Bioinorganic applications of gold and platinum coordination compounds: a brief historical overview and recent advances in 2017

Raphael Enoque Ferraz de Paiva* and Pedro Paulo Corbi*

Inorganic Chemistry Department, Institute of Chemistry, University of Campinas – UNICAMP, P.O. Box 6154, 13083-970, Campinas, SP, Brazil.

Corresponding author: E-mail address: rpaiva@iqm.unicamp.br, ppcorbi@iqm.unicamp.br

ABSTRACT

Gold-based metallo drugs have been studied for a wide variety of medical-related applications, although the antiarthritic auranofin is the only representative within this class that has reached the clinic. Platinum compounds, on the other hand, are the leading class of metallo drugs used against cancer, with very successful representatives worldwide, such as cisplatin, carboplatin and oxaliplatin. In this mini review, we will briefly present the development of gold- and platinum-based metallo drugs throughout the year of 2017.

1. Introduction

Medicinal applications of gold date to antiquity. The oldest records, dated to around 2500 BC, indicate that the Chinese and Arabians were the first to use gold for therapeutic purposes. In the 8th century it was considered as an elixir of youth. In the 19th century, sodium tetrachloridoaurate(I), Na[AuCl4], was prescribed to treat syphilis and chronic alcoholism. In the end of the 19th century, Robert Koch first described the activities of potassium dicyanidoaurate(I), K[Au(CN)4] for the treatment of tuberculosis. With the development of modern Medicine and the emergence of new technologies, the empirical use of gold was replaced by a more rational design of gold-based medicine, to circumvent the toxic effects of K[Au(CN)4]. This approach was responsible for the development of aurothioglucose (Solganol), myocrisin and later of auranofin, compounds used in the treatment rheumatoid arthritis. Curiously enough, the first uses of gold(I) compounds in treatment of rheumatoid arthritis were based on the idea that such illness was caused by a bacterial infection, which was shown to be incorrect.

Mirroring the historical application of gold and gold-containing compounds for the treatment of such a wide variety of diseases, the 2016-2017 period has introduced gold-based metallo drugs for applications including the molecular understanding of the mechanisms of interaction with protein targets and development of new therapeutic agents for HIV, cancer, bacterial infections as well as parasitic infections. Platinum compounds, on the other hand, were intensely studied since the middle 1960’s after the serendipitous discovery of the antitumor activity of cisplatin by Rosenberg. Cisplatin revolutionized the treatment of testicular cancer, leading to cure rates higher than 95%. The mechanism of action of cisplatin is generalized as dependent of 4 steps: cellular uptake, aquation (replacement of the leaving ligands by water molecules), DNA binding (leading to a bending along the helical axis) and finally cellular processing, including recognition of the damage, which ultimately leads to cell death. A well-established structure-activity relationship for cisplatin has been rationalized, and it relies on a square planar Pt(II) center surrounded by monodentate or chelating N-donors (non-leaving groups) and negatively charged monodentate or bidentate ligands (leaving ligands). Oxaliplatin and carboplatin were rationally developed expanding on the general structure of cisplatin. Both compounds feature bidentate ligands that are replaced by water molecules more slowly than the monodentate chlorides found in the structure of cisplatin.

Platinum drugs have been listed on the 2013’s edition of the Model List of Essential Medicines of the World Health Organization, which highlights the relevance of this class of compounds and justifies the extensive research in the field. Some handpicked examples published in the previous year will be discussed here. Within this period, we also highlight the breakthrough discovery regarding the mechanism of action of oxaliplatin, which was demonstrated to be significantly different from that of cisplatin and carboplatin.

ARTICLE INFO

Keywords:
Gold
Platinum
Bioinorganic
Arthritis
Anticancer agents
Antiviral compounds

1. Introduction

1.1 Medicinal applications of gold date to antiquity. The oldest records, dated to around 2500 BC, indicate that the Chinese and Arabians were the first to use gold for therapeutic purposes. In the 8th century it was considered as an elixir of youth. In the 19th century, sodium tetrachloridoaurate(I), Na[AuCl4], was prescribed to treat syphilis and chronic alcoholism. In the end of the 19th century, Robert Koch first described the activities of potassium dicyanidoaurate(I), K[Au(CN)4] for the treatment of tuberculosis. With the development of modern Medicine and the emergence of new technologies, the empirical use of gold was replaced by a more rational design of gold-based medicine, to circumvent the toxic effects of K[Au(CN)4]. This approach was responsible for the development of aurothioglucose (Solganol), myocrisin and later of auranofin, compounds used in the treatment rheumatoid arthritis. Curiously enough, the first uses of gold(I) compounds in treatment of rheumatoid arthritis were based on the idea that such illness was caused by a bacterial infection, which was shown to be incorrect. Mirroring the historical application of gold and gold-containing compounds for the treatment of such a wide variety of diseases, the 2016-2017 period has introduced gold-based metallo drugs for applications including the molecular understanding of the mechanisms of interaction with protein targets and development of new therapeutic agents for HIV, cancer, bacterial infections as well as parasitic infections. Platinum compounds, on the other hand, were intensely studied since the middle 1960’s after the serendipitous discovery of the antitumor activity of cisplatin by Rosenberg. Cisplatin revolutionized the treatment of testicular cancer, leading to cure rates higher than 95%. The mechanism of action of cisplatin is generalized as dependent of 4 steps: cellular uptake, aquation (replacement of the leaving ligands by water molecules), DNA binding (leading to a bending along the helical axis) and finally cellular processing, including recognition of the damage, which ultimately leads to cell death. A well-established structure-activity relationship for cisplatin has been rationalized, and it relies on a square planar Pt(II) center surrounded by monodentate or chelating N-donors (non-leaving groups) and negatively charged monodentate or bidentate ligands (leaving ligands). Oxaliplatin and carboplatin were rationally developed expanding on the general structure of cisplatin. Both compounds feature bidentate ligands that are replaced by water molecules more slowly than the monodentate chlorides found in the structure of cisplatin. Platinum drugs have been listed on the 2013’s edition of the Model List of Essential Medicines of the World Health Organization, which highlights the relevance of this class of compounds and justifies the extensive research in the field. Some handpicked examples published in the previous year will be discussed here. Within this period, we also highlight the breakthrough discovery regarding the mechanism of action of oxaliplatin, which was demonstrated to be significantly different from that of cisplatin and carboplatin.
2. Recent advances on Au(I) chemistry in the context of Bioinorganic Chemistry

Figure 1 shows gold-based metallodrugs published in the literature from 2016 to 2017.

Protein targeting and inhibition

A series of thiolphilic Au(I)-phosphine compounds (3-7) was evaluated by Paiva et al. for chemoselective auration of the C-terminal HIV nucleocapsid protein NCp7 zinc finger F2 (2) and the full-length HIV NCp7 (NC), as probes of nucleocapsid topography. The nature of the phosphine and the co-ligand affect the reactivity with the C-terminal NCp7 F2 and the full-length NC. 13P NMR spectroscopy showed the formation of long-lived [Au(PR3)]−ZnF species in all cases, but a selective interaction was observed for the drug-mapping compound 5 with NCp7 F2. Auranofin (A3) and NCp7 NC inhibition might contribute to the biological effects observed towards cancer cells.

Westmeier et al. studied a series of thiophilic Au(I)-phosphine compounds (3-7) for chemoselective auration of Au(I) metalloepitope ions obtained by the interaction of compound 4 with the zinc fingers NCp7 F2 and Sp1 F3 (where Sp1 is the human transcription factor). Two conformers of the NCp7 F2 “gold finger” were identified in the gas phase using TWIM-MS, while a single conformer was identified for the Sp1 F3 “gold finger”. Collision induced dissociation allowed an unequivocal assignment of the Au(I) binding sites for the major conformers obtained in each reaction. A Cys-Au-Cys coordination was identified for NCp7 F2 “gold finger”, while a Cys-Au-His coordination was observed for the Sp1 F3 “gold finger”.
Meier et al. studied the interaction of a series of gold(III) compounds (both organometallic and coordination, 8-12) with biologically relevant nucleophiles by ESI-MS. Compound 8 reacts readily with 2-ethylglycinine (EtG). Organometallic compounds 9 and 10 show only very minor MS signals for EtG adducts even after 24 h. Readily detectable EtG adducts were observed for 11. Compounds 11 and 12 form adducts with cysteine (c) to a greater extent than 9 and 10. Compound 8 did not form any adducts with either ubiquitin (ub) or cytosine. Compounds 9 and 10 formed mono- and bis-adducts of the type [protein+Ln(AuIII)]− (L is the respective C:N bidentate ligand; n = 1 or 2) with both proteins to a similar extent. Complexes 11 and 12 reacted similarly with both proteins, even leading to the formation of higher order adducts. Compound 8 reacted preferentially with Se-Cys, 9 with Cys, and 10 with His, whereas 11 and 12 undergo redox reactions and oxidize Cys to cystine. The molecular reactivity patterns and binding preferences correlated with the inhibition of TrxR1, i.e., Se-Cys binding leads to potent TrxR1 inhibitors and in some cases to a high antiproliferative activity. The binding preferences imply that the families of coordination and organometallic Au(III) anticancer agents follow different modes of action.

The inhibition of human aquaporin (AQP3) was evaluated by a series of Au(III) complexes (10, 11, 13, 14 and 15) as probes of chemoselective auration of glycerol permeation. The neutral complex 14, with a similar ligand system, was scarcely active. DFT studies showed a good correlation between the compound’s calculated affinity to cysteine residues and their AQP3 inhibition.

Gold(III) compounds (both organometallic and coordination, 8-12) were also shown to be cytotoxic in vitro. The Au(III) inhibition of AQP3 is not related to oxidative damage. Molecular Dynamics studies demonstrated that binding of the compounds to one monomer also affects substrate permeability in an adjacent one. The Au(III) complexes were also shown to be potent inhibitors of human cathepsins (B and L) and of the C-terminal HIV nucleocapsid protein NCp7 zinc finger 2 (F2) and the full-length HIV NC, with a similar binding order adducts. Compound 11 was identified as the most potent inhibitor of the Staphylococcus, Streptococcus spp. and Bacillus clausii) and Gram-negative (E. coli, K. pneumoniae, P. aeruginosa) bacteria and three yeasts belonging to the Candida species. Complex 33 showed a remarkable bacteriostatic antimicrobical activity against Staphylococci, with Minimum Inhibitory Concentration (MIC) values of 1.56 and 3.13 μg/mL for S. haemolyticus and S. aureus, respectively. 32

Antiparasitic properties

A series of gold(I)-alkyne derivatives containing the water soluble phosphines PTA (1,3,5-triaza-7-phospha-1,2-damantane) and DAPTA (3,7-diaicy1-t,3,7-triaza-5-phospha-5,7-bicyclo-[3.3.1]nonane) (compounds 23-30) were tested against the human colon cancer cell line Caco-2 (PD7 and TC7 clones). 30 PTA-containing compounds were more cytotoxic than DAPTA-containing analogs, which correlated well with the higher cellular uptake of the former. The anticancer activity of 23 against colon cancer cell lines happens through the apoptotic pathway and induction of 5-phase arrest in the cell cycle. An increase in the mean survival time and life expectancy in athymic nude mice xenografted with human HCT-116-2u2 cancer cells was observed, with moderate inhibition of tumor growth. 30 

Muenzner et al. 31 investigated the antiproliferative and antivaccarsic properties gold(I) carbene complexes featuring 4-ferrocenyl-substituted imidazol-2-ylidene ligands (31 and 32 were selected as examples). They had low micromolar to nanomolar IC50 (72 h) values against a panel of seven cancer cells. The lipophilic cationic complexes 31 and 32 caused an increase in reactive oxygen species by a ferrocene-dependent mechanism and by inhibition thioredoxin reductase. Both complexes led to a G1 phase cell cycle arrest and a retarded cell migration. Antiangiogenic effect was demonstrated by tube formation assays with endothelial cells. The bissacarbene complex 32 lead to up to 80% xenograft tumor volume reduction in mice.

Antimicrobial properties

The novel heterocyclic cyclometalated complex [Au(py(py-Hmut)] (33) was tested against a panel of ten Gram-positive (belonging to the Staphylococcus, Streptococcus spp. and Bacillus clausii) and Gram-negative (E. coli, K. pneumoniae, P. aeruginosa) bacteria and three yeasts belonging to the Candida species. Complex 33 showed a remarkable bacteriostatic antimicrobial activity against Staphylococci, with Minimum Inhibitory Concentration (MIC) values of 1.56 and 3.13 μg/mL for S. haemolyticus and S. aureus, respectively. 32

Antiparasitic properties

In a Phase 1 clinical trial, auranofin (1) was identified as a broad-spectrum antiparasitic drug, being effective in vitro and in vivo against Entamoeba histolytica and both metronidazole-sensitive and -resistant strains of Giardia intestinalis. 32 Both parasites are the major causes of water and foodborne diseases. Patients were treated daily with 6 mg of auranofin, which corresponds to more than 25 fold the IC50 for E. histolytica and 4 fold that of Giardia.

3. Recent advances on Pt(II) chemistry in the context of Bioinorganic Chemistry

Platinum complexes are still the leading metallodrugs and platinum chemistry with bioinorganic applications has been extensively explored. For that reason, we had to handpick the most noteworthy examples of platinum(II),
has been extensively explored. For that reason, we had to handpick the most noteworthy examples of platinum(II, IV) metallo-drugs published in the literature from late 2016 to late 2017 to be discussed in this minireview. Figure 2 shows the structures of the selected compounds.

Expanding on the understanding of cisplatin-like drugs
Bruno, Lippard, Hamman and co-authors demonstrated that oxaliplatin (35) kills cells by inducing ribosome biogenesis stress, unlike cisplatin (34) and carboplatin (36) that have the same effect through a DNA-damage response. This difference in drug mechanism explains for example an observed lack of efficacy for oxaliplatin in the treatment of malignancies conventionally treated by cisplatin and suggests that alterations in the nature of the ligand (e.g., capping of deep interactions for primary mechanisms of action). The final consequence is that platinum drugs might not function interchangeably with their derivatives in cancer chemotherapy. The authors suggest that the ability of oxaliplatin to cross-link DNA has questionable relevance in cytotoxicity, but it could still lead to the inhibition of RNA synthesis, which would ultimately be responsible for ribosome biogenesis stress.

The mechanism of hypersensitivity of testicular germ cell tumors (TGCTs) to cisplatin was investigated by Avuah, Riddell, Lippard and co-authors. They demonstrated that diethylenetriamine and Me-substituted (diene) Pt(II) aggregates that enhance the intermolecular Pt/Pt and π-π stacking interactions, leading to a luminescence emission centered at 630 nm. The limit of detection of LPS for 40 ng/ml was of 5.7 nM. As a proof-of-concept, the authors also developed polynuclear platinum complexes for rapid and washing-free discrimination of Gram-negative E. coli and Gram-positive S. aureus within 5 min.

Anti-HIV activity
Tosotors, Farrell and co-authors presented to the authors a concept that makes use of the Pt(II) complexes of 2,6-bis(benzimidazol-2-yl)pyridine with hexaethylene glycol methyl ether groups (compound 40) was developed by Zhu, Yu and co-authors. The compound can be used for sensing lipopolysaccharide (LPS) endotoxin and, as consequence, it can be applied in a sensor for rapid discrimination between Gram-negative and Gram-positive bacterial pathogens. In the presence of LPS, 40 binds to negatively charged LPS to form LPS-Pt(II) aggregates that enhance the intermolecular Pt/Pt and π-π stacking interactions, leading to a luminescence emission centered at 630 nm. The limit of detection of LPS for 40 ng/ml was of 5.7 nM. As a proof-of-concept, the authors also developed polynuclear platinum complexes for rapid and washing-free discrimination of Gram-negative E. coli and Gram-positive S. aureus within 5 min.

Bioconjugation
Rivilla, Cosio and co-authors described a novel catalytic system based on covalently modified DNA that promotes 1,3-dipolar reactions between azoethene ylides and maleimides. The catalytic system makes use of the distortion of the double helix of DNA caused by platination of guanine units, similar in nature to the DNA damage caused by platinum chemotherapeutic drugs. As a proof of concept, compound 37 caused a distortion in salmon sperm DNA and an heterobimetallic system was generated using Cu(OTf)2 in situ. This system was able to catalyze (3 + 2) cycloaddition between azoethene ylides and maleimides.

Muhammad, Guo, Wang and co-authors demonstrated that tethering biotin moieties to the Pt(IV) scaffold remarkably increases the cellular uptake of Pt in breast cancer cells, but lowers its accumulation in breast epithelial cells. Using PLA-PEG, DTPA-coupled (38) was the most potent compound (3 + 2) cycloaddition between azoethene ylides and maleimides.

References