with substituted aryl groups to chelate gold(III) for pharmacological testing, and we compared the efficacy of these new gold(III) modified porphyrin complexes with that of cisplatin in suppressing tumour growth.

Experimental

All reagents and solvents were commercial available analytical grade and used as received except, when necessary, there was further purification and drying by standard methods and distillation prior to use. All evaporation of organic solvents was carried out with a rotary evaporator in conjunction with a water aspirator. Melting points were taken on a hot-plate microscope apparatus and are uncorrected. ^{1}H NMR spectra were recorded with a Bruker AV-600 spectrometer. IR spectra were obtained on a Bruker Tensor 27 spectrometer (KBr disc). UV-Vis spectra were obtained on a UV 2501 PC spectrometer. The MS spectra were obtained on a ZAB-HS mass spectrometer with 70 eV. 5, 10, 15, 20-tetraaryl porphyrins (**1–3**) were synthesised by the reported method.[42,43] Elemental analytical data were obtained using a model 240 elementary instrument. Mycoplasma-free newborn calf serum was purchased from Hangzhou Sijiqing Biological Engineering Materials Co., Ltd. Cisplatin (Cis) was the product of Jiangsu Hansen Pharmaceutical Co., Ltd. RPMI 1640, MTT and DMSO were purchased from Sigma-Aldrich Chemical Co.

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Sarcoma 180 mouse tumour cell line (S180) was purchased from Shanghai Institute of Cell Biology, Chinese Academy of Science. The cell line was cultured in RPMI 1640 medium with 10% newborn calf serum serum. It was maintained in a humidified incubator with an atmosphere of 95% air and 5% CO_2 at 37 °C. The cells were continuously passaged once every 3–4 days. Growing cells were collected for experiments.

Preparation 5,10,15-triphenyl-20-substitutedphenyl porphyrins **4–6**
A mixture of benzaldehyde (3.18 g, 30.0 mmol), substituted aromatic aldehyde (10.0 mmol) and freshly distilled pyrrole (2.68 g, 40.0 mmol) in propionic acid (140 mL) was refluxed for 3 h. After completion of the reaction was checked by TLC, the mixture was cooled in an ice-water bath, the crude product filtered and the filter cake was washed thoroughly with methanol (100 mL) then dichloromethane (10 mL). The resulting purple crystals were air dried, the crude product was purified by column chromatography (silica gel, DCM/n-hexane: 1/5 V/V), and recrystallisation from ethanol gave pure products **4–6**.

5-(p-Methoxycarbonylphenyl)-10,15,20-triphenyl porphyrin (**4**): M.p. > 250 °C; ^{1}H NMR ($CDCl_3$, 600 MHz), δ (ppm): –2.79 (s, 2H, inner-NH), 4.11 (s, 3H, –$COOCH_3$), 7.74–7.79 (m, 9H, Ph-CH), 8.21 (d, *J* = 6.6 Hz, 6H, Ph-CH), 8.31 (d, *J* = 7.8 Hz, 2H, Ph-CH), 8.44 (d, *J* = 7.8Hz, 2H, Ph-CH), 8.79 (d, *J* = 4.2 Hz, 2H, Por-CH), 8.85 (s, 6H, Por-CH_3); IR (KBr): υ 3442(s), 3319(w), 2924(w), 2853(w), 1812(m), 1722(s), 1604(w), 1472(w), 1437(w), 1394(w), 1353(w), 1279(s), 1182(w), 1106(w), 800(m), 739(w) cm^{-1}; UV-Vis(CH_2Cl_2)/nm 416, 513, 548, 589, 646. Anal. Calcd for $C_{46}H_{32}N_4O_2$: C, 82.12; H, 4.79; N, 8.33. Found: C, 82.04; H, 4.50; N, 8.62%.

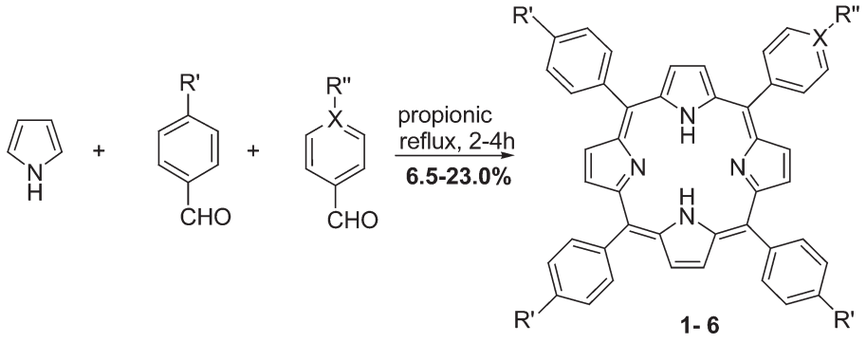
5-(p-Nitrophenyl)-10,15,20-triphenyl porphyrin (**5**): M.p. > 250 °C; ^{1}H NMR ($CDCl_3$, 600 MHz), δ (ppm): –2.79 (s, 2H, inner-NH), 7.75–7.81 (m, 9H, Ph-CH_3), 8.21 (d, *J* = 7.2Hz, 6H, Ph-CH), 8.40 (d, *J* = 8.4Hz, 2H, Ph-CH_3), 8.64 (d, *J* = 8.4Hz, 2H, Ph-CH_3), 8.74 (d, *J* = 4.2Hz, 2H, Por-CH), 8.86–8.90 (m, 6H, Por-CH_3); IR (KBr): υ 3446(s), 2918(w), 2850(w), 1596(w), 1517(w), 1472(w), 1392(w), 1345(m), 1073(w), 840(w), 798(m), 706(m) cm^{-1}; UV-Vis(CH_2Cl_2)/nm 418, 514, 549, 588, 645; Anal. Calcd for $C_{44}H_{29}N_5O_2$: C, 80.10; H, 4.43; N, 10.62. Found: C, 80.02; H, 4.68; N, 10.49%.

5-Pyrdinyl-10,15,20-triphenylporphyrin (**6**): M.p. > 250 °C; ^{1}H NMR ($CDCl_3$, 600 MHz), δ (ppm): –2.82 (s, 2H, inner-NH), 7.75–7.80 (m, 9H, Ph-CH_3), 8.17 (d, *J* = 5.4 Hz, 2H, Ph-CH), 8.21 (d, *J* = 6.6 Hz, 6H, Ph-CH_3), 8.79 (d, *J* = 4.2 Hz, 2H, Ph-CH_3), 8.86–8.90 (m, 6H, Por-CH_3), 9.03 (s, 2H, Por-CH_3); IR (KBr): υ 3446(s), 1634(w), 1590(w), 1473(w), 1396(w), 1351(w), 1070(w), 970(w), 798(m), 710(m), 657(w) cm^{-1}; UV-Vis(CH_2Cl_2)/nm 416, 513, 548, 586, 644. Calcd for $C_{43}H_{29}N_5$: C, 83.88; H, 4.75; N, 11.37. Found: C, 83.62; H, 4.61; N, 11.26%.

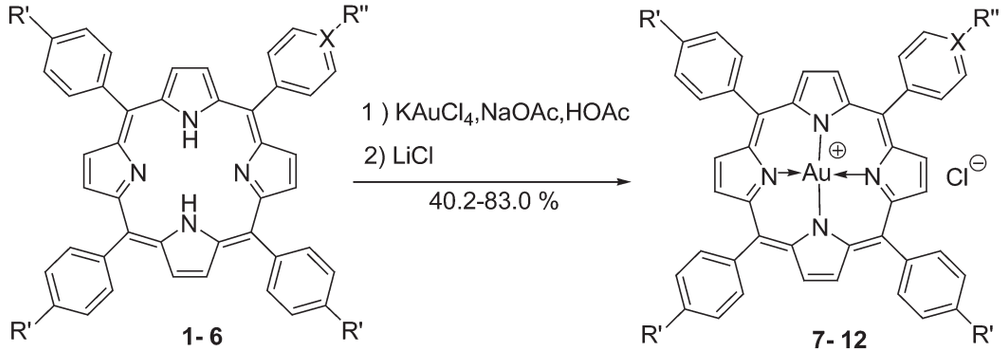
Preparation gold(III) substituted porphyrins **7–12**
A mixture of substituted porphyrin **1–6** (2.5 mmol), $K[AuCl_4]$ (2.82 g, 7.5 mmol) and sodium acetate (2.05 g, 25 mmol) in acetic acid (5 mL) was refluxed for 3 h. After completion of the reaction was checked by TLC, the crude product was obtained by removing acetic acid. Next the solid product was washed thoroughly with dichloromethane then water. The crude product then was purified by column chromatography (silica gel, DCM/methanol: 5/1 V/V). The purified product was dissolved in acetone, and after filtering the mixture solution was treated with LiCl in aqueous acetone. Analytically pure gold(III) porphyrin compounds **7–12** were obtained as chloride salts in 76–85% yields.

5,10,15,20-tetraphenylporphyrinato gold(III) chloride (**7**): M.p. 178–180 °C; ^{1}H NMR (600 MHz, $CDCl_3$), δ (ppm): 7.86 (d, *J* = 7.2Hz, 8H, Ph-CH), 7.89 (d, *J* = 7.2Hz, 4H, Ph-CH), 8.26 (d, *J* = 7.8Hz, 8H, Ph-CH_3), 9.26 (s, 8H, Por-CH_3). IR (KBr): υ 3428(s), 2924(w), 2858(w), 1630(w), 1448(w), 1368(w), 1080(w), 1029(w), 803(w), 757(w), 704(w) cm^{-1}; UV-Vis (CH_2Cl_2)/nm 408, 520; MS: 809.6 (M+1-Cl^-, 100%). Anal. Calcd for $C_{44}H_{28}N_4ClAu$: C, 62.53; H, 3.34; N, 6.63. Found: C, 62.48; H, 3.50; N, 6.68%.

5-p-Methoxyphenyl-10,15,20-triphenylporphyrinatogold(III) chloride (**8**): M.p. 156–158 °C; ^{1}H NMR (600 MHz, $CDCl_3$), δ (ppm): 4.13 (s, 3H), 7.40 (d, *J* = 8.4Hz, 2H), 7.86–7.92 (m, 9H), 8.16 (d, *J* = 8.4 Hz, 2H), 8.24 (d, *J* = 8.4 Hz, 6H), 9.28 (d, *J* = 7.2 Hz, 6H), 9.34 (d, *J* = 5.4 Hz, 2H); IR (KBr): υ 2922 (s), 2856 (w), 1737 (w), 1612 (w), 1453 (w), 1368 (w), 1251 (w), 1176 (w), 1081 (w), 1027 (w), 806 (w), 756 (w), 705 (w) cm^{-1}; UV-Vis (CH_2Cl_2)/nm 408, 520; MS: 839.9 (M+1-Cl^-, 100%). Anal. Calcd for $C_{45}H_{30}N_4OClAu$: C, 61.76; H, 3.46; N, 6.40. Found: C, 61.50; H, 3.58; N, 6.53%.



Scheme 1 Preparation of substituted porphyrin ligands **1–6**.



Scheme 2 Preparation of gold(III) substituted porphyrin ligands.

Table 1 Preparation of substituted porphyrins (**1-6**) and gold(III) porphyrins (**7–12**)

Entry	R′	R″	X	Ligands (yield/%)	Au (III) complexes (yield/%)
1	H	H	C	23.0 (**1**)	78.0 (**7**)
2	H	OCH_3	C	8.8 (**2**)	95.5 (**8**)
3	CO_2CH_3	CO_2CH_3	C	22.0 (**3**)	65.5 **(9)**
4	H	CO_2CH_3	C	9.0 (**4**)	83.0 (**10**)
5	H	NO_2	C	8.5 (**5**)	40.2 **(11)**
6	H		N	6.5 (**6**)	82.0 (**12**)

5,10,15,20-tetra-p-methoxycarbonylphenylporphyrinatogold(III) chloride (**9**): M.p. >250 °C; ^{1}H NMR (600 MHz, $CDCl_3$), δ (ppm): 4.13 (s, 12H, –$COOCH_3$), 8.36 (d, *J* = 7.8 Hz, 8H, Ph-CH), 8.52 (d, *J* = 7.8 Hz, 8H, Ph-CH), 9.18 (s, 8H, Por-$CH_,$; IR (KBr): υ 3433(m), 2923(m), 2856(w), 1717(s), 1609(w), 1436(w), 1278(s), 1185(w), 1107(m), 1024(m), 808(w), 762(w), 708(w) cm^{-1}; UV-Vis(CH_2Cl_2)/nm 408, 519; MS: 1041.8 (M+1-Cl^-, 100%). Anal. Calcd for $C_{52}H_{36}N_4O_8ClAu$: C, 57.98; H, 3.37; N, 5.20. Found: C, 57.80; H, 3.26; N, 5.46%.

5-(p-Methoxycarbonylphenyl)-10,15,20-triphenylporphyrinatogold(III) chloride (**10**): M.p. >250 °C; ^{1}H NMR ($CDCl_3$, 600 MHz), δ (ppm): 4.13 (s, 3H, –$COOCH_3$), 7.82–7.88 (m, 9H, Ph-$CH_,$), 8.30 (s, 6H, Ph-CH), 8.42 (d, *J* = 8.4 Hz, 2H, Ph-$CH_,$), 8.51 (d, *J* = 7.2 Hz, 2H, Ph-$CH_,$), 9.19 (s, 2H, Por-$CH_,$), 9.26–9.27 (m, 6H, Por-CH); IR (KBr): υ = 3414(w), 2921(s), 2852(m), 1737(w), 1601(w), 1498(w), 1460(w), 1357(w), 1242(m), 1176(w), 1079(w), 1026(m), 802(w), 756(w), 702(w) cm^{-1}; UV-Vis(CH_2Cl_2)/nm 410, 521; MS: 868.1 (M+1-Cl^-, 100%). Anal. Calcd for $C_{46}H_{30}N_4O_2ClAu$: C, 61.17; H, 3.35; N, 6.20. Found: C, 61.32; H, 3.60; N, 6.36%.

5-(p-Nitrophenyl)-10,15,20-triphenylporphyrinatogold(III) chloride (**11**): M.p. >250 °C; ^{1}H NMR ($CDCl_3$, 600 MHz), δ (ppm): 7.78–7.82 (m, 9H, Ph-CH), 8.18 (s, 6H, Ph-CH), 8.47 (s, 2H, Ph-CH), 8.65 (s, 2H, Ph-CH), 9.06 (s, 2H, Ph-CH), 9.18 (d, *J* = 8.4 Hz, 6H, Por-CH); IR (KBr): υ 3438(s), 2922(m), 2856(w), 1733(w), 1629(w), 1517(w), 1452(w), 1346(w), 1086(w), 1028(w), 803(w), 756(w), 703(w) cm^{-1}; UV-Vis(CH_2Cl_2)/nm 408, 520; MS: 855.1 (M+1-Cl^-, 100%). Anal. Calcd for $C_{44}H_{27}N_5O_2ClAu$: C, 59.37; H, 3.06; N, 7.87. Found: C, 59.22; H, 3.02; N, 7.92%.

5-pyridinyl-10,15,20-triphenylporphyrinato gold(III) chloride (**12**): M.p. > 250 °C; ^{1}H NMR ($CDCl_3$, 600 MHz), δ (ppm): 7.84–7.91 (m, 9H, Ph-CH), 8.25 (d, *J* = 7.8 Hz, 8H, Ph-CH), 9.14 (d, *J* = 4.2 Hz, 2H, Ph-CH), 9.18 (d, *J* = 5.4 Hz, 2H, Por-CH), 9.26 (s, 4H, Por-CH), 9.29 (s, 2H, Por-CH); IR (KBr): υ 3437(s), 2925(m), 2859(w), 1629(w), 1447(w), 1368(w), 1083(w), 1031(w), 804(w), 759(w), 706(w) cm^{-1}; UV-Vis(CH_2Cl_2)/nm 407, 519; MS: 811.2 (M+1-Cl^-, 100%). Anal. Calcd for $C_{43}H_{27}N_5ClAu$: C, 61.04; H, 3.22; N, 8.28. Found: C, 61.24; H, 3.18; N, 8.52%.

Cytotoxicity assay for gold(III) substituted tetraarylporphyrin chlorides of the effect on S180 cell proliferation: Gold(III) substituted tetraarylporphyrin chlorides were prepared at the concentrations 6.4×10^{-5} mol L^{-1}, 3.2×10^{-5} mol L^{-1}, 1.6×10^{-5} mol L^{-1}, 8×10^{-6} mol L^{-1}, 4×10^{-6} mol L^{-1} and 2×10^{-6} mol L^{-1} respectively. DMSO was used as latent solvent with the highest concentration less than 0.1% in solution of tetraarylporphyrin. The control groups of cisplatin, blank (1640)

Table 2 Cytotoxicity of gold(III) substituted tetra-arylporphyrin chloride against Sarcoma 180 mouse tumour cell line *in vitro*

Number	Symbol	Compound	Dose/μmol L^{-1}	Inhibition rate/%	IC_{50} /μmol L^{-1}
1	**7**	TPPAuCl	32	79.375	10.021
			16	62.344	
			8	43.594	
			4	27.344	
			2	12.031	
			1	5.313	
2	**8**	$TPPOCH_3AuCl$	32	74.112	5.571
			16	78.934	
			8	61.168	
			4	45.178	
			2	27.284	
			1	15.863	
3	**9**	TMOPPAuCl	32	25.781	133.613
			16	31.875	
			8	15.469	
			4	12.188	
			2	11.719	
			1	2.031	
4	**10**	$TPPCOOCH_3AuCl$	32	79.569	2.820
			16	92.386	
			8	88.579	
			4	50.888	
			2	32.487	
			1	31.218	
5	**11**	$TPPNO_2AuCl$	32	37.281	44.133
			16	23.197	
			8	17.398	
			4	2.632	
			2	0.292	
			1	0.000	
6	**12**	TPPPyAuCl	32	53.412	27.683
			16	43.763	
			8	25.480	
			4	16.045	
			2	11.354	
			1	6.557	
7	/	Cisplatin	32	60.501	16.453
			16	46.802	
			8	39.789	
			4	28.998	
			2	23.617	
			1	7.411	

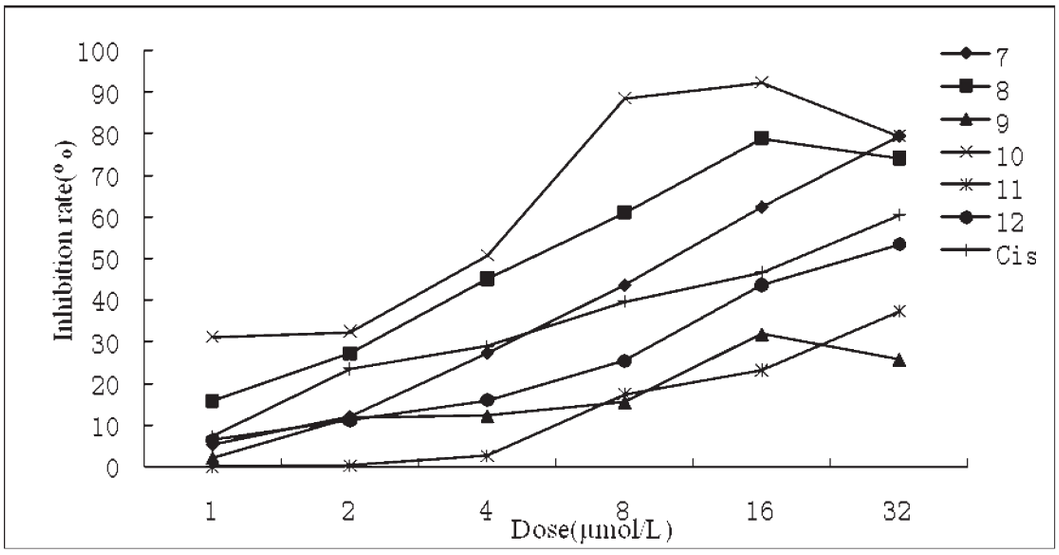


Fig. 1 Inhibition rate of gold(III) substituted tetra-aryl porphyrin chloride against Sarcoma 180 mouse tumour cell line *in vitro*.

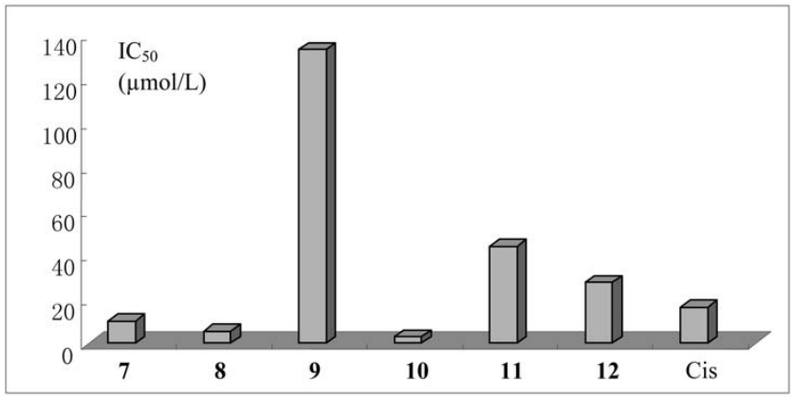


Fig. 2 IC_{50} of gold(III) substituted tetra-aryl porphyrin chloride against Sarcoma 180 mouse tumour cell line *in vitro*.

and DMSO solvent were set up at the same time. The cytotoxicity of gold(III) substituted tetraarylporphyrin chlorides was determined by MTT cytotoxic assay.[44] S180 cells were plated in 96-well plates at 1×10^5/mL and 100 μL/well in complete media. Then the prepared and various amounts of gold(III) substituted-tetraarylporphyrin chloride and cisplatin were plated in 96-well plates containing S180 cells and incubated commonly for 44 h. 100 μL of supernatant liquid was sucked from each hole, 10 μL of MTT (5 mg mL^{-1}) was added in and cultured for 4h; the media was then removed and hydrochloric acid/isopropanol at 100 μL/well was added. After spurging for 5 minutes using the micro oscillator to dissolve the MTT crystal, the OD value was measured at 570nm using a Model Elx 800 Autoplate reader (Bio-Tek Instruments, USA).

All the experimental data were compiled and analysed according to SPSS 15.0 software. Data were expressed as the mean ± SD.

Results and discussion

Schemes 1 and 2 show the synthetic routes to the target gold(III) substituted- tetraarylporphyrin in both the mono-substitutent and four-substituent series. Using reaction conditions similar to those reported previously,[42,43] the substituted porphyrin ligands **1–6** were prepared from the appropriate aromatic aldehydes and pyrrole (Scheme 1) in yield 6.5–23%. Gold(III) porphyrin compounds were synthesised by the treatment of $K[AuCl_4]$ with the porphyrin ligand in the presence of NaOAc in acetic acid. After purification by column chromatography and metathesis reaction with LiCl in aqueous acetone, the gold(III) porphyrin compounds were obtained as chloride salts in 40.2–95.5% yields.

The configuration change of the S180 cells was observed under the microscope. After the cells were seeded in 96-well plates, light, round and dense cells could be seen under the microscope. Drug effects were observed after 44h, showing that cells were significantly reduced from circular into spindle.

The anti-tumour effect of gold(III) substituted tetraarylporphyrin chloride: The results showed that compound **7**, **8** and **9** (1–32 μmol L^{-1}) exert a significant inhibitory effect on the growth of S180 cells, and compound **10** displays more prominent activity than lead compound **7** and cisplatin. Compounds **9**, **11** and **12** have a weaker inhibitory effect on S180 cells, IC_{50} values were more than 10 μ mol L^{-1}, while IC_{50} values of **8** and **10** were less than 10 μmol L^{-1}. (Table 2, Figs 1 and 2)

These results indicate that the gold atom located in the centre of the porphyrin ring has a major impact on the effect of the whole compound. If this atom were substituted by other metal atom such as copper (copper(II) tetraphenylporphyrin: IC_{50}(μmol L^{-1}) > 200), the anti-tumour activity *in vitro* would decrease notably. The gold(III) substituted porphyrin with a methoxycarbonyl- or methoxy-substituted group has greater anti- cancer activity than the lead compound TPPAuCl, which has potential for anti-tumour drugs. Thus, the gold(III) substituted porphyrin MeO_2CTPPAuCl is regarded as a useful lead compound for further structural optimisation, the anti-tumour mechanism of which will be studied in the future.

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