

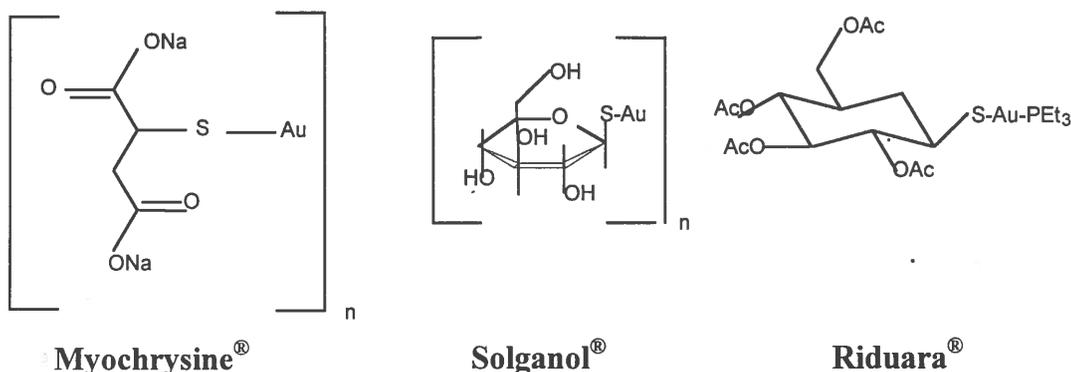
Progress Towards More Effective Gold-Based Pharmaceuticals

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Gold compounds were introduced in medicine when alchemists such as Paracelsus used them as a cure-all for everything from paralysis and fevers to syphilis and alcoholism.^{1a-c} In 1890, Robert Koch was the first to note the bacteriostatic activity of gold when he observed $K[Au(CN)_2]$ inhibiting the growth of tuberculosis bacilli.² Today, gold(I) thiolate complexes are used as treatment for rheumatoid arthritis. Myochrysine[®], Solganol[®], and Allochrysine[®] are injectable gold-containing pharmaceuticals used for this purpose.³ Riduara[®], or Auranofin, is a gold phosphine anti-rheumatic agent taken orally. Auranofin is safer than the injectables, but less effective.^{2,4a,b} In addition to its anti-rheumatic properties, Auranofin also displays anti-tumor activity.^{5a,b} Gold complexes are currently being studied as potential therapy for HIV, malaria, asthma, and a host of other maladies in addition to their anti-tumor and anti-rheumatic properties.²

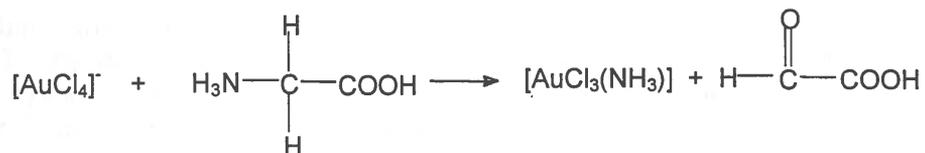


The most common oxidation states of gold are +I and +III.⁶ The inherent problem of side effects is commonly attributed to gold(III) metabolites generated under the oxidative conditions in inflamed tissue.⁷ It is postulated that the active species of the rheumatoid arthritis drugs and anti-tumor drugs are also metabolites of the administered substances, thus explaining the variable clinical responses to gold therapy in terms of side effects and efficacy.³

Investigation of the chemistry and anti-tumor properties of gold(III) complexes is one area of active research toward the development of gold-based drugs. Since gold(III) and platinum(II) are isoelectronic, it is plausible that a gold analogue of cisplatin could be developed for chemotherapy. Studies of four coordinate square-planar complexes of gold(III)(damp), where damp = bidentate 2-((dimethylamino)methyl)phenyl, display anti-tumor activity with substituents of acetato or malonato.^{8a,b} Anti-tumor activity was also evident in similar complexes containing salicylate and thiosalicylate moieties.⁹ It is believed that gold binds to DNA in a fashion analogous to cisplatin, although the varied response from different tumor types suggests a different mechanism of cytotoxicity.^{8a}

Since the mechanism of gold-drug action and toxicity remains unknown, studies of gold(III) reactions with amino acids, peptides, and proteins are a priority in gold-drug

development.^{10,11} Earlier work in this area showed that cystine and methionine are oxidized by gold(III) (see below).^{12a,b} It was recently determined that $[\text{AuCl}_4]^-$ deaminates glycine, alanine, and possibly any N-terminal amino acid.¹⁰ Studies of gold(III) reactions with proteins will provide a more accurate model of gold-drug action by factoring in the effects of secondary and tertiary structure on gold binding sites.¹¹



The use of a toxic enantiomer of a drug can lead to ineffectiveness, or worse, undesirable side effects. Thalidomide, a drug with sedative qualities, was used to treat nausea in pregnant women in the late 1950s.¹³ Unfortunately, (S)-thalidomide produced horrible birth defects. In light of this possibility, using functionalized P-chiral phosphine ligands may alter the effectiveness or toxicity of phosphine containing gold drugs such as Auranofin. Using recent techniques involving chiral organopalladium catalysts, optically pure P-chiral phosphines may be obtained.¹⁴ Although it is not yet certain whether chiral ligands will affect the biological activity of gold complexes, the possibility appears promising.¹⁵

The development of more effective gold-based pharmaceuticals remains an important goal as increasing numbers of ailments, viral, autoimmune, and cancerous, are becoming resistant to existing treatments. With three areas of active research in the inorganic community, chemists are an integral part of improved gold-based drug design. It is probable that advances in the field of gold chemistry will contribute to a making the approaching millenium a healthier one.

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