Antimicrobial Efficacy of Organogold Compounds : An Overview

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Abstract- *The emergence of bacterial resistance to commercial antibiotics is a worldwide concern. Over the last two decades, the number of antibacterial agents discovered and introduced into the market has steadily declined, failing to meet the challenges posed by pathogen resistance to common antibacterial drugs. The development of new classes of compounds to control pathogen virulence is thus urgently required. This perspective summarises the historical development and recent advances in the preparation of small organometallic compounds with gold as a new class of antibacterial agents with clinical development potential. In biomedicine, several chemical procedures have been investigated for the development of biologically stable gold complexes in conjunction with methods, such as chemical treatments or probes. In this Review, we explore the chemistry of next-generation gold pharmaceuticals, including ligands, coordination, oxidation states, and organometallic compounds for the treatment of cancer, inflammation, and infectious disorders, as well as as instruments for chemical biology. Within the past decade, we have been focusing on the development of gold compounds in biomedicine. With the objective to furnish context and a basis for the booming revival of gold, the Review gives readers an accessible review of the utility, development, and mechanism of action of organo-gold compounds.*

I. INTRODUCTION

Organogold chemistry is enjoying a resurgence of interest as useful applications largely physical or medicinal are being found. There is also a wide range of novel molecules some with curious structure. This article reviews the structure and antimicrobial properties of organogold compounds. Herein, we highlight the versatile, effective and valuable use of organogold compounds as antimicrobial agents. Organogold derivatives have been known for almost 100 years. Aurum, Gold, Oro, Or, Złoto are names in various languages for a metal which has captured the imagination of humanity for years until today, due to its golden shine and chemical inertness, leading to its unparalleled use in jewelry, currency, decorations, electronics, and even medicine. In recent years, due to the availability of soluble gold compounds and the observation that gold nanoparticles are catalytically active in a number of reactions, interest has increased in the chemistry of Au(I) and Au(III) complexes. The position of Au in the Periodic Table of the Elements is unique, and the metal is endowed with large relativistic effects, increased ionization energies, and high redox potential.Many fascinating compounds and reactions have been discovered but, until recently, they have found little practical application. However, the last ten to fifteen years have seen the development of new materials with potential applications in non-linear optics, conjugated linear polymers potential molecular wires , liquid crystals, chemical vapour deposition and anti-tumour agents . The popularity of gold as an anti-microbial dwindled with the discovery and subsequent mass-production of Penicillin, with which modern science and medicine entered into the era of antibiotics. Among the Au(III) complexes that have been tested for antimicrobial potential, early studies in the 90s highlighted Au(III) dithiocarbamates, derived from amino acids, that exhibited a larger activity against Streptococcus pneumoniae than the reference antimicrobial agents. So far only limited attention has been paid to the application of Au(III) compounds as potential antimicrobial agents and to the elucidation of their modes. Organic Derivatives Of Gold are Known For Both Of The Common Oxidation states, +1 And +3,And There is an increasing Number Of gold II derivatives. Compounds in which two Rgroups are mutually trans are therefore generally of lower stability ,and other soft ligands usually adopt positions cis to the R group. In this case, harder the perfluoro organic group, considerably show higher stability.Common ligand bond types are : aryl,, alkyl, vinylic, acetylenic. The aryl derivatives are involved in formation of chelates which are limited to gold III complexes.

Dialkylgold (III) Halides and Pseudohalides were the first organogold compounds to be prepared. Diethylbromogold(III) was first prepared by reaction of tetrabromoauric (III) acid with ethylmagnesium bromide, and was later shown to be dimeric with halogen bridges. This dimeric structure is found for all dialkyl (halogeno) gold (III) compounds. The synthesis from Grignard reagents is still commonly used but anhydrous gold(III) halides, especially Au_2Br_6, or their coordination compounds such as [$AuCl_3$ (pyridine)] are now preferred over the hydrated H[$AuBr_4$] as the precursor. Antimicrobial resistance is a serious issue not only in patient care facilities such as hospitals where antibiotics are heavily used but also in surrounding

communities because of rapid sharing of resistant genes between bacteria. As a result, difficult-to-treat forms of infectious diseases caused by pathogenic superbugs are emerging. Most feared are those strains which are no longer treatable by any available antibiotics. There are significant advances in the development of organometallic-containing, and more generally, metal-containing anticancer and anti-malarial compounds. In contrast, very little attention has been paid to the development of organometallic antibacterial drugs. Hence, explorations of metal-based antibacterial compounds are desirable, since the metal-specific mode of action of the metallo-drug may provide opportunities to overcome the development of antibiotic resistance. In this perspective, we present recent advances on the development of such compounds.

II. ANTIMICROBIAL ACTIVITY OF ORGANOGOLD COMPOUNDS

2.1 Biological properties of gold compounds

Gold complexes are promising anticancer and antimicrobial drug candidates. The majority of biologically tested gold complexes focuses on gold ions in the +1 oxidation state and generally bound to thiolates, to various N-heterocyclic carbenes (NHC), to diphos-type and alkyne ligands. There is also an increased interest in the development of anticancer gold(III)-NHC complexes. In comparison to the other classes of biologically investigated gold(I) complexes, gold(I)-alkynyl complexes have been studied to the very limited extent. Studies have shown various compounds to be studied for antimalarial activity for *Plasmodium falciparum* and few strains also have been found showing novel properties as bactericidial activity. The crucial worldwide problem of antimicrobial resistance has prompted researchers to look for new antibacterial medicines with novel targets or methods of treatment. Organogold compounds have recently become identified as a potential class of antibacterial agents. Mechanistic studies show that the multimodal mode of action used by the Au(III) complex to exert its antibacterial activity. Rapid bacterial absorption and ultrastructural membrane damage indicate to direct associations with the bacterial membrane, whereas altered pathways for energy metabolism and membrane integrity, including the TCA cycle and fatty acid biosynthesis enzymes, were discovered by transcriptome analysis. Further research using enzymes showed that the bacterial thioredoxin reductase was strongly reversibly inhibited. Importantly, mammalian cell lines exposed to the Au(III) complex showed no cytotoxicity at therapeutic dosages.

2.2 Gold as an antimicrobial agent

The most important oxidation states of gold in its complexes are +1 and +3. Thiolates, thioethers, cyanide, phosphines and arsines form stable complexes with the Au(I) ion. X-ray crystallography has shown that gold(I) complexes can adopt linear, trigonal or tetrahedral geometries. Gold(I) complexes are stable in non-aqueous aprotic solvents such as acetonitrile. On the other hand, in aqueous solution, gold(I) complexes have a strong tendency to disproportionate forming Au(III) and metallic Au(0) according to the following equation. The gold(III) ion has a d8 closed-shell configuration ([Xe]4f 145d8). The ionic radius of the Au(III) (85 pm) is less than Au(I) (137 pm), which renders the Au(III) ion much less polarisable. Consequently, the Au(III) ion has a preference for ligands containing nitrogen and oxygen donor atoms (hard Lewis bases). Other important ligands which form complexes with the Au(III) ion are chloride, bromide and cyanide. The dominant coordination geometry for gold(III) complexes is square planar, although trigonal bipyramidal and octahedral geometries are also observed. Trigonal bipyramidal and octahedral structures typically exhibit elongated axial bond lengths perpendicular to the square plane. Seven linear phosphine gold(I) complexes having a sulfur atom in the coordination sphere exhibited a different spectrum of in vitro activity against several strains of Gram-positive and Gram-negative bacteria, *Staphylococcus aureus (Staph. aureus)*, *Staphylococcus epidermidis (Staph. epidermidis)*, *Escherichia coli (Esch. coli)* and *Pseudomonas aeruginosa (Ps. aeruginosa)*, and *fungi Candida albicans (Ca. albicans)* and *Aspergillus niger (A. niger)*. On the other hand, chloramphenicol was slightly more active than 6 against *Esch. coli*, but much less active than these gold(I) complexes against Gram-positive bacteria. Au(I) resulted in the formation of [Au(tetz)(PPh3)] complex 22, that had a modest activity only against the investigated Gram-positive bacteria. Au(I)-PPh3 complexes with sulfur and nitrogen-containing ligands,15,18 the phosphine gold(I) complexes with oxygen donors. The antimicrobial activity of gold(I) complexes with diphosphanes, dppe (1,2-bis(diphenylphosphano)ethane) and dppy (1,2-bis(di-3-pyridylphosphano)ethane) has been also evaluated. gold(I) complexes, [Au(cis-Ph2P(CHvCH)PPh2)2]Cl (35) and [Au(Ph2P(CH2)3PPh2)2]Cl, with chelating diphosphine ligands have been reported to manifest modest activities against *Staph. aureus*, and no activity against *Esch. coli* and *Ps. aeruginosa.*

2.3 Future insights of Organogold compounds

The emergence of bacterial resistance to commercial antibiotics is an issue of global importance. During the last two decades, the number of antibacterial agents that have been discovered and introduced into the market has steadily declined and failed to meet the challenges posed by rapidly

increasing resistance of the pathogens against common antibacterial drugs. The development of new classes of compounds to control the virulence of the pathogens is therefore urgently required. This perspective describes the historical development in brief and recent advances on the preparation of small organometallic compounds as new classes of antibacterial agents with potential for clinical development.As a versatile and effective group of metal-based antitumor medicines, gold(III) complexes have evolved. The discovery and development of various ligands, such as chelating nitrogen donors, dithiocarbamates, and C-N cyclometallated ligands, that can strengthen the AuIII cation and prevent its degradation under physiological conditions has made it possible to investigate their potential intracellular targets and mechanisms of action. A number of studies convey evidence that the cellular targets are mitochondria-based, despite the fact that the mechanisms of action illustrated gold-like compounds in biological media are still under exploration. Recent developments in gold(III) biological chemistry also suggest using substances derived to have different pharmacological uses, such the treatment of parasite or viral illnesses.

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