Inhibition of lysosomal cysteine proteases by a series of linear Au(I) complexes

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Throughout history, precious metals have been exploited for their supposed medical properties, but an understanding of the chemistry behind the therapeutic activity has been slow to develop. It has been long since the antiarthritic properties of gold have been recognized. Although several Au(I) complexes are clinically available to treat rheumatoid arthritis (RA), their mechanism of action in the body is not very well understood. Upon ingestion or injection, the Au(I) ligands undergo facile ligand exchange reactions with biological thiolates like cysteine, especially those with low pK_a values. This indicates that Au(I) may inhibit the activity of several enzymes, which are involved in inflammation and joint destruction in RA. Of these enzymes, the family of lysosomal cysteine proteases called cathepsins may be good biological targets for Au(I), as these enzymes have a cysteine with low pK_a value in their active sites. It has been shown previously that clinically available gold-based drugs inhibit cathepsins. In this study, a series of two-coordinate Au(I) complexes with varying phosphorus and sulfur donor ligands were synthesized, characterized and their effect on cathepsin activity tested in order to understand the chemistry behind the antiarthritic properties of Au(I). These complexes inhibited cathepsin non-competitively and reduced its activity to as little as 42 % of the original activity at an inhibitor concentration of 20 μM.