# Improved Antiproliferative Activity and Fluorescence of a Dinuclear Gold(I) Bisimidazolylidene Complex via Anthracene-Modification

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**Abstract:** A straightforward modification route to obtain mono- and di-substituted anthroyl ester bridge functionalized dinuclear Au(I) *bis-N*-heterocyclic carbene complexes is presented. The functionalization can be achieved starting from a hydroxyl-functionalized ligand precursor followed by transmetallation of the corresponding Ag complex or *via* esterification of the hydroxyl-functionalized gold complex. The compounds are characterized by NMR-spectroscopy, ESI-MS, elemental analysis and SC-XRD. The mono-ester Au complex shows quantum yields around 18%. In contrast, the corresponding *syn*-di-ester Au complex, exhibits significantly lower quantum yields of around 8%. Due to insufficient water solubility of the di-ester, only the mono-ester complex has been tested regarding its antiproliferative activity against HeLa- (cervix) and MCF-7- (breast) cancer cell lines and a healthy fibroblast cell line (V79). $IC_{50}$ values of 7.26 μM in the HeLa cell line and 7.92 μM in the MCF-7 cell line along with selectivity indices of 8.8 (HeLa) and 8.0 (MCF-7) are obtained. These selectivity indices are significantly higher than those obtained for the reference drugs cisplatin or auranofin.

*N*-heterocyclic carbenes (NHCs) have been applied in coordination chemistry as promising alternatives to phosphine-type ligands for the stabilization of late transition metals since the early 1990ies.[1] They offer more possibilities for modification and allow a versatile fine-tuning of steric and electronic properties.[1d] For decades, NHC complexes have been applied successfully in catalysis.[1b,2] Recently, they have become more prominent in bioinorganic chemistry for example in the design of metallodrugs due to their ability to stabilize late transition metals exceptionally well.[3]

Especially Au(I) NHC complexes are emerging as promising antitumor agents, potentially overcoming for example resistance issues of clinically applied platinum-based drugs.[4] They are known to inhibit the mitochondrial and cytosolic thioredoxin reductases (TrxR), leading to several apoptotic pathways.[5] Mitochondrial uptake is increased by the delocalized lipophilic cationic (DLC) character of Au(I) *bis*-NHC complexes.[5c,6] Owing to some cancer cell lines possessing a more negative potential in comparison to their healthy analogues, the mitochondrion arose as an attractive target for a more selective anticancer therapy.[5b,c,7]

In contrast to mononuclear Au(I) NHC complexes, dinuclear Au(I) complexes bearing bidentate NHCs exhibit a higher stability towards nucleophilic and reducing blood components (e.g. glutathione).[10] Furthermore, aurophilic interactions might be beneficial for cell imaging studies due to their often observed fluorescence.[11] In addition, functionalization of the bridge between both NHC moieties of the ligand enables potential sites for bioconjugation and the synthesis of theranostic agents.[12] Recently, Au(I) bridge-functionalized NHC complexes (e.g. allyl,[13] hydroxyl[8] or carboxylate[9]) have been reported. The cytotoxic properties of the hydroxyl- and carboxylate-complexes have been evaluated (Figure 1).

Depending on the *N*-substituents, the complexes generate mixtures of different stereoisomers with respect to the methylene bridge. The most lipophilic mesityl *N*-substituted Au(I) complex shows the highest activity, while less bulky wingtips (Me and *i*Pr) result in negligible activity.[8–9] In further studies the

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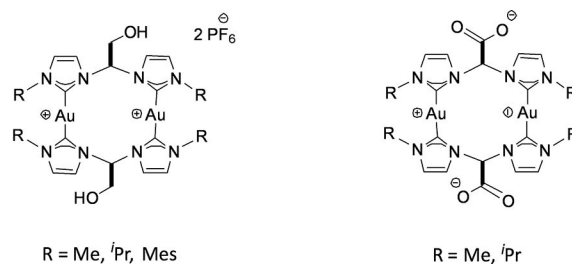
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**Figure 1.** Previously reported hydroxyl[8]- and carboxylate[9]- bridge functionalized Au(I) bis-NHC complexes.

influence of the different isomers on the biological behavior was examined. Although, the *syn-* and *anti-* isomers do not show significant differences in the antiproliferative activity, in the case of $^{i}$Pr N-substituents a higher stability against cysteine was observed for the *syn*-isomer.[8b] However, the synthesis of mesityl *N*-substituted *bis*-imidazolium salts requires long reaction times and significantly hinders subsequent modifications in comparison to less sterically demanding wingtips (Me and $^{i}$Pr).[8a]

Based on these observations, in this work, the literature-known hydroxyl-functionalized NHC system with $^{i}$Pr N-substituents has been selected to study the applicability for bridge modifications. Considering that sterically demanding groups presumably impact the isomerization of the complexes, which might lead exclusively to one major isomer, 9-anthracene-carboxylic acid (9-ACA) was chosen for conjugation.

Due to a post-modification method, the mono- and the di-anthracene-ester of the Au(I) complex can be formed. The novel compounds are characterised by $^{1}$H- and $^{13}$C-NMR spectroscopy, elemental analysis and electrospray mass spectrometry (ESI-MS). In addition, the introduction of the sterically demanding and non-polar anthracene ester group presumably increases the lipophilicity of the complex compared to its hydroxyl-functionalized derivative, which might be beneficial for biological applications. As reported for other Au(I) NHC complexes, lipophilicity has been shown to significantly impact the antiproliferative activity. Complexes with a higher lipophilic character show increased cytotoxicity as a result of a better cellular uptake, in line with the observation that the Mes substituted complex was more active than its $^{i}$Pr and Me counterparts amongst all reported hydroxyl bridge-functionalized *bis*-NHCs.[14] Additionally, anthracene compounds often show fluorescence.[15] Therefore, the novel anthracene ester

modified Au(I) compounds might enable fluorescence microscopy and allow *in vitro* studies of the mechanism of action of this type of complexes. Hence, quantum yields are determined in order to evaluate their potential eligibility for this method.

The imidazolium salt $H_2[^{i}PrL^{OH}]_2(PF_6)$ (**1**) is modified by esterification with excess of anthroyl chloride to give the modified imidazolium salt $H_2[^{i}PrLAnth]_2(PF_6)_2$ (**3**), which is subsequently converted into the corresponding silver(I) complex $Ag[^{i}PrL_{Anth}]_2(PF_6)_2$ (**4**) (Scheme 1, top) by reaction with Ag$_2$O. The modification is conducted with $PF_6^-$ as counter-ion to ensure a better solubility in organic solvents. The imidazolium salt **3** shows the same solubility as the unmodified compound **1**, being soluble in DCM, DMF, DMSO and MeCN. It was characterised by NMR spectroscopy, ESI-MS and elemental analysis. The absence of the OH-triplet and the shift of the CH$_2$ group to 5.50 ppm proofs the successful synthesis, which is additionally confirmed by ESI-MS and elemental analysis data. The complex is isomerically pure, which is confirmed by $^{1}$H-NMR spectroscopy.

Single crystals of **4** suitable for single crystal X-ray diffraction analysis (SC-XRD) were obtained by slow vapor diffusion of diethyl ether into a solution of the complex in acetonitrile (Figure 2).

The complex shows similar structural properties as the unmodified ($Ag[^{i}PrL^{OH}]_2(PF_6)_2$). **4** crystallizes in the anti-exo configuration. The bond length and angles show no unexpected trends in comparison to the unmodified complex, indicating no significant influence of the modification on the metal-NHC bonds. The Ag1–Ag2 distance ($\approx 3.6$ Å) is higher than the sum of van-der-Waals-radii ($\approx 3.4$ Å) and consequently no argentophilic interaction is observed.[16]

After transmetallation to Au(I), the formation of an isomer mixture takes place and could not be prevented (see ESI
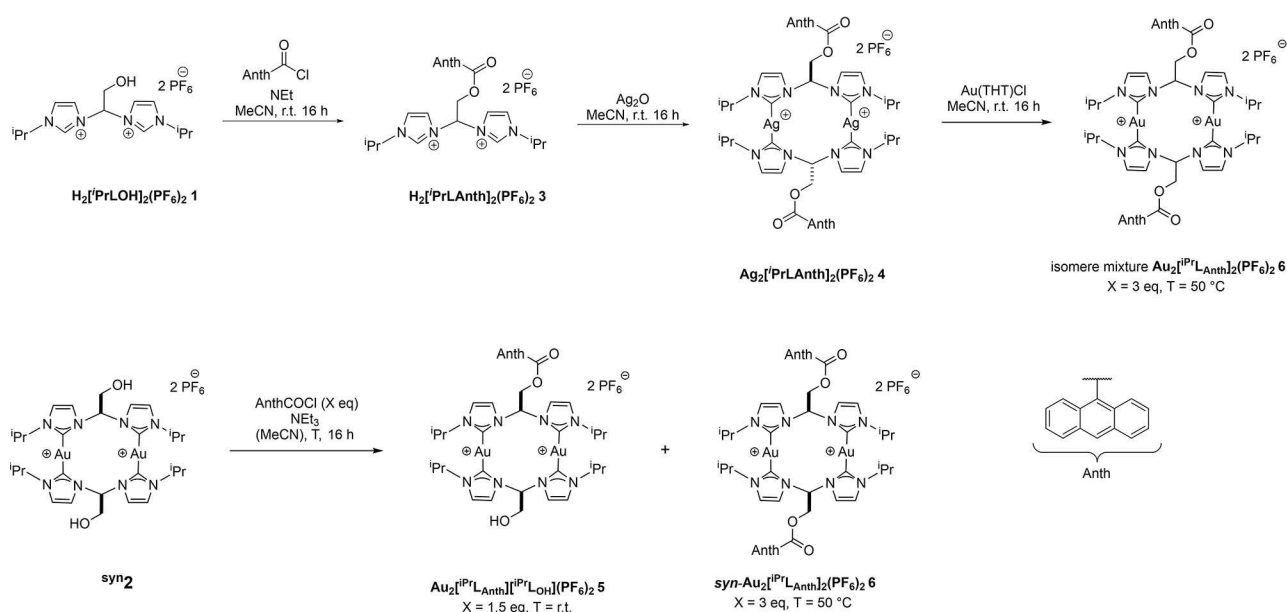


**Scheme 1.** top: Esterification reaction, silver complex formation and transmetallation with Au(THT)Cl leading to an isomer mixture of **6**. Bottom: General post modification of the un-modified Au(I) *bis*-NHC complex. 1.5 eq AnthCOCl, T = 25 °C: mainly **syn-Au$_2$[$^{i}$PrL$_{Anth}$][$^{i}$PrL$_{OH}$](PF$_6$)$_2$ 5**; 3.0 eq AntCOCl, T = 50 °C: **syn-Au$_2$[$^{i}$PrL$_{Anth}$]$_2$ (PF$_6$)$_2$ 6**.
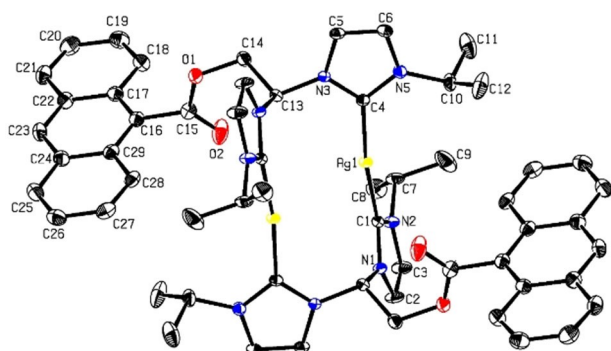
**Figure 2.** ORTEP-style representation of the cationic fragment of **Ag** [$^i$**PrL$_{Anth}$**]$_2$(**PF$_6$**)$_2$ **4**. All atoms are shown using ellipsoids at a 50% probability level. H-atoms, counter-anion and co-crystallized solvents are omitted for clarity. Selected bond length (Å) and angles (°): Ag1-C1 2.0875(16), Ag1-C4 2.0907(16), C1-Ag1-C4 172.43(6). Ag1–Ag2 distance: 3.6 Å.

Figure 4). Several unsuccessful attempts to separate the isomers, either by crystallization or by reversed phase high performance liquid chromatography (RP-HPLC), were undertaken. Thus, an alternative methodology was applied, namely post modification of **Au$_2$[$^i$PrL$^{OH}$]$_2$(PF$_6$)$_2$ (2)**. Prior to esterification, the isomers were separated by HPLC and only the major isomer $^{syn}$**Au[$^i$PrL$^{OH}$]$_2$(PF$_6$)$_2$ ($^{syn}$2)** was further modified (Scheme 1, bottom). The ratio between the mono- and di-esterification products is controlled by the reaction conditions (amount of AnthCOCl and temperature). Treatment with excess of AnthCOCl at 50 °C leads to the di-ester **6**. Reaction at room temperature and 1.5 eq. anthroyl chloride results in a mixture of the un-, mono- and di-esterification product, mainly containing the mono-ester **5**. The mixture is separated by RP-HPLC to yield both complexes. The products are characterised by NMR spectroscopy, ESI-MS and elemental analysis.

The complexes are soluble in organic solvents (e.g. MeCN, DMF, DMSO and DCM), but not well soluble in water. Even in a DMSO/water mixture (1% DMSO) the di-ester **6** partially precipitates at 100 μM concentration, confirming the expected higher lipophilicity *via* esterification. However, the more polar mono-ester **5** shows a suffcient water solubility for further biological applications at this concentration.

To ensure the water solubility of the di-ester, anion exchange to chloride *via* salt metathesis[17] or with an ion exchange resin[18] was attempted similar to the respective literature procedures.

Due to anthracene conjugation, the complexes **5** and **6** show luminescence. Compared to the unmodified complex **2** four additional peaks are observed in the range between 300 nm to 400 nm with the maximum having a wavelength of 364 nm in the UV/vis spectrum (Figure 3 top and ESI-Figure 10). In alignment with literature these four maxima can be assigned to the anthracene moiety.[19] A comparison of the excitation spectrum of complex **5** and the correspondig UV/vis spectrum proofs that those absorption maxima are involved in the fluorescence (Figure 3 top and middle, ESI Figure 14). The emission spectrum depicts one maximum at 479 nm (Figure 3 bot and ESI Figure 13). Compared to the modified imidazolium
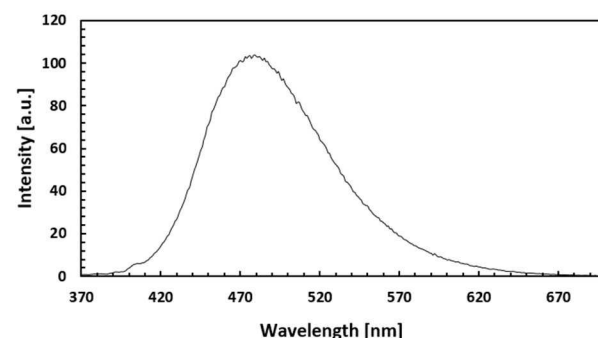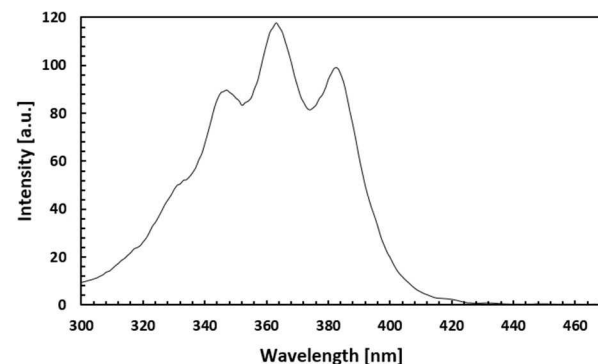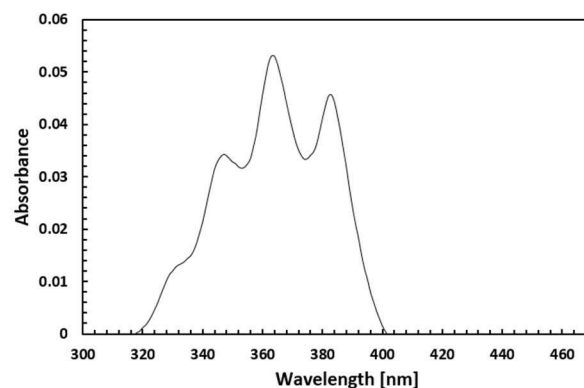


**Figure 3.** UV/vis spectrum (top), excitation spectrum (at $\lambda = 479$ nm, maximum $\lambda_{max} = 363$ nm; middle) and emission spectrum (at $\lambda = 363$ nm, $\lambda_{max} = 479$ nm; bottom) of **5** in acetonitrile.

salt **3** no remarkable differences are observed, regarding the absorption and excitation maxima (see ESI Figures 11–14). However, the quantum yield of 18% is significantly lower (Table 1), in comparison to the imidazolium salt (28%), as reported for various other complexes bearing heavy transition metals.[20]

Although the quantum yields are relativly low, further cell imaging studies *via* fluorescence microscopy should be possi-

**Table 1.** External Quantum yields measured in acetonitrile. Excitation wavelength $\lambda = 350$ nm.

| Compound | Ex. Quantum Yield |
|---|---|
| $^{syn}$**Au$_2$[$^i$PrL$_{OH}$]$_2$(PF$_6$)$_2$** $^{syn}$**2** | – |
| **H$_2$[$^i$PrLAnth]$_2$(PF$_6$)$_2$ 3** | 28% ± 0.7 |
| **Au$_2$[$^i$PrL$_{Anth}$][$^i$PrL$_{OH}$](PF$_6$)$_2$ 5** | 18% ± 0.4 |
| **Au$_2$[$^i$PrL$_{Anth}$]$_2$(PF$_6$)$_2$ 6** | 8% ± 0.2 |

ble, since confocal microscopy was successfully applied at lower quantum yields.[21] Interestingly, although having two anthracene moietys, the di-ester complex **6** exhibits significantly lower quantum yields compared to **5** (8% vs. 18%) (Table 1). Simultaneously when **6** is irridiated at 366 nm, a new species **6\*** is observed in the $^1$H-NMR spectrum in $CD_3CN$. Heating the mixture at 37 °C for 2 h **6** is fully reformed (Figure 4). Indicating a reversible photoreaction. This reaction is also monitored by UV/vis spectroscopy (ESI-figure 18). A similar behavior has been reported for 9-ACA, which undergoes a [2+2] photocycloaddition.[22]

The antiproliferative properties of the mono-ester **5** was evaluated by monitoring its ability to inhibit the growth of two different cancer cell lines. The $IC_{50}$ values determined are presented in Table 2.

HeLa was chosen for a better comparison, since the unmodified complex $^{syn}$**2** was previously tested in this cancer cell line and proven to be inactive ($IC_{50}$ value > 100).[8b] Additionally, the antiproliferative activity against a breast cancer cell line (MCF-7) was investigated, since breast cancer is one of the most common types of cancer. Aimed at investigating the potential selectivity against cancer cell lines, the antiproliferative activity against a normal fibroblast cell line (V79) was tested as well. A selectivity index (SI) is expressed as a ratio of the $IC_{50}$ value of the healthy cell line and the $IC_{50}$ value of the cancer cell line. Due to the insufficient solubility in the cellular medium compound **6** was excluded from these experiments.
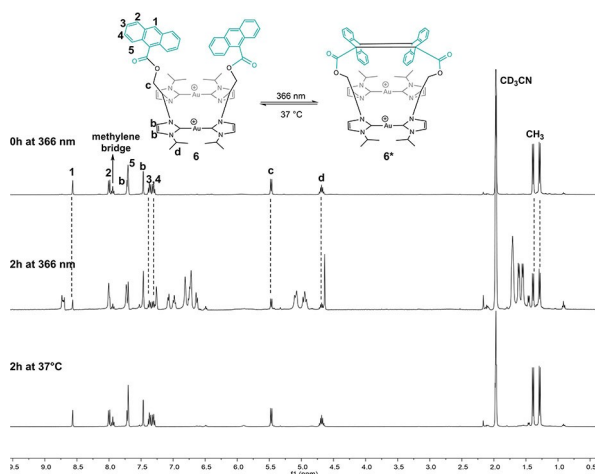
The $IC_{50}$ values were determined by a colorimetric method (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide, MTT assay). As reference drugs, cisplatin and auranofin were also tested in the same cell models under the same conditions using an appropriate range of concentrations (0.7–100 µM). Dose-response curves were obtained after long-term exposure (48 h).

The mono-ester **5** exhibits $IC_{50}$ values in the low µM range, superior to cisplatin in MCF-7 cell line. In contrast, $^{syn}$**2** is inactive ($IC_{50}$ values > 100 µM) in various cell lines (HeLa, HepG2 and A549), thus proving, that the modification of the hydroxyl group with an anthracene ester leads to a drastic improvement of the cytotoxicity.[8]. Moreover, the compound **5** depicts a significantly increased selectivity towards cancer cells (SI ≈ 8) in comparison to both reference drugs auranofin and cisplatin.

In summary, a straightforward modification of hydroxyethyl bridged imidazolium salt **1** with anthracene and the synthesis of the corresponding silver(I) and gold(I) complexes are described. In contrast to its unmodified hydroxyl-functionalized derivative $^{syn}$**2**, the mono-anthracene complex **5** exhibits good cytotoxicity in HeLa and additionally in MCF-7 cancer cell lines with $IC_{50}$ values of 7.3 µM and 7.9 µM, respectively. In addition, it presents a certain degree of selectivity towards tumoral cell lines compared to a healthy one with selectivity indices around 8. Due to the labeling with an anthracene ester, complex **5** exhibits a quantum yield of 18%, which allows for further cell imaging studies. One hydroxyl group of **5** is still available for further post-modifications, which can be used for bioconjugation, enabling a target oriented therapy (e.g. conjugation of a receptor specific peptide) to address certain overexpressed receptors in cancer cells in order to combine the reported cytotoxicity and fluorescence with a high selectivity.



**Figure 4.** Reversible photocycloaddition of 6. Irridiation at 366 nm in $CD_3CN$ for 2 h. Reverse reaction: heating the solution in $CD_3CN$ at 37 °C for 2 h.

**Table 2.** $IC_{50}$ values in µM of the complex 5, cisplatin and auranofin as reference after 48 h incubation time. The selectivity index is given in parentheses.

| compound | HeLa | MCF-7 | V79 |
|---|---|---|---|
| **5** | 7.26 ± 4.3 (8.8) | 7.92 ± 1.0 (8.0) | 63.7 ± 8.6 |
| Cisplatin | 2.8 ± 0.5 (2.6) | 20.6 ± 6.3 (0.3) | 7.4 ± 3.0 |
| Auranofin | 1.23 ± 0.04 (0.21) | 0.28 ± 0.1 (0.96) | 0.27 ± 0.09 |

## Acknowledgements

## Conflict of Interest

The authors declare no conflict of interest.

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