Evaluation of some Tetraalkylammonium Gold(I) and Gold(III) Aurate Salts for Oral Antiinflammatory and Antiarthritic Activity*

GERALD R. GIRARD**, DAVID T. HILL

Department of Medicinal Chemistry, Smith Kline and French Laboratories, P.O. Box 1539, King of Prussia, PA 19406-0939 (U.S.A.)

and MICHAEL J. DIMARTINO

Department of Immunology, Smith Kline and French Laboratories, P.O. Box 1539, King of Prussia, PA 19406-0939 (U.S.A.)

(Received April 28, 1989; revised July 13, 1989)

Abstract

A series of four tetraalkylammonium gold(III) salts, $[R_4N]^+[AuX_4]^-$ (R = Et, Bu; X = Cl, Br) and five tetraalkylammonium gold(I) salts, $[R_4N]^+[AuX_2]^-$ [R = Et, Bu; X = Cl, Br, C_6H_5S, S-Glucose(OAc)$_4$] were prepared, together with $[(Et_3P)_2Au^+][AuCl_2]^-$ (**16**) and evaluated for their oral antiinflammatory [Au(III)] and antiarthritic activity [Au(I)] in comparison with the gold compounds auranofin [Et_3PAuS-Glucose(OAc)$_4$] (AF) and $[(Et_3P)_2Au]^+Cl^-$ (**4**). Synthesis of the complexes $[R_4N]^+[AuX_2]^-$ (R = Et, Bu; X = Cl, Br) was accomplished by reduction of the corresponding Au(III) complex with $C_6H_5NHNH_2$ (X = Cl) or acetone (X = Br). RS^- displacement of Br^- from $[(Bu)_4N]^+[AuBr_2]^-$ gave the thiolates $[(Bu_4)N]^+[Au(SR)_2]^-$ [R = C_6H_5; 2,3,4,6-Glucose(OAc)$_4$]. Admixture in EtOH of $[(Et_3P)_2Au]^+Cl^-$ with $HAuCl_4$ gave **16**. Evaluation of the four Au(III) salts in the carrageenan-induced rat paw edema assay at 20 mg of Au/kg showed little antiinflammatory activity on oral administration (p.o.). The five Au(I) complexes were found to be devoid of significant antiarthritic activity in the adjuvant-induced arthritic rat emodel upon oral administration. Moreover, serum gold levels were below 0.6 μg/ml suggesting poor oral bioavailability. In contrast $[(Et_3P)_2Au^+][AuCl_2]^-$ (**16**) was found to be orally effective with serum Au levels of 5.6 μg/ml and demonstrated significant antiarthritic activity comparable to both AF and the salt **4**.

Introduction

Gold complexes have been used in the treatment of difficult cases of rheumatoid arthritis (RA) for nearly sixty years [2]. The traditional agents, gold sodium thiomalate (**1**) and gold thioglucose (**2**) are effective only when administered by injection [3]. However, the triethylphosphine coordinated gold complex auranofin (AF) (**3**) is effective against RA when given orally [4]. Auranofin has also been found useful in the treatment of juvenile RA (JRA) [5] and has been clinically evaluated for antiasthmatic activity [6]. In addition **3** has been reported to have antineoplastic activity [7]. Subsequent investigation of **3** in fifteen different tumor models has shown that auranofin is active only in the P388 leukemia mouse model [8].

Auranofin exists as a monomer [9] and owes its oral activity to the triethylphosphine ligand which renders the molecule lipophilic [10]. In contrast, **1** and **2** exist as oligomers with the gold atom bridging two S atoms [11]. Thus physical and structural properties appear to influence the effective route of administration and pharmacological profile [12].

Recently, the ionic bisphosphine gold complex $[(Et_3P)_2Au]^+Cl^-$ (**4**) was reported to have auranofin-like activity in the adjuvant-induced arthritic rat model [13]. However, the bioinorganic behavior of **4** differs from that of **3** in that **4** reacts with the disulfide linkages in albumin while **3** is unreactive [14]. The solubility characteristics of **4** are unique because it is soluble in both organic and aqueous media. Unlike **4**, auranofin is non-ionic, soluble in organic media and only slightly soluble in water (<1 mg/ml) [15]. The biological activity of **4** together with its unique physical and solubility properties prompted us to search for other types of gold complexes with similar physical properties and to examine their utility as antiinflammatory and antiarthritic agents.

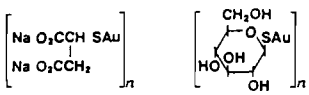
Particularly noteworthy were the tetraalkylammonium gold salts $[R_4N]^+[AuX_4]^-$ and $[R_4N]^+[AuX_2]^-$. These complexes are ionic [16] and were expected to have solubility properties in organic solvents similar to **4**. They differ from **4** in that they

*Presented at the 19th Middle Atlantic Meeting of the American Chemical Society, Monmouth College, West Long Branch, NJ, May 21, 1985; see ref. 1.

**Author to whom correspondence should be addressed.

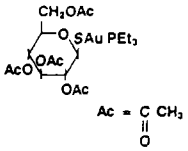
0020-1693/89/$3.50

are non-phosphine coordinated and the gold moiety is negatively charged. The absence of reports of biological data for these complexes prompted us to prepare a series of substituted tetraalkylammonium gold salts and evaluate them for oral activity in the carrageenan-induced rat paw edema assay [Au(III)] and the adjuvant-induced arthritic rat model [Au(I)]. The results of this study together with data obtained from $[(Et_3P)_2Au^+][AuCl_2]^-$ (**16**) are described herein and compared with AF and **4**.



1
gold sodium thiomalate

2
gold thioglucose



3
auranofin

Experimental

Methods

Melting points were obtained using a Thomas-Hoover melting point apparatus and are uncorrected. ^1H NMR spectra were recorded on a Varian EM390 spectrometer at 90 MHz using $CDCl_3$ as a solvent with TMS as internal reference. Serum gold levels were obtained by atomic absorption spectrometry using a Perkin-Elmer Model 303 spectrometer according to a standard procedure [12b, c].

Materials

Compounds **5**, **6**, **7**, **8**, **9**, **11** and **12** were prepared as described [16, 17] and their melting points found comparable to those reported. Compound **9** formed as white needles and was separated manually from $[(Bu)_4N]^+[C_6H_5AuCl_3]^-$ (**10**) coformed as a yellow crystalline material.

Tetrabutylammonium bis(phenylthiolato)aurate(I) (13)

Complex **12** (2.5 g, 4.17 mmol) was added in portions as a crushed solid to a mixture of sodium hydroxide (0.334 g, 8.34 mmol) and thiophenol (0.919 g, 8.34 mmol) in ethanol (60 ml)/water (8 ml) under argon. After 18 h at 25 °C and 48 h at 0 °C, the resulting white solid was collected by filtration, washed with water, dissolved in methylene chloride, dried with anhydrous sodium sulfate, then diluted with ether to precipitate the product which was recrystallized from methylene chloride/ether to give 2.35 g of **13** (85.6%), melting point (m.p.) 67–68 °C. ^1H NMR ($CDCl_3$): δ 7.61(m, 4H, ArH), 6.95(m, 6H, ArH), 3.00(m, 8H, NCH_2), 1.34(m, 16H, CH_2CH_2), 0.85(t, 12H, CH_3). *Anal.* Calc. for $C_{28}H_{46}AuNS_2 \cdot \frac{3}{4}H_2O$: C, 50.08; H, 7.13; N, 2.09. Found: C, 50.27; H, 6.94; N, 2.19%.

Tetrabutylammonium bis[(2,3,4,6-tetra-O-acetyl-1-β-D-glucopyranosyl)thiolatoaurate(I) (14)

Sodium hydroxide (0.334 g, 8.34 mmol) in water (8 ml) was added to a mixture of tetrabutylammonium dibromoaurate(I) (**12**) (2.5 g, 4.17 mmol) and 2,3,4,6-tetra-*O*-acetyl-1-β-D-thioglucose (3.04 g, 8.34 mmol) in ethanol (60 ml) under argon. After stirring at 25 °C for 2 h, the mixture was heated to reflux for 1 h, and then stirred at 25 °C for 18 h. Ethanol was removed *in vacuo*. Water (50 ml) was added and the mixture extracted with chloroform. The chloroform extracts were combined, washed with water, dried (Na_2SO_4) and concentrated to give the product as an amorphous solid.

This material was dissolved in methylene chloride, precipitated with hexane, the solvent decanted, and then dried under vacuum for 18 h to give 1.87 g of **14** (38%) as an amorphous solid. ^1H NMR ($CDCl_3$): δ 5.05 [m, 8H, C(1)H, C(2)H, C(3)H, C(4)H], 4.20 [m, 4H, C(6)H], 3.71 [br s, 2H, C(5)H], 3.25 [m, 4H, NCH_2], 2.16 [s, 6H, CH_3CO], 2.09 [s, 6H, CH_3CO], 2.02 [s, 6H, CH_3CO], 1.98 [s, 6H, CH_3CO], 1.55 [m, 16H, CH_2CH_2], 1.05 [t, 12H, CH_3]. *Anal.* Calc. for $C_{44}H_{74}AuNO_{18}S_2 \cdot H_2O$: C, 44.63; H, 6.47; N, 1.18. Found: C, 44.43; H, 6.18; N, 1.26%.

Tetrachloroaurato bis(triethylphosphine)gold(I) (15) and dichloroaurato bis(triethylphosphine)-gold(I) (16)

A solution of **4** (2.5 g, 5.3 mmol) in ethanol (60 ml) was added to a solution of chloroauric acid tetrahydrate (2.2. g, 5.3 mmol) in ethanol (15 ml). Upon completion of the addition, the mixture was stirred at 25 °C for 1 h. The resulting yellow precipitate was collected, washed with ethanol and dried to give 0.22 g of **15** (10%), m.p. 98–99 °C. *Anal.* Calc. for $C_{12}H_{30}Au_2Cl_4P_2$: C, 18.67; H, 3.92. Found C, 17.27; H, 3.69%.

The yellow ethanol filtrate from **15** became colorless after standing 18 h at 25 °C. The solution was cooled to −10 °C and the resulting white solid collected, washed with cold ethanol and dried to give 1.55 g of **16** (41%), m.p. 86–87 °C. *Anal.* Calc. for $C_{12}H_{30}Au_2Cl_2P_2$: C, 20.55; H, 4.31; N, 10.11. Found: C, 20.66; H, 4.39; N, 10.37%.

Biological Tests

Antiinflammatory Activity

Antiinflammatory activity of the four gold(III) aurate salts was measured by using the carrageenan rat paw edema assay as previously described [18]. Doses of drug equivalent to between 10–20 mg of Au/kg of body weight as suspensions in 0.5% tragacanth were administered orally to male Charles River Lewis or Wistar rats, 1 h before subplantar injection of carrageenan into the right hind paw. The paw edema volume was determined after 3 h.

Antiarthritic activity [19]

Adjuvant arthritis was produced by a single intradermal injection of 0.75 mg of *Mycobacterium butyricum* suspended in white paraffin oil (light N.F.) into the left hindpaw footpad. The injected paw became inflamed (increased vol.) and reached maximum size within 3–5 days (primary lesion). The animals exhibited a decrease in body weight gain during this initial period. Adjuvant arthritis (secondary lesion) occurred after a delay of approximately 10 days and was characterized by inflammation of the non-injected sites (right hind paw), decrease in body weight gain, and further increases in the volume of the injected hind paw. Test compounds as suspensions in 0.5% tragacanth were administered daily, beginning on the day of adjuvant injection for 17 days exclusive of days 4, 5 11 and 12. Drug activity on the primary (left paw day 3) and secondary (both paws day 16) lesions was detected by comparing paw volumes of the treated group with a control arthritis (vehicle) group. Hind-paw volumes were measured by immersing the paw into a Hg reservoir and recording the subsequent Hg displacement [19b]. A compound was considered to have antiarthritic activity if it produced a statistically significant ($p < 0.05$) decrease in the inflamed hindpaw volumes when compared with arthritic controls. The level of significant difference between treated groups and control groups was determined by the Student's *t* test.

Results and Discussion

Chemistry

The compounds prepared are listed in Table 1 [Au(III)] and Table 2 [Au(I)]. The tetrabutylammonium gold(I) thiolates **13** and **14** were prepared in a manner similar to that used by Bowmaker and Dobsen [20] in the synthesis of the bis(triphenylphosphine)iminium gold complexes of the type $[N(PPh_3)_2]^+[Au(SR)_2]^-$, ($R = C_6H_5$, CH_3). Thus, the bromide of tetrabutylammonium dibromoaurate (**12**) was displaced by the phenyl thiolate anion generated *in situ* on treatment of thiophenol with sodium hydroxide in aqueous media to give the thiolate **13** as a white crystalline solid. The tetracetylthioglucose aurate complex **14** was prepared in a similar fashion by displacement of bromide via the thiolate anion of 2,3,4,6-tetra-*O*-acetyl-1-β-D-thioglucose in aqueous ethanol (eqn. (1)).

$$\underset{\mathbf{12}}{[(Bu)_4N]^+[AuBr_2]^-} + 2RSH \xrightarrow{NaOH} [(Bu_4)N]^+[Au(SR)_2]^- \quad (1)$$

The dibromoaurate **12** was prepared from the tetrabromoaurate **8** by reduction using acetone as the reducing agent in refluxing ethanol until the solution turned from purple to colorless (eqn. (2)).

$$\underset{\mathbf{8}}{[(Bu_4)N]^+[AuBr_4]^-} + CH_3C(O)CH_3 \xrightarrow[70\,^\circ C]{EtOH} \underset{\mathbf{12}}{[(Bu)_4N]^+[AuBr_2]^-} + BrCH_2C(O)CH_3 + HBr \quad (2)$$

The aurate **8** was obtained as maroon prisms from the addition of a large excess of tetrabutylammonium bromide to chloroauric acid in aqueous ethanol. Excess bromide ion effects halogen exchange to give the $AuBr_4$ anion. The tetraethylammonium dibromoaurate (**11**) was made from **7** following the same procedures. The tetrachloroaurates **5** and **6** were synthesized by the solid addition of equimolar quantities of either tetraethyl or tetrabutylammonium chloride to a solution of chloroauric acid in ethanol. The resulting yellow solid products were readily isolated by filtration. Phenyl hydrazine hydrochloride was employed to reduce tetrabutylammonium tetrachloroaurate (**6**) (eqn. (3)).

$$2\underset{\mathbf{6}}{[(Bu_4)N]^+[AuCl_4]^-} + C_6H_5NHNH\cdot HCl \longrightarrow \underset{\mathbf{9}}{[(Bu_4)N]^+[AuCl_2]^-} + \underset{\mathbf{10}}{[(Bu_4)N]^+[C_6H_5AuCl_3]^-} + NH_2 + 4HCl \quad (3)$$

A mixture of white crystals of **9** and yellow crystals of the phenyltrichloroaurate **10** could not, in our hands, be separated by crystallization. However, because of their crystal size, **9** and **10** were conveniently separated manually. Compound **10** has been previously reported [16, 17] and was not evaluated for biological activity in this study.

Treatment of $[(Et_3P)_2Au]^+Cl^-$ (**4**) with $HAuCl_4$ in ethanol gave a small amount of yellow solid which was removed by filtration and identified as $[(Et_3P)_2$-

TABLE 1. Antiinflammatory activity of gold(III) aurate salts[a]

Compound	Aurate (20 mg Au/kg)	% Inhibition of carrageenan induced rat paw edema
5	$[(Et)_4N]^+[AuCl_4]^-$	inactive
6	$[(Bu)_4N]^+[AuCl_4]^-$	inactive
7	$[(Et)_4N]^+[AuBr_4]^-$	inactive
8	$[(Bu)_4N]^+[AuBr_4]^-$	inactive
3	auranofin[b]	62

[a] Results are based on 7–8 rats per test group and 12 rats in control group. [b] Data obtained from ref. 22; included for comparison.

TABLE 2. Antiarthritic activity[a] of gold(I) aurate salts[b]

		Hind-paw volume % Reduction from adj. control[c]				
		Injected paw		Uninjected paw	Serum Au (μg/ml)	Incidence of diarrhea
		Day 3[d]	Day 16	Day 16		
3	Auranofin	−11*	−13*	−16*	4.5	5/8(14)[e]
9	$[(Bu)_4N]^+[AuCl_2]^-$	NS	NS	NS	0.3	0/8[f]
11	$[(Et)_4N]^+[AuBr_2]^-$	NS	NS	NS	0.4	0/8
12	$[(Bu)_4N]^+[AuBr_2]^-$	−11*	−8	+3	0.6	0/8
13	$[(Bu)_4N]^+[Au(SC_6H_5)_2]^-$	−1	−6	+1	0.4	0/8
14	$[(Bu)_4N]^+[(OAc)_4Glucose\text{-}S]_2Au]^-$	NS	NS	NS	0.6	0/8
16	$[(Et_3P)_2Au]^+[AuCl_2]^-$	−15*	−15*	−21*	5.6	5/8(14)[e]
4	$[(Et_3P)_2Au]^+Cl^-$	−15**	−18**	−18**	3.6	

[a] Adjuvant-induced arthritic rat assay; see 'Experimental'. [b] Dose calculated on 10 mg Au/kg. [c] % Reduction from adj. control = (hind-paw vol. of untreated adj. control rat − hind-paw vol. of treated rat)/hind-paw vol. of adj. control rat. Non-adj. control hind-paw vol. approximates a 50% reduction from that of adj. control rat. [d] * = Statistically significant; single asterisk denotes $p < 0.05$ as significant differences from control with use of Student's t test; **denotes $p < 0.01$; NS = not significant. [e] 5 of 8 rats had diarrhea on day 14. [f] No diarrhea observed during the 16 days of the experiment.

$Au]^+[AuCl_4]^-$ (**15**). Like **10**, compound **15** was not tested for biological activity. After standing overnight, the yellow filtrate turned colorless. The filtrate was cooled and the white crystalline product was collected and determined to be $[(Et_3P)_2Au]^+[AuCl_2]^-$ (**16**).

The aurate salts were expected to have solubility characteristics similar to those of **4**. Of the gold(III) aurates, only **5** was soluble in water. Solubility in methanol, acetone and chloroform varied, but **8** was soluble in all three solvents. Complex **5** was insoluble in chloroform, **6** and **7** were slightly soluble and all were soluble in acetone and hot methanol (no quantitative solubility data was obtained). In the gold(I) aurate series, **13** and **16** were soluble in water. All of the gold(I) aurates were soluble in the above-mentioned organic solvents.

Biology

Antiinflammatory assay

The carrageenin rat paw edema assay has been commonly used to evaluate both qualitatively and quantitatively the antiinflammatory activity of a variety of compounds [21]. It is a rapid (3 h), convenient (same day) *in vivo* assay and has been employed in the evaluation of potential chrysotherapeutic agents. Of those gold drugs presently used in the clinic, only auranofin has been found to inhibit carrageenin-induced paw edema [22] although Et_3P coordinated gold imides have been found active [23]. In this test, Charles River Wistar rats are treated with the drug and the animals hydrated. After one hour 0.05 ml of 1% carrageenan suspension is injected into the plantar surface of the right hind paw. Paw volume is measured before and three hours after carrageenin injection by mercury displacement. This model was selected for evaluating the gold(III) salts because of the reported toxicity associated with $NaAuCl_4$ [3, 24] and the shorter duration of the assay.

The antiinflammatory activity of auranofin and the four gold(III) aurates, **5**–**8**, at an oral dose of 20 mg Au/kg are displayed in Table 1. Auranofin was earlier reported to produce a 62% inhibition of rat paw edema at a dose of 20 mg Au/kg and a serum gold level of 3.8 μg/ml [22]. The gold(III) aurates showed no significant antiinflammatory activity in this assay when compared to controls. Serum gold levels were not determined; therefore, the oral bioavailability of these complexes remains unknown. However, high serum gold levels do not necessarily correlate with activity. For example, gold sodium thiomalate (**1**) and gold thioglucose (**2**) produced serum gold levels approximately seven times higher than auranofin but did not significantly inhibit edema [22].

Antiarthritic Activity

The gold complexes were evaluated for antiarthritic activity in an adjuvant-induced arthritic rat model. An inflammatory arthritis is experimentally induced by injecting an oily suspension of *M. butyricum* into the left hind paw footpad of the rat. Subsequently, immune mediated inflammation and arthritis develops in the uninjected (right) hind paw and other joints. This model of arthritis responds to certain classes of antiarthritic drugs, including chrysotherapeutic (gold-based) agents [25]. Comparison of the left hind-paw volume (i.e. swelling) at day 3 for

treated and adjuvant control animals provides a measure of the antiinflammatory activity of a gold complex. Measurement of the right hind-paw swelling at day 16 monitors the immunoregulatory, as well as antiinflammatory, activity.

The antiarthritic activity of auranofin, the gold(I) aurate salts **9**, **11**–**14** and the ionic phosphine complexes **4** and **16** are shown in Table 2. These activities were obtained following oral dosing of the gold compounds calculated on the basis of 10 mg of Au/kg. Auranofin showed significant activity on the primary lesion on day 3 and day 16 and the secondary lesion on day 16. Serum gold levels were measured at 4.5 μg/ml indicating significant oral absorption. Diarrhea was observed in 5 of 8 rats on day 14. Diarrhea occurred throughout the course of AF administration but diminished as the experiment progressed.

The gold(I) aurate salts **9**, **11**, **13** and **14** showed no significant activity on day 3 or day 16 when dosed orally at 10 mg of Au/kg. Serum gold levels ranged between 0.3 and 0.6 μg/ml indicating oral bioavailability of gold less than that observed for auranofin. No diarrhea was observed in these animals. The butylammonium salt **12**, however, showed significant activity on day 3 only with serum gold level of 0.6 μg/ml and no evidence of diarrhea.

The mixed bisphosphine gold aurate **16** was the only aurate which showed significant antiarthritic activity on both day 3 and day 16. The effect of **16** in inhibiting swelling in both the injected and uninjected paw was comparable to auranofin and gave a serum gold level of 5.6 μg/ml. Like **3**, diarrhea was observed in 5 of 8 animals on day 14 suggesting a relationship between oral activity and the occurrence of diarrhea. None of the gold(I) salts appeared toxic, and 100% survival was noted. Comparison of the data obtained with **16** to that of the monogold salt **4** reveals **4** to have approximately the same activity although the serum gold level was somewhat less (3.6 μg/ml). No data regarding diarrhea were obtained with **4**.

The reason for the observed lack of activity with this limited group of alkylammonium aurate salts remains speculative but may be related to poor oral bioavailability. Analysis of the biological data suggests coordination of gold with Et_3P may be required for significant oral bioavailability as evident by serum gold levels sufficiently high to correlate with a biological response (>2.5 μg Au/ml) [25]. To date, gold compounds without Et_3P coordination have not been observed to be orally active at 20 mg of Au/kg. Alternatively, displacement of X^- from $[AuX_2]^-$ by biological nucleophiles which appear to play a role in gold absorption and transport may be inhibited by the negative charge of the anion. Nevertheless, the lack of activity with this class of compounds, albeit limited in number, has precluded further interest.

Acknowledgements

The authors thank Ms. Edie Reich and Joe Zimmerman of the Analytical Chemistry Department of SK&F Laboratories for the elemental analyses and serum gold measurements, respectively. A special thanks is also due to Dr Blaine Sutton for his interest and encouragement in this work.

References

1 G. R. Girard, M. J. DiMartino and D. T. Hill, *19th Middle Atlantic Meet.of Am. Chem. Soc., West Long Branch, NJ, May 21, 1965, Abstr.* MEDC 155.
2 J. Forestier, *Bull. Mem. Soc. Med. Hop. Paris, 53* (1929) 323.
3 A. J. Lewis and D. T. Walz, *Prog. Med. Chem., 19* (1982) 1.
4 K. K. Bandilla and B. Missler, *Clin. Rheumotol., 6* (Suppl. 2) (1987) 35; J. L. Abruzzo, *Ann. Intern. Med., 105* (1986) 274.
5 E. J. Brewer and E. H. Giannini, *Arthritis Rheum., 30* (4, Suppl.) (1987) S31, Abstract 131.
6 D. I. Bernstein, I. L. Bernstein, S. S. Bodenheimer and R. G. Pietrusko, *J. Allergy Clin. Immunol., 81* (1988) 6.
7 T. M. Simon, D. H. Kunishima, G. J. Vibert and A. Lorber, *Cancer Res., 41* (1981) 94.
8 C. K. Mirabelli, R. K. Johnson, C. M. Sung, L. Faucette, K. Muirhead and S. T. Crooke, *Cancer Res., 45* (1985) 32.
9 D. T. Hill and B. M. Sutton, *Cryst. Struct. Commun., 9* (1980) 679.
10 D. L. B. Bryan, Y. Mikuriya, J. C. Hempel, D. Mellinger, M. Hashim and R. F. Pasternack, *Inorg. Chem., 26* (1987) 4180.
11 (a) D. T. Hill. B. M. Sutton, A. A. Isab, T. Razi, P. J. Sadler, J. M. Trooster and G. H. M. Calis, *Inorg. Chem., 22* (1983) 2936; (b) M. A. Mazid, M. T. Razi, P. J. Sadler, G. N. Greaves, S. J. Gurman, M. H. J. Koch and J. C. Phillips, *J. Chem. Soc., Chem. Commun.*, (1980) 1261.
12 (a) D. T. Walz, M. J. DiMartino, L. W. Chakrin, B. M. Sutton and A. Misher, *J. Pharmacol. Exp. Ther., 197* (1976) 142; (b) D. T. Walz, D. E. Griswold, M. J. DiMartino and E. E. Bumbier, *J. Rheumatol., 7* (1980) 820; (c) D. T. Walz, M. J. DiMartino and A. Misher, *Ann. Rheum. Dis., 30* (1971) 303.
13 A. A. Isab, A. L. Hormann, D. T. Hill, D. E. Griswold, M. J. DiMartino and C. F. Shaw III, *Inorg. Chem., 28* (1989) 1321.
14 (a) M. T. Razi, G. Otiko and P. J. Sadler, *J. Inorg. Biochem., 12* (1980) 317; (b) M. T. Razi, G. Otiko, P. J. Sadler, *Am. Chem. Soc. Symp. Ser., 209* (1983) 371.
15 M. T. Razi, P. J. Sadler, D. T. Hill and B. M. Sutton, *J. Chem. Soc., Dalton Trans.*, (1983) 1331.
16 P. Braunstein and R. J. H. Clark, *J. Chem. Soc., Dalton Trans.*, (1973) 1845.
17 P. Braunstein and R. J. H. Clark, *Inorg. Chem., 13* (1974) 2224.
18 D. T. Walz, M. J. DiMartino, C. L. Griffin and A. Misher, *Arch. Int. Pharmacodyn., 185* (1970) 337.
19 (a) D. T. Walz, M. J. DiMartino and A. Misher, *J. Pharmacol. Exp. Ther., 178* (1971) 223; (b) E. F. Webb and D. E. Griswold, *J. Pharmacol. Methods, 12* (1984) 149.
20 G. A. Bowmaker and B. C. Dobson, *J. Chem. Soc., Dalton Trans.*, (1981) 267.
21 M. J. DiMartino, D. E. Griswold, B. A. Berkowitz, G. Poste and N. Hanna, *Agents Actions, 20* (1987) 113.
22 D. T. Walz, M. J. DiMartino, D. E. Griswold, A. P. Intocia and T L. Flanagan, *Am. J. Med., Proc. Symp. Oral Gold Therapy in Rheumatoid Arthritis: Auranofin*, (1983) 90.

23 S. J. B. Price, M. J. DiMartino, D. T. Hill, R. Kuroda, M. A. Mazid and P. J. Sadler, *Inorg. Chem., 24* (1985) 3425.
24 C. F. Shaw III, *Inorg. Prespect. Biol. Med., 2* (1978) 287.
25 B. M. Sutton, E. McGusty, D. T. Walz and M. J. DiMartino, *J. Med. Chem., 15* (1972) 1095.