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In vitro Biological Activities of Gold(I) and Gold(III) Bis (N-Heterocyclic Carbene) Complexes

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The aim of this research is to evaluate for the first time the in vitro leishmanicidal activity and inhibition of α-glucosidase and β-glucuronidase of new gold(I) and gold(III) complexes involving N-heterocyclic carbene (NHC) ligands, with the general formula $[Au(X)_n(NHC)R_2][BF_4]$ (X=Cl, OAc, R = various aromatic and aliphatic substituents). The Au(III) complexes were shown to have a significant antileishmanial activity, and were also found to be more potent inhibitors of α-glucosidase and β-glucuronidase enzymes than the standard drugs. Some complexes were also identified as potent anti-inflammatory agents with activity comparable to that of tested standard drugs, allopurinol and ibuprofen. These gold complexes were also evaluated for their in vitro cytotoxic activity against HeLa (cervical cancer), MCF-3 (breast cancer), and 3T3 (mouse fibroblast) cell lines.

Recent advancements in transition-metal-based compounds have found wide medical applications. The use of *cisplatin* to treat ovarian cancer and the discovery of the gold-based drug *auranofin* to treat rheumatoid arthritis are among the numerous examples that have seen transition metal complexes combat human ailments. Nowadays, large libraries of platinum-, palladium-, ruthenium- and gold-containing molecules are being synthesized for therapeutic purposes.[1–3]

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Au(I) and Au(III) complexes are known to have in vitro cytotoxicity. However, these complexes have not reached clinical trials due to their high cardiotoxicity.[1] Dithiacarbimate containing Au(III) complexes have also shown potent anti-tumor properties (in vitro and in vivo).[4–7] The phosphine ligands attached to Au(I) complexes are known to influence their antitumor efficacy against HeLa cell lines.[8–9] Unfortunately, after *auranofin*, no gold complex has yet to reach the stage of clinical application. In modern medicine, the use of gold-based compounds has been limited to two gold salts to treat rheumatoid arthritis, Au(I)-thiolate and *auranofin* (Au(I)-thiolate-triethylphosphine).[10]

Similarly, dithiacarbimate Au(III) complexes have been shown to be selective towards triple-negative breast cancer cells.[4,6] Phosphine-gold(I) complexes having halides, alkynyls, sugar derivatives and thiolates as ligands have been evaluated for their anti-cancer activities and cytotoxic effects against various cancer cell lines, including cervical and breast cancer cells and were shown to be highly active.[11–14] In particular, pyrazole or imidazole containing Au(I) complexes have shown 70 times more anti-proliferative effect than cisplatin against ovarian cancer cells (A2780/S) and its cisplatin-resistant cells (A2780/R).[15]

Gold(I) and gold(III) complexes are also known to be effective against cutaneous leishmaniasis and malarial parasites.[16–18] Gold complexes are known to be more effective on parasites than macrophages.[19–20] Au(III) tetrachloride complexes are also reported to have anti-HIV activity.[21–22]

Recently, the broad applications of NHC-based (NHC=N-heterocyclic carbene) gold(I) and (III) complexes in catalysis and their biological activities have also attracted much interest from researchers and the pharmaceutical sector.[23–29] Benzimidazole- and imidazole-containing drugs are currently in use as antiviral, antifungal, antihelmentic and diuretic.[30] They are also known to treat peptic ulcer as proton pump inhibitors.[30] The N-heterocyclic carbene (NHC) is the key structural feature of benzimidazole- and imidazole-like structures that can effectively coordinate with metals, such as gold, to afford Au-NHC complexes. A long list of Au-NHC complexes displaying anticancer or cytotoxic activities has been reported all through the literature.[31–51] In addition, Au-NHC complexes are known to have antibacterial activity against biofilm forming pathogens,[52] as well as antileishmanial,[53] antiproliferative and thioredoxin reductase (TrxR) inhibition properties.[54]

We recently reported on the applications of gold(I)-NHC complexes as potent bioactive compounds.[55] Herein, we extend this investigation to include gold(I)- and gold(III)-bis (NHC) complexes.

The previously described gold complexes[56] [Au (BMIM)$_2$[BF$_4$], [Au(BMIM)$_2$Cl$_2$][BF$_4$], [Au(BMIM)$_2$(OAc)$_2$][BF$_4$] [Au (BMIM)$_2$(OAcF)$_2$][BF$_4$], [Au(BMIM)(IPr)Cl$_2$][BF$_4$], [Au(IPr)$_2$Cl$_2$][BF$_4$], [Au(IPr)(ICy)Cl$_2$][BF$_4$], [Au(IPr)(I^{t}Bu)Cl$_2$][BF$_4$] and [Au(IPr)(IMes)Cl$_2$] [BF$_4$] (**1-9**) were herein investigated for their in vitro anti-inflammatory (reactive oxygen species) activity (Figure 1). These

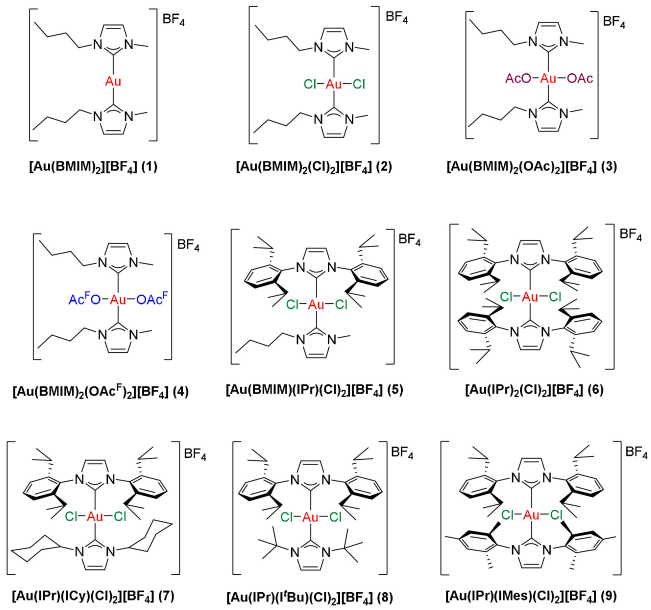

Figure 1. Previously synthesized gold-NHC complexes that were evaluated for biological activity during this study.[56].

complexes were also evaluated for their α-glucosidase and β-glucuronidase inhibition potential. Their activities against HeLa (cervical cancer), MCF-3 (breast cancer) and 3T3 (mouse fibroblast) cell lines were also tested as well as their antileishmanial activity against L. *major* promastegotes, and promising results were obtained.

1. Enzyme inhibition activity

1.1. Inhibition assay for α-glucosidase activity

α-Glucosidase (AGH, E.C3.2.1.20) belongs to the carbohydrate-hydrolases group and it is a membrane-bound enzyme located at the epithelium of the small intestine. It is a key enzyme of dietary carbohydrate in humans, as it breaks down starch and disaccharides to glucose molecules.[57,58] α-glycosidase plays a crucial role in postprandial hyperglycemia keeping in a normal range the blood glucose levels. Inhibitors of that enzyme may be effective as they function as potential drugs to retard the carbohydrate digestion and control the glucose absorption in the small intestine.[59] Therefore, the retardation of the action of AGH may be one of the most effective approaches to control the non-insulin-dependent diabetes mellitus which is one of the main adult diseases.[60–63]

In that context, we have investigated gold(I) and (III) complexes (**1-9**) as potent in vitro AGH inhibitors in comparison to the standard AGH inhibitor drug, acarbose. Complexes **2** ($IC_{50}=7.3\pm0.23$ μM), **3** ($IC_{50}=6.6\pm0.11$ μM), **4** ($IC_{50}=99\pm0.95$ μM), **5** ($IC_{50}=12.1\pm0.13$ μM), **7** ($IC_{50}=1.5\pm0.01$ μM) and **9** ($IC_{50}=1.5\pm0.1$ μM) were identified as potent α-glucosidase inhibitors, showing more activity than the standard drug acarbose ($IC_{50}=840\pm1.73$ μM). Complexes bearing chlorides or acetate groups (**2-5**, **7**, and **9**) were found to be the most active members of this series. Complexes **7** and **9** were the most active of this series and, when compared to the inactivity of **6** and **8**, no clear trend in structure/activity relationship could be observed. Complex **1**, which lacked chlorides or acetates ligands, was found to be inactive. In comparison, it could be noted that all the above gold(III) complexes are still less active than the most active gold(I) (IC_{50} up to 0.7 ± 0.01 μM) complexes that were reported in our earlier publication.[55] Results are summarized in Table S1 (see Supporting Information).

1.2. β-Glucuronidase inhibition assay

β-Glucuronidase (β-D-Glucuronidase) is an enzyme classified as a member of the glycoside hydrolase family and it is regularly used for in vitro drug metabolism studies. It is actively involved in the hydrolytic cleavage of drug-glucuronide conjugates which is called glucuronidation. Glucuronidaton is an enzymatic process that primarily takes place in the liver, converting lipophilic xenobiotics and endogenous compounds into metabolites that are more water soluble, and thus, more readily excreted in the urine or bile. The gene is expressed in most of the tissues and body fluids.[64–66] The expression level of the gene was found to be higher in certain diseases, such as inflammatory joint disease, hepatic disease and acquired immunodeficiency syndrome (AIDS).[67] Hepatic disorders, rheumatoid arthritis, renal diseases, urinary tract infections, epilepsy, neoplasm of bladder and testes, larynx and colon carcinoma have also been associated with hyperactivity of β-glucuronidase.[68–69]

In order to evaluate the effect of β-glucuronidase on glucuronide formation rates, various β-glucuronidase inhibitors are usually used. The gold complexes **1–9**, were evaluated compared to the primary β-glucuronidase inhibitor used for in vitro assays and which is D-saccharic acid 1,4-lactone (saccharolactone). Complexes **2** ($IC_{50}=21.5\pm0.76$ μM), **3** ($IC_{50}=1.03\pm0.08$ μM), **4** ($IC_{50}=17.7\pm0.94$ μM), **5** ($IC_{50}=9.28\pm0.25$ μM), **6** ($IC_{50}=3.87\pm0.06$ μM), **7** ($IC_{50}=1.46\pm0.06$ μM), **8** ($IC_{50}=1.28\pm0.02$ μM) and **9** ($IC_{50}=2.27\pm0.08$ μM) were found to be potent inhibitors with more activity than the standard D-saccharic acid 1,4-lactone ($IC_{50}=45.75\pm2.16$ μM). When BMIM-based complexes were used, acetate ligands were necessary to have a high activity (complex **3** compared to **1–2** and **4–5**). In the IPr series (**6-9**), complexes bearing NHCs with N-alkyl groups showed the most activity (**7-8** vs **6–9**). The presence of

chloride or acetate ligands proved to be essential as demonstrated by complex **1**, which was found to be inactive. Results are summarized in Table S1 (see Supporting Information).

1.3. Anti–inflammatory activity (Respiratory burst assay)

The human body encounters a huge number of stimuli on a daily basis, many of which result in injuries or infections and thus damage human cells and tissues. Inflammation is used by the human body as a response to overcome and repair such damages. Typical signs of inflammation include redness, warmth, swelling and pain. Inflammation is involved in many other prevalent human diseases. Chronic inflammation leads to common inflammatory diseases, such as rheumatoid arthritis and osteoarthritis. Mediators of inflammation play an important role in maintaining a balance in acute inflammatory response. Usually, non-steroidal anti-inflammatory drugs (NSAIDs) and glucocorticoids are used for the treatment of various kinds of inflammatory disorders. Many of these drugs possess serious adverse effects. Therefore, the search for more effective anti-inflammatory agents continues.

Gold complexes **1–9** were evaluated for their in vitro anti-inflammatory activity, using respiratory burst assay, and then compared to allopurinol and ibuprofen as standard inhibitors. Complexes **3** ($IC_{50}=4.4\pm0.1$ μM), **4** ($IC_{50}=6.2\pm1.9$ μM), **5** ($IC_{50}=7.6\pm0.7$ μM), **7** ($IC_{50}=6.3\pm1.2$ μM), **8** ($IC_{50}=15.2\pm2.3$ μM) and **9** ($IC_{50}=3.3\pm0.8$ μM) were found to be potent inhibitors with activities comparable to tested standard drugs allopurinol ($IC_{50}=2.0\pm0.01$ μM) and ibuprofen ($IC_{50}=11.2\pm1.9$ μM). Complexes **1**, **2** and **6** were found to be inactive. No clear trend can be observed here; however, it seems that smaller NHC co-ligands are more favourable as seen in the **6–9** series (**9** vs **6** and **7** vs **8**). Results are summarized in Table S1 (see Supporting Information).

2. Antileishmanial activity

Infections caused by protozoan paracites of the genus *Leishmania* are a major problem worldwide.[70] The disease usually affects the poorest regions, and it is transmitted by the bite of a sand fly, causing visceral, cutaneous or mucocutaneous leishmaniasis.[71–74] There are three forms of the disease. Different species of the parasite cause each form. Cutaneous leishmaniasis (Oriental button) affects the skin and is usually not serious. Visceral leishmaniasis damages the internal organs and can be life-threatening. Visceral leishmaniasis is also known as kala-azar. Mucocutaneous leishmaniasis (ulceration of the skin and hyperdevelopmnet of the mucous membranes) can lead to partial or complete destruction of the mucous membranes found in the nose, throat, and mouth.[75–76] The occurrence of leishmaniasis has worsened with the emergence of the HIV/*Leishmania* co-infection[70,77] and with the development of drug-resistance by parasites. An increase in the incidents of leishmaniasis can be associated with environmental changes, populations of rodents and finally the increased worldwide incidence rate of leishmaniasis.[78–82] One of the main strategies to combat this phenomenon and to discover new therapeutic leads is to investigate new classes of potentially bioactive compounds.

Therefore, we estimated the in vitro anti-protozoal activity of the newly synthesized gold complexes **1–9** against *Lesihmania major* promastigotes. Compounds **1** ($IC_{50}=0.11\pm0.02$ μM), **2** ($IC_{50}=0.37\pm0.07$ μM), **3** ($IC_{50}=0.86\pm0.2$ μM), **4** ($IC_{50}=0.35\pm0.31$ μM), **5** ($IC_{50}=0.32\pm0.04$ μM), **6** ($IC_{50}=0.12\pm0.03$ μM), **7** ($IC_{50}=1.62\pm0.02$ μM), **8** ($IC_{50}=0.33\pm0.02$ μM) and **9** ($IC_{50}=0.34\pm0.12$ μM) were found to be potent antileishmanial agents, showing high activity when compared to the standard antileishmanial drugs pentamidine ($IC_{50}=14.96\pm0.364$ μM) and amphotericine B ($IC_{50}=0.31\pm0.01$ μM). Comparing the first set of complexes **1–5**, we observe that compounds bearing chloride and $Ac^{F}O$ ligands are better than those bearing acetate ligands (**2** and **4** vs **3**). In addition, gold(I) complex **1** is shown to be the most active compound. While analysing the IPr series (**6-9**) and considering the *N*-aryl and *N*-alkyl series separately, we see a better activity when the second NHC is larger (**6** vs **9** and **8** vs **7**). IPr, being the largest of this series (complex **6**), is subsequently the most active. In general, these results show a significantly higher activity than the best active compounds (IC_{50} up to 3.01 ± 0.29 μM) that were reported in our previous gold(I) series.[55] Results are summarized in Table S1 (see Supporting Information).

3. Cytotoxic activity

Cytotoxicity is the substance's ability of being poisonous to cells. Cytotoxicity is critical to the body's immune system. Low cytotoxicity to healthy cell and high cytotoxicity to cancerous cells is the ultimate goal of many anticancer drugs.[83–84]

The in vitro cytotoxicity of complexes **1–9** was evaluated against HeLa, MCF-7 cancer and 3T3 normal cell lines. Almost all complexes showed a good cytotoxic activity against HeLa, MCF-7 and 3T3 cell lines. Complexes **2** and **5** were found to be non-cytotoxic against the MCF-7 cell line (Table S1, see Supporting Information). Compared to Doxorubicine ($IC_{50}=0.51\pm0.15$ μM), which was used as a standard drug against the HeLa cancer cell line, complexes **7** ($IC_{50}=0.08\pm0.003$ μM), **8** ($IC_{50}=0.3\pm0.02$ μM) and **9** ($IC_{50}=0.08\pm0.003$ μM) showed the most promising results affording comparable to better activities. Doxorubicine was also used as a standard against MCF-3 cancer cell line. Complexes **7** ($IC_{50}=0.172\pm0.008$ μM) and **9** ($IC_{50}=0.17\pm0.002$ μM) showed the most activity towards the latter, surpassing that of Doxorubicine ($IC_{50}=0.92\pm0.01$ μM). Concerning the 3T3 cell line, all complexes showed comparable activities to the standard drug used, cycloheximide ($IC_{50}=0.26\pm0.12$ μM). These results are significantly better than the ones obtained previously with the gold(I) series[55] in all three cell lines, indicating that we are heading in the right direction.

We have successfully evaluated one Au(I)- and 8 Au(III)-bis (NHC) complexes for their in vitro α-glucosidase and β-glucuronidase enzyme inhibition as well as their anti-inflammatory and antileishmanial activities. Promising results were obtained, highlighting the high activity of the gold(III) complexes; compared to the previously reported gold(I) series, these results showed similar, and in some cases, higher,

biological activity. Cytotoxicity tests showed these complexes to possess comparable or better activities than the standard drugs used, and by far surpassing the previously reported gold (I) series. No clear and general trend could be extrapolated; however, both neutral and anionic ligands seem to be crucial for the observed activity and therefore this needs to be carefully tuned for optimal activity. The results of in vitro assays indicate the biological significance and importance of Au-bis (NHC) complexes, more particularly Au(III)-based complexes bearing chloride or acetate ligands, and their potential towards new and innovative discoveries in this field.

Supporting Information Summary

Results of all biological evaluations for complexes **1–9** (Table S1) and details of all experimental procedures and assays are placed in supporting information.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: Anti-inflammatory · Cytotoxicity · Enzyme inhibition · Gold complexes · N-heterocyclic carbene

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