the highest σ selectivity is reached for log k_w values close to 2.

Experimental Section

Lipophilicity. The apparent lipophilicity of most compounds was measured at pH 7.5 by a RP-HPLC method previously described.[4] The method yields capacity factors extrapolated to 0% methanol, i.e. log k_w values that are taken as a direct measure of apparent lipophilicity.[11] Missing values were estimated from derived fragmental values and are given in parentheses.

Correction for ionization (to yield "true" lipophilicity) was not undertaken. Indeed, the compounds exist as neutral molecules, zwitterions, cations (N^+), and anions (O^-), suggesting complex ionization schemes. We have measured with previously described methods[12] the pK_a values of 3PPP. The two macroscopic pK_a values, 9.77 (± 0.08) and 9.33 (± 0.06), as obtained by potentiometry, could be attributed to the functional groups N and OH, respectively, by studying the UV spectra of 3PPP as a function of pH to establish the pK_a value of the phenolic group. The corresponding pK_a values of dopamine are 8.57 (N) and 10.08 (OH)[13] and for apomorphine 7.20 (N) and 8.92 (OH).[14]

In all correlation equations, the regression coefficients are reported together with their 95% confidence limits.

Acknowledgment. We thank Agneta Fougberg and Maria Lindbäck for performing most of the HPLC lipophilicity measurements. This study was supported by the Swiss National Science Foundation (Grant 3.539-0.83 to B.T. and H.v.d.W.).

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Antitumor Activity of Bis(diphenylphosphino)alkanes, Their Gold(I) Coordination Complexes, and Related Compounds[1]

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Bisphosphines related to bis(diphenylphosphino)ethane (dppe) and their gold complexes are described that are active in a spectrum of transplantable tumor models. When administered ip on days 1–5 at its maximally tolerated dose (MTD) of 40 μmol/kg, dppe reproducibly gives 100% increase in life span (ILS) in mice bearing ip P388 leukemia. Coordination of chlorogold(I) to each phosphine in dppe gave a complex that had similar activity but at a much lower dose level than dppe; the MTD for the gold(I) complex was 7 μmol/kg. Among other metal complexes of dppe, the Au(III) complex was active (>50% ILS) whereas Ag(I), Ni(II), Pt(II), Pd(II), and Rh(I) complexes were inactive. Among dppe analogues, replacement of phenyl groups with ethyl or benzyl groups resulted in inactivity for both ligands and the corresponding gold complexes whereas substitution with cyclohexyl or heterocyclic ring systems yielded ligands and/or gold complexes with antitumor activity. Among substituted-phenyl dppe and dppe$(AuCl)_2$ analogues, 3-fluoro, 4-fluoro, perdeuterio, 4-methylthio, and 2-methylthio analogues were active; 4-methyl, 3-methyl, 4-methoxy, 4-dimethylamino, and 4-trifluoromethyl analogues were marginal or inactive. Analogues in which the ethane bridge of dppe or dppe$(AuCl)_2$ was varied between one and six carbons, unsaturated or substituted, revealed that activity was maximal with ethane or *cis*-ethylene. Compounds with good P388 activity were also active in other animal tumor models.

There has been widespread interest in the potential antineoplastic activity of transition-metal complexes for the past decade following the serendipitous discovery of the antitumor activity of cisplatin in the late 1960s.[2] Cisplatin was developed to clinical trial on the basis of its activity in animal tumor models, primarily L1210 leukemia, P388 leukemia, and B16 melanoma. The drug has subsequently been shown to have a broad spectrum of activity in animal tumor models and in a number of human solid tumors, particularly in genitourinary carcinomas. On the basis of the activity of platinum complexes, other transition metal containing complexes have been investigated as potential antitumor agents. Rhodium and palladium complexes have been the most thoroughly evaluated, but none of the complexes of metals other than platinum has, to date, shown sufficient activity to warrant development to clinical trial.

Until recently, there has been minimal evaluation of gold complexes in animal tumor models. However, in 1981 Simon et al. reported that auranofin, (1-thio-β-D-glucopyranose 2,3,4,6-tetraacetato-*S*)(triethylphosphine)gold, a gold-containing complex used in the treatment of rheumatoid arthritis, possessed significant antitumor effects in animals bearing ip P388 leukemia.[3] We have subse-

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(1) Presented in part at the following: (a) Proceedings of the American Association of Cancer Research, Houston, TX, May 1985; Abstracts 1001, 1007, 1008. (b) Proceedings of the American Association for Cancer Research, Los Angeles, CA, May 1986; Abstracts 1114, 1115. (c) 190th National Meeting of the American Chemical Society, Chicago, IL, Sept 1985; paper MEDI 14. (d) 192nd National Meeting of the American Chemical Society, Anaheim, CA, Sept 1986; paper INORG 11.
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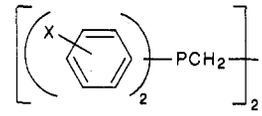
Table I. Synthetic Ligands[a]

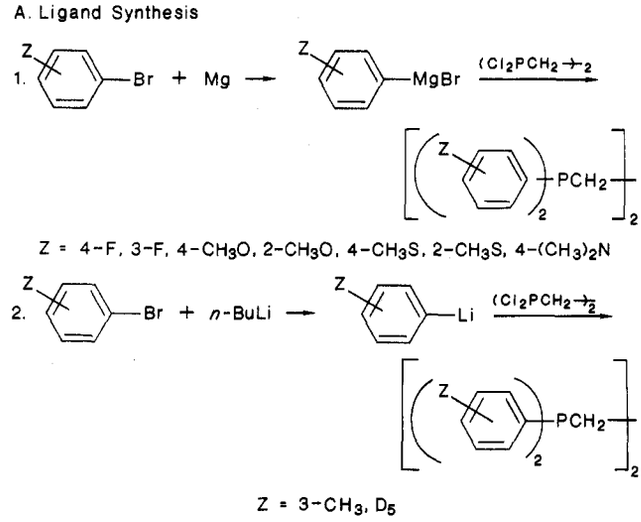


no.	X	formula[b]	mp, °C	% yield	recrystn solvent[c]	method
10	4-F	$C_{26}H_{20}F_4P_2$	129–130	77	A	1
11	3-F	$C_{26}H_{20}F_4P_2$	65–68	53	A	1
15	4-OH	$C_{26}H_{24}O_4P_2 \cdot 2H_2O$	168–171	11	D, F	*d*
13	3-CH_3	$C_{30}H_{32}P_2$	88.5–90.5	43	A	2
16	4-CH_3O	$C_{30}H_{32}O_4P_2$	108–110	76	B	1
17	2-CH_3O	$C_{30}H_{32}O_4P_2$	195–196.5	56	C	1
18	4-CH_3S	$C_{30}H_{32}P_2S_4$	147–148	48	A, D	1
19	2-CH_3S	$C_{30}H_{32}P_2S_4 \cdot 0.5H_2O$	213–216	40	A, D	1
20	4-$(CH_3)_2N$	$C_{34}H_{44}N_4P_2$	208–210	45	E	1
21	D_5	$C_{20}D_{20}H_4P_2$	139.5–140.5	47	A	2

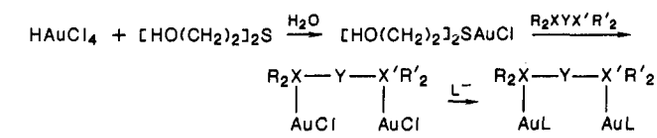
[a] All compounds gave IR and NMR spectra consistent with structures. [b] All compounds gave elemental analyses within ±0.4% of theoretical values. [c] Solvents: A = EtOH, B = *i*-PrOH, C = THF, D = $CHCl_3$, E = acetone, F = EtOAc. [d] See Experimental Section.

Scheme I

A. Ligand Synthesis



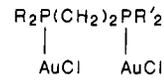
B. Gold Complexes (see Tables II–IV for symbols)



quently evaluated auranofin in a number of tumor models and have found no tumors other than P388 that respond to the drug.[4] In an attempt to identify other gold-containing complexes with in vivo antitumor activity, we evaluated a diverse spectrum of gold complexes and related ligands by utilizing several murine tumor models. These studies demonstrated that certain monophosphine gold(I) complexes, including (triethylphosphine)gold(I) thiolates (auranofin analogues), had activity in P388 leukemia.[5] However, like auranofin, the active compounds of this structural type were inactive in other tumor models.

In this paper we describe gold complexes of bisphosphines related to 1,2-bis(diphenylphosphino)ethane (dppe) that reproducibly demonstrate greater activity than auranofin in P388 leukemia and are active in other murine tumor models as well. Studies directed toward elucidation of the mechanism of action of representative compounds from this series suggest that these cytotoxic agents are mechanistically distinct from established antitumor drugs.[6-8]

Table II. Gold Complexes[a]



no.	R, R′	formula[b]	mp, °C	% yield	recrystn solvent[c]
1a	C_5H_5	$C_{26}H_{24}Au_2Cl_2P_2$	290–292	85	A, B
2a	CH_3CH_2	$C_{10}H_{24}Au_2Cl_2P_2$	165–168	64	B
3a	c-C_6H_{11}	$C_{26}H_{48}Au_2Cl_2P_2$	277–278	75	A, B
4a	$C_6H_5CH_2$	$C_{30}H_{32}Au_2Cl_2P_2$	231–232	33	C
5a	2-furyl	$C_{18}H_{16}Au_2Cl_2O_4P_2$	270–271	80	A, B
6a	2-thienyl	$C_{18}H_{16}Au_2Cl_2P_2S_4$	270–272	42	A, B
7a	2-pyridyl	$C_{22}H_{20}Au_2Cl_2N_4P_2$	292–293	41	B, D
7b[f]	2-pyridyl	$C_{34}H_{42}Au_2N_4O_{10}P_2S_2 \cdot 5H_2O$[e]	Am[d]	60	D, F
8a	4-pyridyl	$C_{22}H_{20}Au_2Cl_2N_4P_2$	241–242	45	C
9a	CH_3CH_2, C_6H_5	$C_{18}H_{24}Au_2Cl_2P_2$	186–187	57	A, E
10a	4-FC_6H_4	$C_{26}H_{20}Au_2Cl_2F_4P_2$	271–272	95	B, D
11a	2-FC_6H_4	$C_{26}H_{20}Au_2Cl_2F_4P_2 \cdot H_2O$	244–245	98	D, E
12a	4-$CH_3C_6H_4$	$C_{30}H_{32}Au_2Cl_2P_2$	228–230	78	A, E
13a	3-$CH_3C_6H_4$	$C_{30}H_{32}Au_2Cl_2P_2$	210–212	72	A, E
14a	4-$CF_3C_6H_4$	$C_{30}H_{20}Au_2Cl_2F_{12}P_2$	295–297	43	A, F
15a	4-HOC_6H_4	$C_{26}H_{24}Au_2Cl_2O_4P_2$	190–196	32	B, D
16a	4-$CH_3OC_6H_4$	$C_{30}H_{32}Au_2Cl_2O_4P_2 \cdot EtOH$	205–207	67	A, F
17a	2-$CH_3OC_6H_4$	$C_{30}H_{32}Au_2Cl_2O_4P_2$	278–280	87	–
18a	4-$CH_3SC_6H_4$	$C_{30}H_{32}Au_2Cl_2P_2S_4$[e]	221–222	35	A, E
19a	2-$CH_3SC_6H_4$	$C_{30}H_{32}Au_2Cl_2P_2S_4$	262–263	37	A, E
20a	4-$(CH_3)_2N$-C_6H_4	$C_{34}H_{44}Au_2Cl_2N_4P_2$	290–295	33	A, E
21a	C_6D_6	$C_{26}D_{20}H_4Au_2Cl_2P_2 \cdot DMF$	287–289	46	A, G

[a] All compounds exhibited IR and NMR spectra consistent with structures. [b] All compounds gave elemental analyses within ±0.4% of theoretical values except where noted. [c] Solvents: A = EtOH, B = CH_2Cl_2, C = CH_3CN, D = MeOH, E = $CHCl_3$, F = acetone, G = DMF, H = Et_2O, I = hexane, J = HOAc, K = H_2O. [d] Am = amorphous. [e] Calcd for **7b** H 4.11, found 3.48. Calcd for **18a** C 34.39, found 33.62. [f] Thioglucose analogue of **7a**.

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Table III. Gold Complexes[a]

$(C_6H_5)_2X-Y-X'(C_6H_5)_2$
$AuCl \quad AuCl$

no.	Y	X	formula[b]	mp, °C	% yield	recrystn solvent[c]
22a	–	P	*m*			
23a	CH_2	P	$C_{25}H_{22}Au_2Cl_2P_2$	271–273[e]	59	A, B
24a	*cis*-CH=CH	P	$C_{26}H_{22}Au_2Cl_2P_2$	240–242[f]	61	E, H
25a	*trans*-CH=CH	P	$C_{26}H_{22}Au_2Cl_2P_2$	262–264[g]	65	A, B
26a	C≡C	P	$C_{26}H_{20}Au_2Cl_2P_2$	260–261[h]	92	A, B
27a	$CH_2CH(CH_3)$	P	$C_{27}H_{26}Au_2Cl_2P_2$	Am (*R*, *S*)[d]	97	B, I
28a	$CH(CH_3)CH(CH_3)$	P	$C_{28}H_{28}Au_2Cl_2P_2$	269–271	49	D, B
29a	$(CH_2)_3$	P	$C_{27}H_{26}Au_2Cl_2P_2$	256–257[i]	92	A, B
30a	$(CH_2)_4$	P	$C_{28}H_{28}Au_2Cl_2P_2$	257–259	94	A, B
31a	$(CH_2)_5$	P	$C_{29}H_{30}Au_2Cl_2P_2$	94	56	A, B
32a	$(CH_2)_6$	P	$C_{30}H_{32}Au_2Cl_2P_2$	201–202[f]	90	B, H
33a	1,4-C_6H_4	P	$C_{30}H_{24}Au_2Cl_2P_2$[l]	>300	83	A, B
34a	1,2-C_6H_4	P	*m*			
35a	$(CH_2)_2$	P, As	$C_{26}H_{24}AsAu_2Cl_2P$	245	91	D, E
36a	$(CH_2)_2$	As	$C_{26}H_{24}As_2Au_2Cl_2$	216–217[j]	74	A, E
37a	$(CH_2)_2$	S	$C_{14}H_{14}Au_2Cl_2S_2$	148–149[k]	32	A

[a–d] See corresponding footnotes in Table II. [e] Reference 25, mp 273 °C. [f] Reference 26, melting point not reported. [g] Reference 27, mp 262–263 °C. [h] Reference 28, mp 262–265 °C. [i] Reference 29, mp 268 °C. [j] Reference 28, mp 221–224 °C. [k] Reference 30, melting point not reported. [l] Calcd for C 39.54, found 39.11. [m] Gold complexes not synthesized.

Table IV. Gold Complexes[a]

$(C_6H_5)_2P(CH_2)_2P(C_6H_5)_2$
$AuL \quad AuL$

no.	L	formula[b]	mp, °C	% yield	recrystn solvent[c]	$[\alpha]^{25}_D$ (1% MeOH)
39a	Cl_3	$C_{26}H_{24}Au_2Cl_6P_2$	192	72	E	
45a	Br	$C_{26}H_{24}Au_2Br_2P_2$	299–300[e]	82	F	
46a	$OCOCH_3$	$C_{30}H_{30}Au_2O_4P_2$	196–198	85	B, I	
48a[i]	Cl^-, $[(C_6H_5)_2PCH_2-]_2$	$C_{52}H_{48}Au_2Cl_2P_4$	298–302	41	E, H	
49a	SCN	$C_{28}H_{24}Au_2N_2P_2S_2$	247–248[f]	80	A, B	
50a	SCF_3	$C_{28}H_{24}Au_2F_6P_2S_2$	204–206	61	*g*	
51a	SCSOEt	$C_{32}H_{34}Au_2O_2P_2S_4$	158–159	79	B, I	
53a	$SCH_2CH(NH_2)CO_2Et$	$C_{36}H_{44}Au_2N_2O_4P_2S_2$[h]	Am[d]	76	*g*	
54a	SGlu	$C_{38}H_{46}Au_2O_{10}P_2S_2$	147–149	52	*g*	–3.2
55a	$SGluAc_4$	$C_{54}H_{62}Au_2O_{18}P_2S_2$	Am[d]	93	*g*	–67.6
56a	SeGlu	$C_{38}H_{46}Au_2O_{10}P_2Se_2$	130–135	69	J, K	10.7
57a	$SeGluAc_4$	$C_{54}H_{62}Au_2O_{18}P_2Se_2$	110–118	35	*g*	–52.7
58a	SGal	$C_{38}H_{46}Au_2O_{10}P_2S_2 \cdot 1.5H_2O$	Am[d]	13	D, H	3.9
59a	SMan	$C_{38}H_{46}Au_2O_{10}P_2S_2$	Am[d]	49	F	52.2
60a	$SManAc_4$	$C_{54}H_{62}Au_2O_{18}P_2S_2$	Am[d]	47	A	52.1
61a	$C{\equiv}CCH_2OH$	$C_{32}H_{30}Au_2O_2P_2$	179–181	17	B	

[a–d] See corresponding footnotes in Table II. [e] Reference 31, melting point not reported. [f] Reference 23, mp 228–230 °C. [g] Purified by chromatography; see Experimental Section. [h] Calcd for **53a** C 39.71, found 40.21. [i] Cyclic; 10-membered ring; ionic structure.

Table V. Triphos and Tetraphos Gold Complexes[a]

no.	structure	formula[b]	mp, °C	% yield	recrystn solvent[c]
62a	$[(C_6H_5)_2PCH_2CH_2]_2PC_6H_5$ (AuCl, AuCl)	$C_{34}H_{33}Au_3Cl_3P_3$	173–177	70	A, E
63a	$[(C_6H_5)_2PCH_2CH_2PCH_2]$ (AuCl, AuCl)	$C_{42}H_{42}Au_4Cl_4P_4$	184–186	94	B, I
64a	$[(C_6H_5)_2PCH_2CH_2]_3P$ (AuCl, AuCl)	$C_{42}H_{42}Au_4Cl_4P_4$	181–183	86	B, D
65a	$[(C_6H_5)_2PCH_2]_3CCH_3$ (AuCl)	$C_{41}H_{39}Au_3Cl_3P_3$	>190[d]	43	B, H

[a–c] See corresponding footnotes in Table II. [d] Reference 32, softens above 190 °C, melting point not reported.

Chemistry

Bisphosphine ligands and their gold complexes are described in Tables I–V. The non-gold transition metal dppe complexes were obtained from commerical sources (see Experimental Section), and their structures are shown in Table VII. An outline of the general syntheses of the bisphosphine gold complexes **1a–37a** and **45a–61a** is shown in Scheme I. The phosphine ligands were commercially available or, in the case of **10**, **11**, **13**, and **16–21**, prepared via coupling of an aryl Grignard reagent or aryllithium derivative with 1,2-bis(dichlorophosphino)ethane in a manner similar to published procedures.[9] The bis[gold(I)

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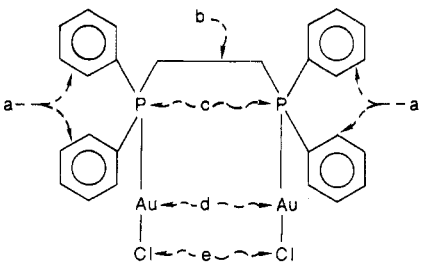
chlorides] **1a–37a** were formed via addition of a stoichiometric amount of ligand either in a solution or as a slurry to a solution of freshly prepared chloro(thiodiglycol)gold, $[HO(CH_2)_2]_2SAuCl$. The latter was formed by reducing chloroauric acid in water with excess thiodiglycol at 0 °C. This procedure, described earlier[10] for monophosphine gold complexes, presents several advantages over more traditional routes to gold(I) complexes.[11] First, it affords a water-soluble intermediate gold(I) complex as well as a water-soluble oxidation product ($[HO(CH_2)_2]_2SO$). Second, the phosphine or other appropriate ligand displaces the thiodiglycol, forming an insoluble chlorogold(I) complex, which precipitates from the reaction medium and drives the reaction to completion. This procedure thus facilitates product isolation. Lastly, the phosphine, frequently employed in excess as the reducing agent as well as the coordinating ligand, results in formation of unwanted phosphine oxide. Thus, the use of thiodiglycol to reduce gold conserves the phosphine ligand. This procedure works equally well in the synthesis of the arsenic, sulfur, triphos, and tetraphos complexes **35a–37a** and **62a–65a**.

Oxidation of **1a** to the trichlorogold(III) complex **39a** was accomplished by passing a stream of chlorine gas through a solution of **1a** in CH_2Cl_2. Although phosphines coordinate gold(III), the conditions for formation of these complexes frequently lead to reduction products. Nucleophilic substitution of chloride in **1a** with a variety of anionic species gave the complexes **45a–61a**. Of special note is the preparation of the SCF_3-substituted complex **50a** by metathesis of **1a** with $AgSCF_3$.[12] The latter compound is unique among silver thiolates because of its solubility in organic solvents. The thiosugar gold(I) complexes **54a**, **55a**, and **58a–60a** were made by direct displacement of the chloride in **1a** with a sodium thiosugar to give hydroxythiosugar gold complexes (**54a**, **58a**), by treatment of tetraacetyl-1-thioglucose plus K_2CO_3 to give **55a**, or by K_2CO_3 hydrolysis of an acetylated sugar thiouronium hydrobromide followed by displacement of the chloride to yield the acetylated thiosugar gold derivative (**60a**). Alternatively, NH_4OH hydrolysis of **60a** in methanol gave **59a**. This procedure was also used to make the selenium gold complex **56a** from the acetylated congener **57a**. The latter was prepared by K_2CO_3 hydrolysis of the selenouronium tetraacetylglucose hydrobromide[13] and then coupling with **1a**. The hydroxy compounds **54a**, **56a**, **58a**, and **59a** were made in an effort to increase solubility in polar delivery vehicles. The 2-pyridyl thioglucose gold complex **7b** appeared immediately soluble in water at ambient temperature.

Compound **61a**, the only complex with a gold–carbon bond, was synthesized by cuprous chloride catalyzed coupling of propargyl alcohol with **1a** in a manner similar to that for other gold alkyne complexes.[14] Lastly, **66a**, a gold–nitrogen bond complex, was prepared as described.[22]

Results and Discussion

A number of analogues of dppe and $dppe(AuCl)_2$ were made and evaluated in animal tumor models in order to identify compounds with adequate solubility and to maximize antitumor activity. The analogues of dppe-



$(AuCl)_2$ (**1a**) described in this paper represent modifications at five sites on the molecule: (a) substitution of hydrogen on the terminal phenyl groups or replacement of the terminal phenyl groups with alkyl or heterocyclic moieties; (b) modification of the ethane bridge; (c) replacement of one or both phosphorus atoms with arsenic or sulfur atoms; (d) replacement of Au(I) with other transition metals or deletion of the metal to give the free phosphines or phosphine oxides; or (e) substitution of other anions for chloride.

Initially, antitumor activity was assessed in mice bearing ip P388 leukemia. In most experiments, dppe (**1**) and $dppe(AuCl)_2$ (**1a**) were included in order to determine by comparison whether analogues showed improved activity. All compounds with appreciable antitumor activity were evaluated in at least two independent dose–response studies to obtain an accurate estimate of the maximally tolerated dose (MTD) and the degree and reproducibility of the antitumor effect. The criterion for activity was the maximum ILS achieved at a dose that was tolerated by the host animal. A compound was considered active if it reproducibly gave >50% increase in life span (ILS). In vivo dose–potency was measured by toxicity (i.e., lethality) and is defined by the MTD. In vitro potency is measured by cytotoxicity and is defined by the concentration that reduces clonogenicity of a cultured tumor cell line by 50%.

The antitumor activity of dppe and $dppe(AuCl)_2$ analogues modified in the terminal phenyl substituents is shown in Table VI. Compounds that met the criterion for activity include compounds with terminal substitutions such as phenyl (**1**, **1a**), perdeuteriophenyl (**21**, **21a**), cyclohexyl (**3**, **3a**), *p*-fluorophenyl (**10**, **10a**), *m*-fluorophenyl (**11**, **11a**), *p*-(methylthio)phenyl (**18**, **19a**), and *o*-(methylthio)phenyl (**19a**). In two instances, i.e., 2-furyl (**5**) and 2-thienyl (**6**), the ligand alone was active whereas the gold complex was inactive. In contrast, for 2-pyridyl-substituted (**7**) and *o*-methoxyphenyl-substituted congeners (**17**), the gold complexes (**7a**, **7b**, and **17a**, respectively) were active while the ligands were not. In general, ligands had lower dose–potency in vivo than their corresponding chlorogold(I) complexes. Several gold complexes, e.g., benzyl (**4a**), tolyl (**12a** and **13a**), and 2-thienyl (**6a**), showed greater dose–potency in vivo than $dppe(AuCl)_2$ (**1a**) and were potent cytotoxins in vitro, yet these congeners had no

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Table VI. Biological Evaluation of Dppe Analogues: Influence of Terminal Substitution (R, R'), Phosphine Linker Substitution (Y), and Phosphorus Replacement (X, X')

$R_2XYX'R_2$

					ligand		bis(chlorogold) complex	
no.[a]	R	Y	X	X'	MTD,[c] μmol/kg	P388 ILS_{max}[c]	MTD,[c] μmol/kg	P388 ILS_{max}[c]
1, 1a	C_6H_5	$(CH_2)_2$	P	P	50	107 ± 4	7	98 ± 4
2, 2a	CH_3CH_2	$(CH_2)_2$	P	P	310	neg[d]	60	neg
3, 3a	c-C_6H_{11}	$(CH_2)_2$	P	P	76	68, 80	18	60, 80
4, 4a	$C_6H_5CH_2$	$(CH_2)_2$	P	P	44	neg	4	neg
5, 5a	2-furyl	$(CH_2)_2$	P	P	180	60, 50	5	neg
6, 6a	2-thienyl	$(CH_2)_2$	P	P	38	60, 65	3	neg
7a, 7a,b[b]	2-pyridyl	$(CH_2)_2$	P	P	60	neg	7	55, 60
8, 8a	4-pyridyl	$(CH_2)_2$	P	P	80	35, 37	14	neg
9, 9a[h]	CH_3CH_2, C_6H_5	$(CH_2)_2$	P	P	>300[g]	neg	20	neg
10, 10a	4-FC_6H_4	$(CH_2)_2$	P	P	17	60, 55	9	80, 75
11, 11a	2-FC_6H_4	$(CH_2)_2$	P	P	68	45, 65	9	60, 55
12, 12a	4-$CH_3C_6H_4$	$(CH_2)_2$	P	P	26	neg	4	neg
13, 13a	3-$CH_3C_6H_4$	$(CH_2)_2$	P	P	70	neg	4	neg
14, 14a	4-$CF_3C_6H_4$	$(CH_2)_2$	P	P	48	38 ± 18	7	37, 44
15a	4-HOC_6H_4	$(CH_2)_2$	P	P		e	35	neg
16, 16a	4-$CH_3OC_6H_4$	$(CH_2)_2$	P	P	62	neg	8	neg
17, 17a	2-$CH_3OC_6H_4$	$(CH_2)_2$	P	P	120	neg	12	44, 79
18, 18a	4-$CH_3SC_6H_4$	$(CH_2)_2$	P	P	55	58, 35	8	37, 65
19, 19a	2-$CH_3SC_6H_4$	$(CH_2)_2$	P	P	110	51 ± 17	8	70 ± 28
20, 20a	4-$(CH_3)_2NC_6H_4$	$(CH_2)_2$	P	P	>220[g]	neg	8	neg
21, 21a	C_6D_5	$(CH_2)_2$	P	P	60	80, 95	7	40, 65
22	C_6H_5	-	P	P	320	neg		f
23, 23a	C_6H_5	CH_2	P	P	670	40, 40	59	65, 50
24, 24a	C_6H_5	*cis*-CH=CH	P	P	61	60, 70	5	105, 77
25, 25a	C_6H_5	*trans*-CH=CH	P	P	320	neg	28	33, 36
26, 26a	C_6H_5	C≡C	P	P	>300[g]	neg	37	neg
27, 27a	C_6H_5	$CH_2CH(CH_3)$	P	P	78	86 ± 7	7	43 ± 6
28, 28a	C_6H_5	$CH(CH_3)CH(CH_3)$	P	P	113	73, 40	7	44 ± 15
29, 29a	C_6H_5	$(CH_2)_3$	P	P	78	75, 65	7	62 ± 13
30, 30a	C_6H_5	$(CH_2)_4$	P	P	66	45, 55	7	40, 45
31, 31a	C_6H_5	$(CH_2)_5$	P	P	18	50, 40	4	55, 55
32, 32a	C_6H_5	$(CH_2)_6$	P	P	280	neg	4	40, 35
33, 3a	C_6H_5	1,4-C_6H_4	P	P	>600[g]	neg	26	neg
34	C_6H_5	1,2-C_6H_4	P	P	72	70, 55		f
35, 35a	C_6H_5	$(CH_2)_2$	P	As	89	neg	9	neg
36, 36a	C_6H_5	$(CH_2)_2$	As	As	82	neg	17	neg
37, 37a	C_6H_5	$(CH_2)_2$	S	S	1000	neg	90	neg

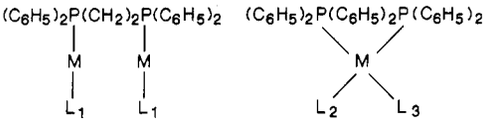
[a] Compound numbers followed by an **a** refer to bis(chlorogold) complexes whereas those without an **a** refer to the ligand only. [b] An analogue with this substitution pattern and thioglucose ligands in place of the chloride anions (i.e., compound **7b**) had an MTD of 13 μmol/kg and a P388 ILS_{max} of 65 ± 6. [c] Maximally tolerated dose in μmol/kg per day when administered ip on a daily × 5 treatment schedule beginning 24 h after tumor implantation. Maximum increase in life span (ILS equivalent to T/C × 100) produced in a dose–response of 4 or 5 dose levels of drug. ILS is the prolongation of median life span over that seen in control animals. Values separated by commas represent determinations from independent dose–response studies; for compounds that were evaluated three or more times, the ILS_{max} shown is the mean ± SE of the values obtained in all experiments in which an analogue was tested. Mice were inoculated up with 10^6 P388 leukemia cells, and antitumor activity was evaluated by established techniques.[33] [d] Negligible. A compound was considered to have negligible antitumor activity if it failed to produce >30% ILS in two experiments. [e] Ligand not evaluated. [f] Bis(chlorogold) complex was not prepared. [g] Inactive and nontoxic at highest dose level tested. [h] CH_3CH_2 on X, C_6H_5 on X'.

antitumor activity. These results suggest that there are definite structural requirements for antitumor activity at the terminal positions of the dppe molecule.

Data for ligands and chlorogold(I) complexes in which the bridge between the two phosphorus atoms was varied is also shown in Table VI. Antitumor activity was maximal when there was a two-carbon link between the phosphorus atoms. The flexible ethane-bridged (**1**, **1a**) and the *cis*-ethylene-bridged (**24**, **24a**) compounds were active, whereas the *trans*-ethylene-bridged (**25**, **25a**) and rigid ethyne-bridged (**26**, **26a**) compounds were inactive. Compounds with a methyl group on one or both of the ethane carbons had good activity as ligands (**27**, **28**), but the gold complexes (**27a**, **28a**) were only marginally active. Although dose–potency in vivo was not diminished by increasing the length of the bridge, antitumor activity was generally reduced. With bridge-modified congeners, it was again noted that certain analogues, i.e., **27a**, **28a**, and **30a**, had equivalent or greater dose–potency in vivo compared to **1a** yet had diminished antitumor activity. These results suggest that the phosphines should be in close proximity to each other to afford antitumor activity. X-ray crystallographic studies of **1a** have determined that the compound is capable of existing as two conformationally distinct pseudopolymorphs.[15] This suggests that freedom of rotation about the ethane bridge allows for adoption of different configurations including a conformation comparable to that observed for the *cis*-ethylene complex (**24a**). The importance of this conformational property to antitumor activity is supported by the fact that **1a** and **24a** showed equivalent in vivo activity whereas the *trans*-ethylene-substituted (**25a**) and ethyne-substituted complexes (**26a**) were inactive. This conformational requirement suggests a role for metal chelation in the antineoplastic mechanism of these compounds. Studies of the interaction of dppe and related bisphosphines with copper support this contention.[6]

Substitution of phosphorus with certain other coordinating atoms is feasible. Mixed phosphine–arsine (**35**, **35a**), bisarsine (**36**, **36a**), and bissulfide (**37**, **37a**) congeners were

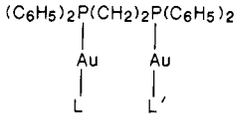
Table VII. Biological Evaluation of Dppe Analogues: Influence of Metals (M)



no.[a]	M	L_1	L_2	L_3	MTD,[b] μmol/kg	P388 ILS_{max}[b]
1	free phosphine				50	107 ± 4
38	phosphine oxide				300	neg[c]
1a	Au(I)	Cl			7	98 ± 4
39a	Au(III)	Cl_3			16	95, 62
40a	Ag(I)	NO_3			8	neg
41a	Pt(II)		Cl	Cl	24	neg
42a	Ni(II)		Cl	Cl	30	neg
43a	Pd(II)		Cl	Cl	35	neg
44a	Rh(I)		Cl	$P(C_6H_5)_3$	46	neg

[a-c] See footnotes *a*, *c*, and *d* of Table VI.

Table VIII. Biological Evaluation of Dppe Analogues: Influence of Ligand Trans to Phosphines



no.[a]	L	L′	MTD,[b] μmol/kg	P388 ILS_{max}[b]
1a	Cl	Cl	7	98 ± 4
45a	Br	Br	13	116, 80
46a	$OCOCH_3$	$OCOCH_3$	4	73, 64
47a	PEt_3	PEt_3, $2NO_3^-$	3	95, 70
48a	$-P(C_6H_5)_2CH_2CH_2P(C_6H_5)_2-$, $2Cl^-$		6	76 ± 11
49a	SCN	SCN	7	48 ± 8
50a	SCF_3	SCF_3	6	57 ± 15
51a	SCSOEt	SCSOEt	6	51 ± 13
52a	$SCSNEt_2$	$SCSNEt_2$	15	44, 50
53a	$SCH_2CH(NH_2)$-COOEt	$SCH_2CH(NH_2)$-COOEt	6	50, 56
54a	SGlu	SGlu	5	71 ± 25
55a	$SGlu(Ac)_4$	$SGlu(Ac)_4$	3	neg[c]
56a	SeGlu	SeGlu	5	neg
57a	$SeGlu(Ac)_4$	$SeGlu(Ac)_4$	4	neg
58a	SGal	SGal	3	111 ± 19
59a	SMan	SMan	5	90, 74
60a	$SMan(Ac)_4$	$SMan(Ac)_4$	3	neg
61a	$C{\equiv}CCH_2OH$	$C{=}CCH_2OH$	9	75, 61
66a	phthalimide	phthalimide	4	83, 74

[a-c] See footnotes *a*, *c*, and *d* of Table VI.

evaluated (Table VI). Substitution of one or both phosphorus atoms resulted in loss of antitumor activity for both the ligands and their chlorogold(I) complexes.

A number of other metal complexes of dppe were evaluated (Table VII). The gold(I) (**1a**) and gold(III) (**39a**) complexes were active whereas complexes with Ag(I) (**40a**), Pt(II) (**41a**), Ni(II) (**42a**), Pd(II) (**43a**), and Rh(I) (**44a**) were inactive. The phosphine oxide of dppe (**38**) was also inactive.

The nature of the substituent trans to the phosphine on gold(I) also influenced antitumor activity (Table VIII). Chloride (**1a**), bromide (**45a**), acetate (**46a**), and thioglucose (**54a**) ligands were active. None of the other ligands gave a complex with activity superior to **1a**. Whereas thiosugar ligands gave active complexes, the selenoglucose (**56a**) was inactive. This may be due to the higher affinity of gold(I) for selenium than for sulfur.[16] Whereas the thioglucose (**54a**) and thiomannose (**59a**) analogues were active, the corresponding acetylated thiosugar analogues (**55a**, **60a**) were inactive. These results are in contrast with those observed for compounds related to auranofin in which acetylated and deacetylated congeners had equivalent in vitro cytotoxic activity, in vivo dose–potency, and in vivo antitumor activity.[5]

Triphos and tetraphos ligands and their chlorogold(I) complexes were evaluated (Table IX). The triphos ligand (**62**) was active whereas its gold complex (**62a**) was marginal. The converse was demonstrated for linear tetraphos (**63**, **63a**). The thioglucosylgold(I) complex of tetraphos (**63b**) had activity similar to that of the chlorogold(I) congener (**63a**). Two branched phosphines had minimal antitumor activity either as ligands (**64**, **65**) or chlorogold(I) complexes (**64a**, **65a**).

Many of the bisphosphine ligands and gold complexes that were evaluated for antitumor activity in vivo were also evaluated for cytotoxicity against murine B16 melanoma cells in vitro by using a clonogenic assay (Table X). No relationship was found between cytotoxicity and antitumor activity in this class of compounds; many gold complexes devoid of antitumor activity were potent cytotoxic agents. A similar observation was made earlier with compounds related to auranofin.[5] However, in the present study, a number of bisphosphine ligands with excellent antitumor activity (e.g., **3**, **6**, **10**, **62**) did not demonstrate cytotoxicity in vitro at a concentration of 100 μM.

None of the evaluated analogues demonstrated a clear-cut superiority in activity over **1** and **1a**. In addition, for the vast majority of compounds tested, complexation of the bisphosphine ligands with gold (and other metals) increased their in vitro and in vivo dose–potency by 5–

Table IX. Biological Evaluation of Dppe Analogues: Comparative Activity of Multiphos Ligands and Their Chlorogold(I) Complexes

		ligand		chlorogold(I) complex[b]	
no.[a]	structure of ligand	MTD,[c] μmol/kg	P388 ILS_{max}[c]	MTD,[c] μmol/kg	P388 ILS_{max}[c]
1, 1a	$(C_6H_5)_2PCH_2CH_2P(C_6H_5)_2$	50	107 ± 4	7	98 ± 4
62, 62a	$(C_6H_5)P[CH_2CH_2P(C_6H_5)_2]_2$	60	80, 50	6	30, 40
63, 63a,b[d]	$[CH_2P(C_6H_5)CH_2CH_2P(C_6H_5)_2]_2$	95	neg[e]	8	72 ± 23
64, 64a	$P[CH_2CH_2P(C_6H_5)_2]_3$	95	35, 30	5	45, 45
65, 65a	$H_3CC[CH_2P(C_6H_5)_2]_3$	305	neg	15	40, 30

[a] See footnote *a* or Table VI. [b] Chlorogold coordinated to each phosphorus atom. [c] See footnote *c* of Table VI. [d] The complex with thioglucose ligands in place of chloride anions (i.e., compound **63b**) had an MTD of 4 μmol/kg of P388 ILS_{max} values of 100% and 55%. [e] See footnote *d* of Table VI.

Table X. Cytotoxicity of Dppe, Related Compounds, and Their Gold(I) Complexes against Murine B16 Melanoma Cells in Vitro[a]

ligands		metal complexes	
no.	IC_{50}, μM	no.	IC_{50}, μM
1	60	1a	8
2	>100	2a	17
3	>100	3a	14
4	>100	4a	4
5	>100	5a	17
6	>100	6a	6
7	>100	7a	4
9	>100	9a	2
10	>100	10a	8
11	>100	11a	6
12	>100	12a	3
13	>100	13a	7
16	66	16a	7
21	50	21a	8
22	>100		
23	>100	23a	6
24	25	24a	7
25	40	25a	10
26	23	26a	23
27	50	27a	4
28	50	28a	17
29	72	29a	2
30	>100	30a	3
31	>100	31a	2
32	>100	32a	2
33	>100	33a	13
34	28		
35	55	35a	4
36	>100	36a	7
37	>100	37a	30
38	>100		
		39a	4
		45a	4
		46a	6
		48a	3
		49a	4
		50a	30
		51a	70
		54a	2
		55a	3
		60a	5
62	>100	62a	5
63	67	63a	9
64	58	64a	10
65	50	65a	50

[a] Compounds were dissolved in DMSO and added to monolayer B16 melanoma cells in exponential growth for 2 h. Cells were washed and incubated for 5–7 days in fresh medium until visible colonies were evident. The IC_{50} was determined by interpolation to be the concentration that reduced colony-forming ability by 50%.

10-fold while, in most cases, not significantly altering in vivo antitumor activity. This increase in potency for the gold coordination complexes is an important consideration due to the limited aqueous solubility of this class of compounds. For example, the poor solubility and susceptibility to oxidation of **1** would preclude its formulation for parenteral use in clinical studies. Therefore, an objective of our synthetic strategy was to identify a gold complex that had significantly greater aqueous solubility while retaining the antitumor activity of **1**. Toward this end, congeners were synthesized in which the Cl was replaced with a variety of ligands. While the chlorogold(I) complex **1a** is virtually insoluble in water, the thioglucosylgold(I) and analogue, **54a**, is soluble at 0.5 mg/mL and has sufficient solubility in aqueous ethanol for parenteral formulation.

To determine the therapeutic potential of this class of compounds, dppe (**1**), dppe$(AuCl)_2$ (**1a**), and the thioglucose analogue (**54a**) were evaluated in a spectrum of transplantable murine tumors. As summarized in Table

Table XI. Spectrum of Activity of Compounds **1**, **1a**, and **54a** in Transplantable Murine Tumors[a]

tumor model	1	1a	54a
ip tumors			
P388 leukemia	++ 107 ± 4% ILS	++ 98 ± 4% ILS	++ 71 ± 25% ILS
M5076 reticulum cell sarcoma	++ 74 ± 8% ILS	++ 74 ± 10% ILS	++ 71 ± 21% ILS
B16 melanoma	+ 38 ± 7% ILS	+ 30 ± 11% ILS	+ 32% ILS
B16 melanoma-F10	–	–	–
Lewis lung carcinoma	++ 69% ILS	–	nt
Madison lung carcinoma	++ 50% ILS	–	nt
colon carcinoma 26	–	–	–
L1210 leukemia	++ 56% ILS	+ 33% ILS	nt
iv tumor			
P388 leukemia	–	–	–
sc tumors			
M5076 reticulum cell sarcoma	–	–	–
B16 melanoma	–	–	nt
Lewis lung carcinoma	–	–	nt
Madison lung carcinoma	–	–	nt
colon carcinoma 26	–	–	–
colon carcinoma 07/A	–	–	–
mammary carcinoma 13/c	–	–	–
mammary carcinoma 16/C	+ 88% TGI	++ 94% TGI	+ 87% TGI
ADJ-PC6 plasmacytoma	++ 94% TGI	++ 96% TGI	nt

[a] ++ indicates >50% increase in life span (ILS) in ip tumors and >90% tumor growth inhibition (TGI) in sc tumor models; + indicates >30% ILS in ip tumors and >75% TGI in sc tumors; – indicates >30% ILS in ip tumors and <75% TGI in sc tumors; nt = not tested. Values shown are means ± SEM at MTD from three or more experiments (values without SEM are optimal responses from single dose–response studies).

XI, dppe (**1**) demonstrated antitumor activity against ip L1210 leukemia, ip M5076 reticulum cell sarcoma, ip B16 melanoma, ip Lewis lung carcinoma, ip Madison lung carcinoma, and sc mammary carcinoma 16/c. The dppe–gold complexes **1a** and **54a** were active in three of the tumor models in addition to ip P388. Neither **1**, **1a**, nor **54a** had activity against systemic (iv-inoculated) P388 leukemia. This result is not unusual since other antitumor agents such as doxorubicin and actinomycin D, which are curative against ip P388, are devoid of activity against the iv implanted tumor model.[17,18]

Evaluation of dppe (**1**) for antitumor activity was reported previously.[19] In that report, dppe, formed as a byproduct of a reaction to synthesize an alkylating agent based on a (2-chloroethyl)phosphine, was reported to be cytotoxic in vitro, but was active in only one of two in vivo tests in sarcoma 180, was marginally effective in adenocarcinoma 755, and was inactive in Walker sarcoma 256 and L1210 leukemia. The in vivo dose levels of dppe (**1**) reported by these authors were invariably lethal in our studies. Since dppe is readily oxidized and dppe oxide (**38**) is devoid of antitumor activity and has low dose–potency, it is possible that the compound previously described may have been oxidized prior to evaluation. In all of our work with the compounds discussed in this paper, drugs were formulated immediately prior to administration to tumor-bearing animals.

In conclusion, bisphosphines related to dppe have antitumor activity in P388 leukemia and other murine tumor models. Complexation of dppe and related ligands to gold yields compounds with antitumor activity which are more

potent with respect to MTD in vivo and cytotoxicity in vitro. Complexation of dppe to transition metals other than gold (i.e., platinum, palladium, silver, nickel, rhodium) results in loss of antitumor activity. In a number of instances (e.g., **1a** vs **12a**, **13a**, **16a**, or **35a**; **54a** vs **55a**), minor structural modifications result in complete loss of antitumor activity yet the inactive compounds retain potent cytotoxic activity in vitro and have a similar quantitative toxicity profile in vivo, i.e., an MTD similar to that of active analogues.

Experimental Section

Melting points were determined in open glass capillaries with a Thomas-Hoover melting point apparatus and are uncorrected. NMR and IR spectra of all new compounds were consistent with assigned structures. Optical rotations were measured by using a Perkin-Elmer Model 241C polarimeter. Preparative high-pressure liquid chromatography (HPLC) (**54a**, **55a**, **58a**) was carried out on a Waters Prep 500 chromatograph.

Preparation of Complexes. Materials: Ligands. The phosphine ligands **1–4**, **9**, **12**, **14**, **22**, **23**, **26–36**, and **62–65** were purchased from Strem Chemicals, Inc., Newburyport, MA 01950. The *cis*- and *trans*-ethylene ligands **24** and **25** were bought from Organometallics, Inc., East Hampstead, NH 03826. Parish Chemical Co., Ovem, UT 84057, supplied the sulfide **37**, and Alfa Products, Danvers, MA 01923, was the source of the phosphine oxide **38**. The heterocyclic ligands **5–8** were synthesized by coupling the appropriate heterocycloorganometallic with 1,2-bis(dichlorophosphino)ethane as described.[20]

Ligands: Synthesis. The syntheses of all phosphine ligands were carried out under an argon atmosphere with appropriately dried solvents (Et_2O, THF), and the ligands are listed in Table I. Mg turnings were activated by covering with solvent and adding both I_2 and 1,2-dibromoethane together. 1,2-Bis(dichlorophosphino)ethane was purchased from Strem Chemicals, and the aryl halides employed in making the aryl organometallic reagents were bought from Aldrich Chemical Co., Inc., Milwaukee, WI 53233.

Method 1. 1,2-Bis[bis(4-fluorophenyl)phosphino]ethane (10). 4-Bromofluorobenzene (12 g, 68.5 mmol) in THF (100 mL) was added dropwise to Mg (1.68 g, 69.1 mmol) in THF (10 mL) while the temperature was maintained at 30–40 °C. After being stirred for 2 h, the reaction mixture was cooled to −80 °C and 1,2-bis(dichlorophosphino)ethane (dcpe) (2.65 g, 11.4 mmol) in THF (40 mL) was added over 40 min. The mixture was allowed to warm to ambient temperature overnight and quenched with saturated aqueous NH_4Cl, the organic layer was separated, and the volatiles were removed at reduced pressure. The residue was extracted with EtOAc, the extracts were dried ($MgSO_4$), and the solvent was removed at reduced pressure to give a white solid. Recrystallization from EtOH gave 4.13 g (77%) of **10**; mp 129–130 °C. Anal. ($C_{26}H_{20}F_4P_2$) C, H.

Method 2. 1,2-Bis[bis(3-methylphenyl)phosphino]ethane (13). 3-Bromotoluene (17.1 g, 0.1 mol) in Et_2O (100 mL) was added dropwise over 45 min to 36.5 mL (0.095 mol) of a 2.6 M solution of *n*-BuLi in hexane. The mixture was allowed to warm to ambient temperature, stirred for 1 h, and then cooled to 0 °C. Dcpe (4.63 g, 0.02 mol) in Et_2O (50 mL) was added over 15 min. The mixture was allowed to warm to ambient temperature over 1 h, cooled to 0 °C, and quenched with saturated aqueous NH_4Cl (100 mL). The Et_2O layer was separated and dried ($MgSO_4$) and the solvent removed at reduced pressure to give 13.5 g of pale yellow oil. Crystallization from cold EtOH gave 3.9 g (43%) of **13** as a white solid; mp 88.5–90.5 °C. An analytical sample from EtOH had mp 91–92.5 °C. Anal. ($C_{30}H_{32}P_2$) C, H, P.

1,2-Bis[bis(4-hydroxyphenyl)phosphino]ethane (15). A mixture of **16** (4.1 g, 7.9 mmol) and 48% HBr (35 mL) was refluxed overnight, cooled, and the precipitate collected. Recrystallization from MeOH gave 1.4 g of material. Analytical TLC revealed the presence of several components. Recrystallization from 2-propanol gave 0.8 g of brown solid. This was dissolved in 5% $NaHCO_3$ (50 mL), extracted with EtOAc, dried ($MgSO_4$), and the solvent removed to give 0.6 g of glassy, white material. Dissolving in EtOAc and drying (Na_2SO_4) gave 0.4 g (11%) of **15**. Chromatography (silica gel, 1:2 EtOAc/$CHCl_3$) gave an analytical sample, mp 168–171 °C as a dihydrate. Anal. ($C_{26}H_{24}O_4P_2 \cdot 2H_2O$) C, H, P.

Metal Complexes. The Pt–dppe complex **41a** was obtained from Aesar, Johnson Matthey, Inc., Seabrook, NH 03874; the Ni complex **42a** was purchased from Strem Chemicals; the Pd complex **43a** was bought from Alfa Products; the Rh complex **44a** and the Au complexes **47a** and **52a** were supplied by Johnson Matthey, Inc., West Chester, PA 19380. The $AgNO_3$–dppe complex **40a** was prepared as described.[21]

Gold Complexes. The dppe bis(gold phthalimide) complex **66a** was made as described.[22]

Diphosphine Bisgold(I) Chloride Synthesis. General Method: [μ-1,2-Bis(diphenylphosphino)ethane]bis[chlorogold(I)] (1a). Thiodiglycol (11.0 g, 0.09 mol) in MeOH (50 mL) was added over 15 min to a solution of $HAuCl_4 \cdot (H_2O)_4$ (12.4 g, 0.03 mol) in H_2O (100 mL)/MeOH (150 mL) kept at 0 °C. After the mixture was stirred for an additional 15 min, dppe (1) (6.12 g, 15 mmol) in $CHCl_3$ (100 mL)/MeOH (100 mL) was added to the colorless solution, yielding an immediate precipitate. After the mixture was warmed to ambient temperature (2 h), MeOH (0.5 L) was added and the product collected, slurried with CH_2Cl_2/EtOH, filtered, and dried to give 11.0 g (85%) of **1a**; mp 290–292 °C (lit.[11] mp 291 °C).

Note: The above general procedure was used to prepare *all* the chlorogold(I) complexes listed in Tables II–V. The insoluble ligands were added as slurries and the reaction mixtures stirred overnight.

[μ-1,2-Bis(diphenylphosphino)ethane]bis[trichlorogold(III)] (39a). Chlorine gas was bubbled through a solution of **1a** (0.9 g, 1.04 mmol) in $CHCl_3$ (100 mL) for 0.5 h at ambient temperature. After an additional 0.5 h, the product was collected, washed with $CHCl_3$, and dried to give 0.76 g (72%) of **39a**; mp 192 °C dec. Anal. ($C_{26}H_{24}Au_2Cl_6P_2$) C, H.

[μ-1,2-Bis(diphenylphosphino)ethane]bis[bromogold(I)] (45a). A mixture of **1a** (0.86 g, 1 mmol), NaBr (1.03 g, 10 mmol) in DMF (33 mL), and H_2O (10 mL) was stirred for 24 h at ambient temperature (precipitate formed). H_2O (100 mL) was added and the mixture filtered. The collected solid was washed with H_2O, slurried with acetone, and dried to give 0.78 g (82%) of **45a**; mp 299–300 °C. Anal. ($C_{26}H_{24}Au_2Br_2P_2$) C, H, Br.

[μ-1,2-Bis(diphenylphosphino)ethane]bis[acetatogold(I)] (46a). A mixture of **1a** (0.38 g, 0.44 mmol) and silver acetate (0.32 g, 1.9 mmol) in CH_2Cl_2 (25 mL) was stirred overnight at ambient temperature. The precipitate was collected and the solvent removed in vacuo. Crystallization of the residue from CH_2Cl_2/hexane gave 0.34 g (84%) of **46a**; mp 196–198 °C. Anal. ($C_{30}H_{30}Au_2O_4P_2$) C, H.

Dichlorobis[μ-1,2-bis(diphenylphosphino)ethane]digold(I) (48a). A solution of dppe (1) (2.32 g, 5.8 mmol) in $CHCl_3$ (100 mL) was added to a slurry of **1a** (5.0 g, 5.8 mmol) in $CHCl_3$ (0.5 L) maintained at ambient temperature. After 45 min, the mixture became homogeneous, and the solvent was removed in vacuo. The residue was dissolved in a minimum amount of $CHCl_3$ and anhydrous Et_2O added. After cooling, the precipitate was collected and dried to give 3.0 g (41%) of **48a**; mp 298–302 °C. Anal. ($C_{52}H_{48}Au_2Cl_2P_4$) C, H, Cl, P.

[μ-1,2-Bis(diphenylphosphino)ethane]bis[thiocyanatogold(I)] (49a). A mixture of **1a** (1.0 g, 12 mmol) and NaSCN (1.2 g, 15 mmol) in H_2O (50 mL), DMF (20 mL), and $CHCl_3$ (100 mL) was stirred overnight at ambient temperature. The mixture was poured into H_2O (400 mL), the layers were separated, and the aqueous phase was extracted with $CHCl_3$. The combined extracts were washed with H_2O and dried ($MgSO_4$), and the solvent was removed in vacuo. CH_2Cl_2 and EtOH were added, and the solution was cooled to −20 °C. The product was collected and recrystallized (CH_2Cl_2/EtOH) to give 0.83 g (80%) of **49a**; mp 247–248 °C (lit.[23] mp 228–230 °C). Anal. ($C_{28}H_{24}Au_2N_2P_2S_2$) C, H, N.

[μ-1,2-Bis(diphenylphosphino)ethane]bis[[(trifluoromethyl)thio]gold(I)] (50a). $AgSCF_3$[12] (1.45 g, 6.96 mmol) in CH_3CN (200 mL) was added dropwise to a suspension of **1a** (3.0 g, 3.48 mmol) in $CHCl_3$ (500 mL) and the mixture stirred for 48 h at ambient temperature. The precipitate was collected, the

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solvent removed in vacuo, and the residue chromatographed (silica gel, $CHCl_3$) to give 2.1 g (61%) of **50**; mp 204–206 °C. Anal. ($C_{28}H_{24}Au_2F_6P_2S_2$) C, H.

[μ-1,2-Bis(diphenylphosphino)ethane]bis[(*O*-ethyldithiocarbonato)gold(I)] (51a). A mixture of **1a** (1.0 g, 1.2 mmol) and KS_2COEt (1.3 g, 8.1 mmol) in $CHCl_3$ (50 mL)/EtOH (75 mL) was stirred overnight at ambient temperature. The solvent was removed in vacuo, the residue dissolved in $CHCl_3$, washed with H_2O, and dried (Na_2SO_4), and the solvent removed. The residue was slurried with EtOH and the insoluble material recrystallized from CH_2Cl_2/hexane to give 0.95 g (79%) of **51a**; mp 158–159 °C. Anal. ($C_{32}H_{34}Au_2O_2P_2S_4$) C, H.

[μ-1,2-Bis(diphenylphosphino)ethane]bis[[(L-2-amino-2-carbethoxyethyl)thio]gold(I)] (53a). NaOH (0.186 g, 4.64 mmol) in EtOH (50 mL)/H_2O (5 mL) was added to L-cysteine ethyl ester hydrochloride (0.43 g, 2.32 mmol) in EtOH (45 mL) and the mixture stirred for 15 min. A slurry of **1a** (1.0 g, 1.16 mmol) in $CHCl_3$ (75 mL) was added and the mixture stirred for 2 h. The solvent was removed in vacuo, the residue dissolved in $CHCl_3$, washed with H_2O, and dried ($MgSO_4$), and the solvent removed in vacuo. Chromatography (SiO_2, CH_2Cl_2/2% Et_2NH) of the residue gave 0.96 g (75%) of **53a** as an amorphous solid. Anal. ($C_{36}H_{44}Au_2N_2O_4P_2S_2$) C, H, N.

[μ-1,2-Bis(diphenylphosphino)ethane]bis[(1-thio-β-D-glucopyranosato-*S*)gold(I)] (54a). A solution of **1a** (5.0 g, 5.8 mmol) in $CHCl_3$ (500 mL)/EtOH (200 mL) was added to a rapidly stirred solution of sodium thioglucose (2.53 g, 11.6 mmol) (Sigma Chemical Co., St. Louis, MO 63178) in H_2O (100 mL)/EtOH (300 mL). After 72 h, the solvent was removed in vacuo. Preparative HPLC (silica gel, 15% MeOH/CH_2Cl_2) of the residue gave 3.57 g (52%) of **54a** as an amorphous solid: mp 130 °C; $[\alpha]^{25}$ −3.6° (1% CH_3OH). Anal. ($C_{38}H_{46}Au_2O_{10}P_2S_2$) C, H.

[μ-1,2-Bis(diphenylphosphino)ethane]bis[(2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranosato-*S*)gold(I)] (55a). A solution of **1a** (1.0 g, 1.16 mmol) in CH_2Cl_2 (100 mL) was added dropwise to a solution of K_2CO_3 (0.32 g, 2.32 mmol) and 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranose (0.84 g, 2.32 mmol) (Aldrich) in H_2O (40 mL)/EtOH (150 mL) followed by additional $CHCl_3$ (50 mL)/EtOH (50 mL). After 1 h, the solvent was removed in vacuo, the residue dissolved in $CHCl_3$ and washed with H_2O (2×), the organic layer dried ($MgSO_4$), and the solvent removed in vacuo. Preparative HPLC (silica gel, 20% EtOAc/$CHCl_3$) of the residue gave 1.6 g (91%) of **55a** as a white amorphous solid; $[\alpha]^{25}$ −67.6° (1% CH_3OH). Anal. ($C_{54}H_{62}Au_2O_{18}P_2S_2$) C, H.

[μ-1,2-Bis(diphenylphosphino)ethane]bis[(1-seleno-β-D-glucopyranosato-*Se*)gold(I)] (56a). A mixture of **57a** (0.71 g, 0.44 mmol) and sodium methoxide (0.05 g, 0.92 mmol) in MeOH (40 mL) was stirred at ambient temperature for 3 h (TLC showed disappearance of **57a**) and then quenched by the addition of glacial acetic acid (0.053 mL). The colorless solution was concentrated under reduced pressure. The solid residue was washed repeatedly with H_2O, collected, and dried in vacuo to give 0.39 g (69%) of **56a** as a pale yellow solid: mp 130–135 °C; $[\alpha]^{25}$ 10.65° (0.87% CH_3OH). Anal. ($C_{38}H_{46}Au_2O_{10}P_2Se_2$) C, H.

[μ-1,2-Bis(diphenylphosphino)ethane]bis[(2,3,4,6-tetra-*O*-acetyl-1-seleno-β-D-glucopyranosato-*Se*)gold(I)] (57a). A solution of K_2CO_3 (0.69 g, 5 mmol) in H_2O (3 mL) was added to a solution of (2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)selenoisourea hydrobromide[13] (2.78 g, 5.2 mmol) in 1:1 H_2O/MeOH (100 mL) kept at 0 °C (salt forms as a precipitate). After the mixture was stirred for 0.5 h, a solution of **1a** (2.16 g, 2.5 mmol) in $CHCl_3$ (150 mL) was added. After 1 h, the $CHCl_3$ layer was separated and the solvent removed in vacuo. Flash chromatography of the residue (silica gel, 1:1 EtOAc/$CHCl_3$) gave 1.4 g (35%) of **57a** as an amorphous solid: mp 110–118 °C; $[\alpha]^{25}$ −52.5° (1% CH_3OH). Anal. ($C_{54}H_{62}Au_2O_{18}P_2Se_2$) C, H.

[μ-1,2-Bis(diphenylphosphino)ethane]bis[(1-thio-β-D-galactopyranosato-*S*)gold(I)] (58a). A mixture of sodium thiogalactose (1.25 g, 5.4 mmol) (Sigma) and **1a** (2.35 g, 2.72 mmol) in EtOH (150 mL)/H_2O (20 mL)/$CHCl_3$ (200 mL) was stirred for 18 h at ambient temperature. The solvent was removed in vacuo and the residue subjected to preparative HPLC (silica gel, 20% MeOH/CH_2Cl_2) to give 0.64 g of an oil. Treatment with acetone gave a solid, which was recrystallized from MeOH/Et_2O to give 0.4 g (13%) of **58a** as an amorphous solid; $[\alpha]^{25}$ 3.9° (1% CH_3OH). Anal. ($C_{38}H_{46}Au_2O_{10}P_2S_2 \cdot 1.5H_2O$) C, H.

[μ-1,2-Bis(diphenylphosphino)ethane]bis[(1-thio-α-D-mannopyranosato-*S*)gold(I)] (59a). A mixture of **60a** (1.0 g, 2.1 mmol), concentrated NH_4OH (15 mL), and MeOH (100 mL) was stirred for 18 h at ambient temperature and the solvent removed in vacuo. H_2O and MeOH were added to the residue, and the mixture was acidified to pH 4 with glacial acetic acid. The solvent was removed in vacuo and the residue washed with water. Chromatography of the residue (silica gel, 30% MeOH/CH_2Cl_2) gave an oil, which solidified on treatment with acetone to give 0.38 g (49%) of **59a** as an amorphous white solid; $[\alpha]^{25}$ 52.2° (1% CH_3OH). Anal. ($C_{38}H_{46}Au_2O_{10}P_2S_2$) C, H.

[μ-1,2-Bis(diphenylphosphino)ethane]bis[(2,3,4,6-tetra-*O*-acetyl-1-thio-α-D-mannopyranosato-*S*)gold(I)] (60a). A solution of K_2CO_3 (0.42 g, 3.1 mmol) in H_2O (10 mL) was added to a solution of (2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl)thiopseudourea hydrobromide[24] (1.35 g, 2.77 mmol) in water (15 mL) kept at 0 °C. After 15 min, EtOH (75 mL) was added, the mixture was stirred for 10 min, and **1a** (1.08 g, 1.25 mmol) in $CHCl_3$ (100 mL) was added. The mixture was stirred overnight, the organic layer separated, dried ($MgSO_4$), and filtered, and the solvent removed in vacuo. Recrystallization of the residue (EtOH) gave 0.87 g (47%) of **60a** as an amorphous white solid; $[\alpha]^{25}$ 52.1° (1% CH_3OH). Anal. ($C_{54}H_{62}Au_2O_{18}P_2S_2$) C, H, P.

[μ-1,2-Bis(diphenylphosphino)ethane]bis[(3-hydroxypropynyl)gold(I)] (61a). A heterogeneous mixture of **1a** (3.46 g, 4.0 mmol), propargyl alcohol (2.24 g, 2.32 mL, 40 mmol), $H_2NOH \cdot HCl$ (0.05 g, 0.7 mmol), and cuprous chloride (0.015 g, 0.15 mmol) in isopropylamine (75 mL) was stirred under an argon atmosphere. After 10 min (no reaction), additional propargyl alcohol (1.12 g, 20 mmol) was added (slight exotherm), and the mixture became homogeneous within 15 min. After 0.5 h, the solution was filtered through activated carbon that had been prewashed with isopropylamine, and the volatiles were removed at reduced pressure to give a thin oil. Treatment with water resulted in the formation of a yellow solid, which was dissolved in THF (40 mL) and decolorized with activated carbon pretreated with THF. The THF solution was diluted with Et_2O (200 mL) and the resulting white solid collected, dried in vacuo, dissolved in CH_2Cl_2, treated with activated carbon, and cooled to −20 °C. The resulting 0.63 g (17%) of white crystalline **61a** was collected; mp 179–180.5 °C. Anal. ($C_{32}H_{30}Au_2O_2P_2$) C, H, P.

[μ-1,2-Bis(di-2-pyridylphosphino)ethane]bis[(1-thio-β-D-glucopyranosato-*S*)gold(I)] (7b). A mixture of sodium thioglucose (0.33 g, 1.5 mmol) (Sigma) and **7a** (0.6 g, 0.69 mmol) in $CHCl_3$ (75 mL)/MeOH (75 mL)/H_2O (10 mL) was stirred for 2 h at ambient temperature and the solvent removed at reduced pressure. The residue was dissolved in $CHCl_3$, the solid collected, dissolved in MeOH, and filtered, and the solvent removed at reduced pressure. Recrystallization of the residue from cold acetone gave 0.49 g (60%) of **7b** as a white solid. Anal. ($C_{34}H_{42}Au_2N_4O_{10}P_2S \cdot 5H_2O$).

Biological Evaluation. P388 leukemia cells (10^6) were inoculated ip in $B6D2F_1$ mice. Twenty-four hours later, if the tumor inoculum proved to be free of bacterial contamination (as determined by incubation in thioglycolate broth), animals were randomized into groups of six and housed in shoe-box cages. Gold complexes and ligands were dissolved in a minimal volume of

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either *N,N*-dimethylacetamide (DMA) or ethanol. An equal volume of saline was added; if the drug precipitated, an equal volume of Cremophor-EL (polyethoxylated castor oil, Sigma) was added and then saline qs to a concentration such that the desired dose was delivered in 0.5 mL. Formulations were prepared immediately prior to injection. The compounds were administered ip on days 1–5 (i.e., treatment was initiated 24 h after tumor inoculation) at five logarithmically spaced dosage levels to identify the MTD and the level of antitumor activity produced at this dose. Each experiment included three groups of six animals as untreated controls and animals treated with a positive control, cisplatin (Sigma), at two dose levels. Animals were monitored daily for mortality, and experiments were terminated after 45 days. The end point was median survival time (MST) and increase in life span (ILS), which is the percentage of increase in MST relative to untreated controls. Untreated controls inoculated ip with 10^6 P388 leukemia cells generally survived for a median of 9–11 days. In 66 experiments, cisplatin at 2 mg/kg per day produced 125 ± 38% ILS. In all experiments cisplatin was active (>50% ILS).

A number of other murine tumor models were maintained by serial transplantation in syngeneic mice and were implanted ip and/or sc for drug evaluation. Tumor models used included the following: M5076 reticulum cell sarcoma, B16 melanoma, and Lewis lung carcinoma (maintained in C57B1/6 mice and evaluated in B6D2F$_1$ mice; Madison 109 lung carcinoma and colon carcinoma 26 (maintained and evaluated in BALB/c mice); mammary adenocarcinomas 16/c and 13/c (maintained and evaluated in C3H mice). All tumors were obtained from the National Cancer Institute tumor bank at Frederick Cancer Research Center, Frederick, MD.

For evaluation in the slower growing solid tumor models, compounds formulated as described above were administered ip daily for 10 days beginning 1 day after tumor implantation. The compounds were administered in each tumor model at five logarithmically spaced dosage levels which encompassed the maximally tolerated dose. Activity was assessed by inhibition of tumor growth at the site of implant for sc tumors and prolongation of median life span for sc and ip tumors. Tumor volume was determined when tumors in untreated control mice averaged about 1000 mm^3 (2–3 weeks after inoculation). Tumor volume was estimated by measurement of perpendicular diameters with vernier calipers using the equation of length × [width]^2 × 0.5.

Cytotoxicity was determined in a clonogenic assay using B16 melanoma cells growing in monolayer culture as previously described.[5]

Acknowledgment. We thank Edie Reich for the elemental analysis and optical rotation measurements. Helpful discussions with Prof. Steven Lippard, Prof. Peter Sadler, and Dr. Judith Hempel are also gratefully acknowledged. Lastly, we thank Dr. John Statler, Johnson Matthey, Inc. for supplies of **47a** and **52a**. We thank Susanne Young and Greta Givens for their excellent typographical assistance.

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