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Synthesis and anti-cancer activities of a pair of enantiomeric gold(I) complexes containing sulfanyl-substituted P-stereogenic phosphines

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Abstract

A pair of enantiomeric gold(I) complexes containing enantiomerically pure 2,3-dimethyl-7-phenyl-5-(phenylsulfanyl)-7-(*R/S*)-phosphabicyclo[2.2.1]hept-2-ene has been prepared and in vitro cytotoxicity tests showed that both the enantiomers are relatively nontoxic against healthy lymphocytes, but are highly potent against suspension and monolayer human tumor cell lines.

Chemotherapeutic applications of gold(I) complexes for the treatment of rheumatoid arthritis have been extensively studied for more than 60 years.[1] Several thiolate-supported gold drugs, such as Myochrysine and Solganol are commercially used in modern medicine. Excitingly, it was discovered in the mid 1980s that some phosphine-supported gold(I) complexes, such as Auranofin, show significant anti-tumor activities.[2] However, unlike thiols and other sulfur compounds, phosphines are not natural products and are generally difficult to prepare. Therefore, previous clinical tests of such anti-cancer gold complexes have been limited to some simple and non-designed phosphines that are available commercially. Nevertheless, these pioneering works showed that the anti-cancer activities of Au(I)–phosphine complexes are critically dependent on the molecular architecture of the phosphine ligands.[3] Recently, we established a versatile approach to the synthesis of functionalized phosphines containing resolved phosphorus stereogenic centers.[4] With this approach, a wide range of biologically active functional groups can be systematically incorporated into the phosphine ligands. Hence, drug properties such as acidity and solubility can be systematically controlled by selected functionality. Furthermore, we believe that the introduction of drug chirality is an important strategy for drug design, as it is widely recognized that separate stereoisomers and enantiomers of a drug behave very differently in their interactions with the biological systems. Thus, stereoisomerism provides a critical selectivity on the spectrum of drug

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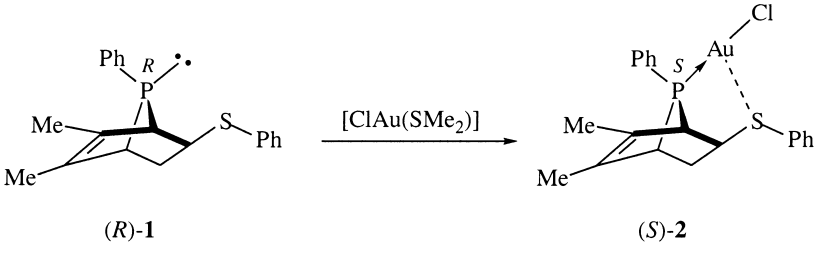
activity, their toxicology, metabolism and pharmacodynamics. In our design, chiral phosphorus donors are directly bound to the biologically active gold drug centers and hence, have strong impetus on the drug selectivity. We now delineate the asymmetric synthesis and preliminary biological evaluation of a pair of enantiomeric gold(I) complexes containing the sulfanyl-substituted P-chiral phosphine [ClAu{(±)-**1**}].

Both enantiomerically pure forms of the phosphine ligand **1** were obtained in high yields from the cycloaddition reaction between phenyl vinyl sulfide and 3,4-dimethyl-1-phenylphosphole in the presence of a chiral organopalladium template.[5] The optically active *exo*-cycloadducts coordinated as stable *P*,*S*-bidentates to palladium(II). However, they functioned only as P-bound monodentate ligands exclusively to Au(I) ions. Thus, when (*R*)-**1** was treated with a stoichoimetric quantity of [ClAu(SMe_2)] in CH_2Cl_2, the linear complex [ClAu{(*S*)-**1**}] was obtained exclusively (Scheme 1). It is noteworthy that the apparent inversion of configuration that takes place at the phosphorus stereogenic center when (*R*)-**1** is coordinated to gold, is merely a consequence of the CIP sequence rules.[6] Prior to crystallization, the 202 MHz ^{31}P NMR spectrum of crude (*S*)-**2** in $CDCl_3$ exhibited a sharp singlet at δ 90.8. The neutral complex was subsequently crystallized from CH_2Cl_2–Et_2O as bright yellow prisms (52%), $[\alpha]_D$ +75.0 (*c*=1.0, CH_2Cl_2), mp 169–171°C (decomp.). The solid state molecular structure and coordination chemistry of (*S*)-**2** have been determined by single crystal X-ray analysis (Fig. 1).[7] The study reveals that, as desired, the *exo*-substituted cycloadduct coordinates to gold as a monodentate ligand via the bridgehead phosphorus atom. The P–Au–Cl unit is nearly linear and the sulfur atom is not directly involved in metal complexation although it is evident that there is an intramolecular long range interaction between sulfur and gold[Au(1)···S(1)=3.234(2) Å].[8,9]



(*R*)-**1** (*S*)-**2**

Scheme 1.

The enantiomeric complex (*R*)-**2**, with $[\alpha]_D$ −75.0 (*c*=1.0, CH_2Cl_2), was obtained similarly from the reaction between (*S*)-**1** and [ClAu(SMe_2)]. The in vitro anti-tumor activities of both (*R*)- and (*S*)-**2** were examined using four suspension and one monolayer human tumor cell lines (Table 1). In addition, the undesired cytotoxicity of these complexes against healthy human cells was also evaluated with the lymphocyte cells. The enantiomerically pure complexes clearly show profound in vitro anti-cancer effects against all the suspension and the monolayer tumor cell lines used. Furthermore, both enantiomers do not show marked biological effects on healthy lymphocytes. Encouraged by these early results, we are currently investigating the in vivo anti-tumor activities of (*R*)- and (*S*)-**2** and other related chiral gold complexes containing functionalized phosphine ligands.

Acknowledgements

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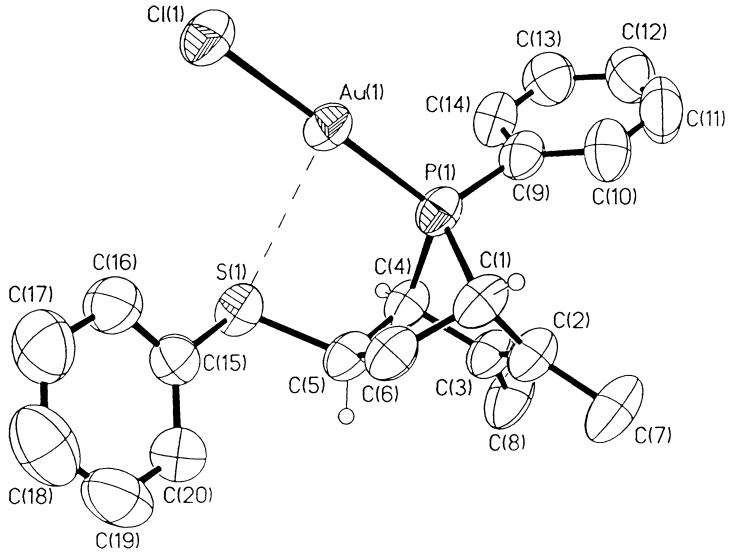

Figure 1. Molecular structure and absolute stereochemistry of (*S*)-**2**. Selected bond lengths (Å) and angles (deg.); Au(1)–P(1) 2.237(1), Au(1)–Cl(1) 2.294(1), Au(1)–S(1) 3.234(1), P(1)–C(1) 1.848(6), P(1)–C(4) 1.839(6), P(1)–C(9) 1.827(7), C(1)–C(2) 1.523(8), C(2)–C(3) 1.337(9), C(3)–C(4) 1.548(8), C(4)–C(5) 1.541(9), C(5)–C(6) 1.565(8), C(1)–C(6) 1.526(10), C(5)–S(1) 1.847(6), C(15)–S(1) 1.773(6), Cl(1)–Au–P(1) 177.1(1), S(1)–Au–P(1) 75.0(1), Au(1)–P(1)–C(1) 114.4(1), Au(1)–P(1)–C(4) 116.8(2), Au(1)–P(1)–C(9) 116.9(2), C(1)–P(1)–C(4) 81.1(2)

Table 1
Cytotoxicity of (*R*)- and (*S*)-**2**: the IC_{50} (μM) value of the enantiomers in vitro (correlation coefficients are given in parentheses)[a]

Cell lines	(*R*)-**2**	(*S*)-**2**
Raji[b]	1.2(0.94)	0.8(0.98)
P3HR-1[b]	0.5(0.94)	0.5(0.99)
Molt-4[c]	1.5(0.98)	1.5(0.96)
Daudi[b]	1.2(0.99)	1.0(0.98)
Mahlavu[d]	2.5(0.94)	3.0(0.98)
Lymphocytes	>10.0	>10.0

[a]After culturing, the cells were allowed to react with drugs in the same culturing media for 2 h. Six samples were used in each test. The IC_{50} was determined by interpolation to be the concentration that reduced colony-forming ability by 50%. [b]Suspension B-cell lymphoma. [c]Suspension T-cell Leukemia. [d]Attach liver cancer cells.

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7. Crystal data for (*S*)-**2**: $[C_{20}H_{21}AuClPS]$, M=556.81, orthorhombic, space group $P2_12_12_1$, a=9.5537(1), b=9.8850(1), c=21.0944(1) Å, V=1992.1(1) Å^3, Z=4, D_c=1.857g cm^{-3}, μ(Mo-K$_\alpha$)=77.03 cm^{-1}, F(000)=1072. A yellow prism with dimensions 0.55×0.38×0.23 mm was used for diffraction studies. A total of 13 044 independent reflections were measured on a Siemens SMART CCD diffractometer with Mo-K$_\alpha$ radiation (graphite monochromator) using ω-scans. All the non-hydrogen atoms were refined anisotropically. The full-matrix least-squares analysis based on F^2 with absorption corrected data gives R_1=0.0325 and wR_2=0.0748. The absolute stereochemistry was determined unambiguously by refining the Flack parameter [x=−0.01(1)].
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9. It should be noted that complex (*S*)-**2** contains a sulfur stereogenic center of *S* absolute configuration when the long range sulfur–gold interaction is taken into consideration.