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In Vitro Anti-Atherogenic Properties of N-Heterocyclic Carbene Aurate(I) Compounds

Eleni Sioriki,[a] Ronan Lordan,[b] Fady Nahra,[a] Kristof Van Hecke,[a] Ioannis Zabetakis,[b]* and Steven P. Nolan[a][c]*

Abstract: The anti-atherogenic (anti-inflammatory) properties of various aurate(I) salts, of the general formula [NHC·H][$AuCl_2$] (NHC = N-heterocyclic carbene) have been investigated. The aurates are easily synthesized and obtained in analytically pure form. In addition, the biological activity of these compounds against atheromatosis via *in vitro* inhibition of platelet-activating factor (PAF) induced platelet aggregation was probed. All complexes were found to possess anti-aggregatory properties *in vitro* with [IPr*·H][$AuCl_2$] **6** being the most potent inhibitor of PAF in micromolar concentration. Based on our findings, we conclude that these simply assembled aurates are a very promising class of PAF-inhibitors and anti-inflammatory drugs.

With the projected increase in world population and increased life-expectancy, chronic diseases and especially cardiovascular diseases (CVD) have become the most important leading causes of death, worldwide.[1] CVD is likely to reach epidemic proportions in the coming decades.[2,3] These chronic multifactorial inflammatory diseases are characterized by the development of lesions on the intima wall of medium and large-sized arteries, called atheromata or atherosclerotic plaques. After decades of lethargic progression, these lesions progress suddenly and cause stenosis, thus limiting blood-flow or even arterial rupture causing characteristic clinical manifestations such as distal ischemia, progressive clot formation, and stroke.[4]

One of the most potent mediators of inflammation that plays a crucial role in atherosclerosis is platelet-activating factor (PAF) (1-*O*-alkyl-2-acetyl-*sn*-glycero-3-phosphocholine);[5] which is a well-established biologically active glyceryl-ether phospholipid with 16-18 carbons at *sn*-1 position of the glycerol backbone (Figure 1).[5] PAF modulates angiogenesis, thrombosis, oncogenic transformation, tumor growth, metastasis and the mechanism of atherogenesis (atheromatosis).[4-6] PAF is considered to be a primitive and global cellular bio-regulator[5,8,9] that was initially recognized from its potential cumulative action to platelets but intense studies have shown a broader potent biological activity in numerous cell types and tissues.[10–12]

PAF exerts its biological actions through a unique seven-transmembrane G-protein-coupled receptor known as the PAF-receptor (PAF-R) located on the plasma membrane of a wide variety of mammalian cells, such as leukocytes, neutrophils, platelets, macrophages and endothelial cells.[13,14] PAF and PAF-like molecules are specific, structurally-defined ligands that exclusively bind to PAF-R with exceedingly high affinity.[15–17] Engagement of the PAF-R by PAF or PAF-like lipids triggers an assortment of intracellular signalling cascades. This initiates biochemical mechanisms that induces functional responses of PAF-R bearing cells that then initiate or amplify inflammatory and thrombotic events.[18]

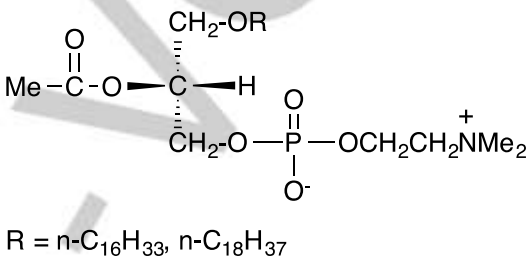

Figure 1. Chemical structure of PAF (1-*O*-alkyl-2-acetyl-*sn*-glycero-3-phosphocholine)[5]

PAF induced inflammatory processes are intensely involved in the initiation and progression of atherosclerosis.[6] PAF is also involved in coronary artery constriction, modulation of myocardial contractility, and the generation of arrhythmias, which relate to cardiac disorders such as ischemia, infarction, and sudden cardiac death.[19,20] Mediators of inflammation play an important role in maintaining a balance in an acute inflammatory response. Therefore, many biochemical and enzymatic markers have been suggested for the determination of inflammation and cardiovascular disease.[21] Synthetic PAF-inhibitors, such as Rupatadine[22] and natural dietary sources[7,23] have demonstrated their ability to inhibit PAF-induced platelet aggregation in washed rabbit platelets and in human platelets.

Transition metal compounds have a wide range of medical applications. Platinum, palladium, ruthenium, and gold metal complexes have been synthesised by the pharmaceutical industry for a number of medicinal applications that include anti-viral, anti-bacterial, anti-rheumatic and anti-inflammatory efficacy.[24] Metals were first used 50 years ago, when Cisplatin (cis-diamminedichloroplatinum(II)) was shown to inhibit cellular division in *Escherichia coli* and was later studied for its anti-tumor activity.[25,26] Cisplatin has since been shown to inhibit PAF-induced platelet aggregation.[27] Previous research on gold metal complexes has shown that they also possess putative bioactivities that may be useful in medicinal applications, particularly in relation to cancer treatment.[28,29] To date, only two gold salts have been developed for medicinal purposes, Au(I)thiolate and auranofin (Au(I)-thiolate triethylphosphine), which have been used in the treatment of rheumatoid arthritis.[28,30] Other complexes have not yet entered clinical trial due to their high cardiotoxicity.[24]

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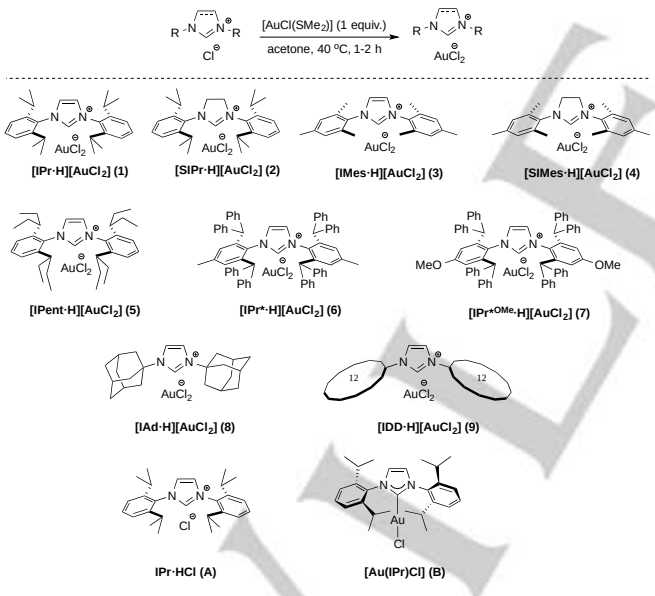
Previous studies have shown that metal complexes, such as square planar rhodium(I) organometallic complexes and a series of novel octahedral rhodium(III) complexes possess potent antithrombotic properties.[27] Recently, NHC-based (NHC = N-heterocyclic carbene) complexes have attracted substantial interest as these compounds possess broad applications in the field of medicine.[31] NHC ligands, are neutral 2-electron donors, that have been extensively used to stabilize organometallic species due to their strong donating properties and tunable steric bulk.[32] In the particular case of gold complexes, the use of NHC ligands has allowed for the isolation of typically unstable species and for the development of highly active homogeneous catalysts.[33] As we have significant expertise in the area of NHCs, of transition-metal bearing NHC ligands and their uses, we sought to investigate the potential anti-atherogenic properties of various recently synthesized aurate(I)-NHC salts as well as evaluate their *in vitro* biological activities against PAF induced platelet aggregation.

As it is clear that PAF plays a critical role in inflammatory processes, the promising results of PAF inhibitor studies evoke the need for the development of more synthetic PAF inhibitors. In this study, nine gold complexes (**1-9**) were synthesized and fully characterized *via* NMR spectroscopy, elemental analysis and mass spectroscopy (Scheme 1). Furthermore, single crystals of complexes **4**, **7** and **9** were grown and their molecular structures were unambiguously elucidated *via* X-ray diffraction analysis (Figure 2). All complexes were air and moisture stable, with the exception of **4**, which decomposed upon prolonged exposure to air. Thus, this complex was excluded from the present biological assays.



Scheme 1. Gold-imidazoli(ni)um, gold-NHC complexes and Imidazolium evaluated for biological activity against PAF.

All gold(I) complexes were synthesised according to our previously reported simple procedure (Scheme 1).[34] X-ray analysis of complexes **4**, **7** and **9** showed that the aurates were indeed formed with a linear [Cl-Au-Cl]$^-$ anion in all cases, along with the [NHC·H]$^+$ as the counter-cation.[35] The family of complexes consists of simple anion/cation pairs where the cation is a saturated or unsaturated imidazole-based heterocycle bearing either alkyl or aryl groups of various size on the heterocyclic nitrogens.

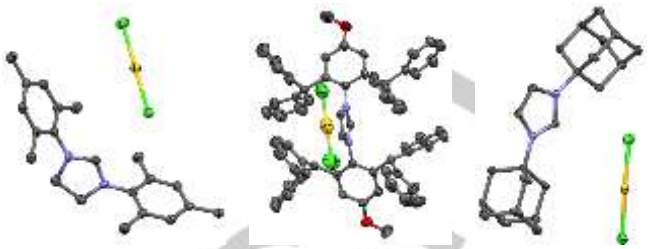


Figure 2. Thermal ellipsoid representations of complexes **4**, **7** and **9** (from left to right) at 50% probability. Solvent molecules and all hydrogen atoms are omitted for clarity.

The putative antithrombotic and anti-inflammatory effects of novel gold *N*-heterocyclic carbene complexes were next assessed. Previous reports have shown that metal complexes can inhibit PAF-induced platelet aggregation in washed rabbit platelets (WRP) and rabbit platelet-rich plasma (PRP) *in vitro* through the PAF receptor dependent pathway.[27] All of the gold compounds tested in this study possessed strong antithrombotic activity as indicated by their IC_{50} value expressed in µM (Table 1), thus confirming that these simple gold metal complexes can inhibit PAF-induced platelet aggregation on human platelets *in vitro*.

Table 1. Inhibition of PAF-induced platelet aggregation in human PRP by gold metal complexes (mean ± SD, n = 3).

Metal Complex	Formula	IC_{50} (µM) (mean ± SD, n =3)
1	[IPr·H][AuCl$_2$]	2.01 ± 0.15^b
2	[SIPr·H][AuCl$_2$]	2.96 ± 0.76^c
3	[IMes·H][AuCl$_2$]	1.67 ± 0.15^b
5	[IPent·H][AuCl$_2$]	1.62 ± 0.36^b
6	[IPr*·H][AuCl$_2$]	0.98 ± 0.24^a
7	[IPr*^{OMe}·H][AuCl$_2$]	1.66 ± 0.38^b
8	[IDD·H][AuCl$_2$]	1.58 ± 0.06^b
9	[IAd·H][AuCl$_2$]	1.69 ± 0.31^b
A	[IPr·HCl]	3.52 ± 1.39^c
B	[AuCl(IPr)]	515.49 ± 102.58^d

^{a,b,c,d} Values with similar superscripts indicate no significant statistical difference; different superscripts indicate significant differences among the different metal complexes (P<0.05) when means are compared using a Fisher's LSD multiple comparison test.

The IC_{50} values reflect the inhibitory strength of each compound towards PAF induced platelet aggregation (Table 1). A low IC_{50} value indicates a strong inhibitory effect against PAF for a given concentration of the metal complexes. The complexes synthesized in this study have displayed varying levels of inhibition against the interactions of PAF and the PAF-R in human platelets. As can be seen in Table 1, complex **6** exhibited the lowest IC_{50} value (0.98 µM ± 0.24) indicating that this complex was the most potent against PAF-induced platelet aggregation. The IC_{50} value for c **6** was significantly different from all other complexes. Furthermore, when comparing the IC_{50} of **1**, **3**, **5**, **7**, **8**, and **9**, no significant difference is noticed. These similar IC_{50} values may be due to the fact that there are only subtle structural and electronic differences between these complexes that lead to similar antithrombotic activity; it appears that alkyl or aryl substituents on the nitrogen atoms do not significantly influence the change in activity. However, when comparing **6** to the closely related **7**, we see a significantly higher activity in the case of **6**, which most likely is due to

electronic effects and/or solubility issues (since the difference between **6** and **7** lies mainly in their electronic properties). The presence of a methoxy group may account for this difference as the lies at the periphery of the complex and may affect solubility in the biological medium.[36] In contrast, complex **2** had a much higher IC_{50} value than all other aurates in this study; this could be due to the noticeable change in electronic properties since this is the only complex bearing a saturated backbone. These data indicate that major electronic variations, especially on the NHC backbone, could be key for further developments in future aurate-NHC drug design. These avenues are presently being explored in our laboratories.

Two other compounds were tested to quantify any background activity for ligand and neutral complexes. Compound **A**, [IPr•HCl], was examined to study the activity, if any, of the imidazolium ligand and compound **B**, [AuCl(IPr)], to model the neutral Au(I) system.[28,29,34] Compound **A** contains the IPr core without the gold moiety (only Cl^- as counterion; this will serve as a blank and will thus allow us to confirm the need for the gold moiety when compared to its close counterpart complex **1**) and compound **B** represents another class of gold complexes that have shown potential in previous biological studies, though having lower activity than the aurate-class showcased herein. It is clear from Table 1 that compound **B** was far less potent than the other complexes (515.49 µM ± 102.58), however this compound possessed a relatively low IC_{50} in comparison to those tested on WRP in the literature. In contrast compound **A** demonstrated a lower IC_{50} (3.52 µM ± 1.39) than compound **B**; however, this is still higher than all the other aurate complexes.

These data highlight the important difference between the various classes of NHC compounds studied herein (NHC-aurates **1-9** vs gold-NHC compound **B** vs gold-free imidazolium compound **A**), where the combination of the gold moiety and NHC salt present in the aurates seems to be crucial for higher activity. To the best of our knowledge, metal complexes have not been tested in human PRP; therefore, for the first time, this study has confirmed that these gold complexes possess anti-aggregatory properties against PAF-induced platelet aggregation *in vitro*.

In previous research, WRP were the preferred method of platelet aggregometry studies, due to their stability and longevity while testing. Rabbit platelets also exhibit similar physiological modes of platelet activation and aggregation to human platelets, and thus is one of the main experimental models of choice to replicate human platelets.[37,38] Therefore, the observed IC_{50} values of the studied gold complexes against PAF-induced platelet aggregation can cautiously be compared with the IC_{50} values of metal complexes determined using rabbit PRP and WRP in previous studies. The obtained IC_{50} values of the aurates are within range of the IC_{50} values determined in studies of rhodium and ruthenium metal complexes by PAF-induced platelet aggregation in WRP. Rhodium complexes possessed IC_{50} values of 0.015 - 2.6 µM in WRP, and IC_{50} values of 18 - 582 µM in rabbit PRP, whereas ruthenium complexes had IC_{50} values ranging from 0.18 – 11.8 µM in WRP and 10.5 – 900 µM in rabbit PRP.[27,38] Of note, the iridium and ruthenium complexes are obtained through multistep synthetic routes whereas the present gold complexes are obtained after simply mixing a gold precursor and a commercially available (or synthetically straightforwardly obtained) imidazolium salt. Interestingly, the NHC-aurates presented here inhibit PAF-induced platelet aggregation to the same order of magnitude of known natural and pharmaceutical PAF antagonists, namely Web 2170 (Bepafant), BN 52021 (Ginkgolide B), Cedrol and Rupatadine (0.02 µM, 3.6 µM, 13 µM and 0.26 µM respectively in WRP).[39–44] Therefore, these gold complexes may be viable for further research and development for the purpose of anti-inflammatory therapeutic agents for non-communicable diseases such as cardiovascular disease and cancer. Further *in vivo*, *ex vivo*, and clinical research is required in order to establish the efficacy of these compounds as therapeutic agents.

PAF orchestrates its biological activity through a specific seven-transmembrane receptor coupled with G-proteins (PAF-R). Therefore, it is proposed that these gold compounds may possess anti-inflammatory and anti-atherogenic effects. PAF-R antagonists have exhibited promising results *in vitro* and *in vivo* as anti-angiogenic molecules in several cancer cells and tumors.[45] Gold complexes similar to those tested in this study, have already exhibited anti-inflammatory activity (respiratory burst assay) and cytotoxicity against HeLa (cervical cancer), MCF-3 (breast cancer), and 3T3 (mouse fibroblast) cell lines.[29] Notably, PAF has been implicated in coordinating angiogenesis, oncogenic transformation, tumour growth, and metastasis in cancer (AA). Research has shown that PAF plays a significant metastatic role in difficult to treat cancers such as melanoma, where it has shown to promote metastasis *in vivo*. Furthermore, it has been demonstrated that the PAF-R antagonist PCA4248 has inhibited experimental human melanoma lung metastasis in nude mice.[46] Therefore, as similar gold complexes to those synthesized for this study possess anti-cancer activity,[28,29] further research on the antagonistic actions of the herein presented aurates against the PAF-R is warranted and currently ongoing in our group, as they are potentially powerful anti-metastatic agents.

In summary, the present work has evaluated for the first time the structural and potent antithrombotic properties of gold *N*-heterocyclic carbene complexes towards PAF-induced aggregation of human PRP, at concentrations comparable with those of classical PAF-inhibitors. The simple and atom-economical synthetic route to these aurates renders them attractive from an accessibility perspective. The inhibitory effect of all aurate compounds was tested and expressed by their IC_{50} value in µM. All complexes were found to possess anti-aggregatory properties *in vitro* with **6** being the most potent inhibitor of PAF in micromolar concentration. Based on our findings, we can conclude that these aurates are indeed a very promising class of PAF-inhibitors and anti-inflammatory drugs. Further investigations into molecular design are ongoing with the aim of reaching even higher levels of efficacy in the *in vitro* biological activity detailed in this study.

Acknowledgements

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Keywords: Platelet-activating factor • N-heterocyclic carbene • Aurate • atheromatosis • Anti-atherogenic

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Entry for the Table of Contents

Layout 1:

COMMUNICATION

A series of NHC-aurates were synthesised and evaluated for the first time for their anti-atherogenic properties towards PAF-induced aggregation of human PRP. Both the gold and NHC moieties were shown to be crucial for achieving good activity. All complexes were found to possess *in vitro* anti-aggregatory properties.

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