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A novel natural chlorin metal complex containing gold(I) in the macrocycle periphery

Viktor A. Pogorilyy,* Valeria I. Efimova, Julia S. Kartava, Sergey I. Tikhonov, Maxim N. Usachev and Mikhail A. Grin

M. V. Lomonosov Institute of Fine Chemical Technologies, MIREA – Russian Technological University, 119571 Moscow, Russian Federation. E-mail: pogorilviktor@gmail.com

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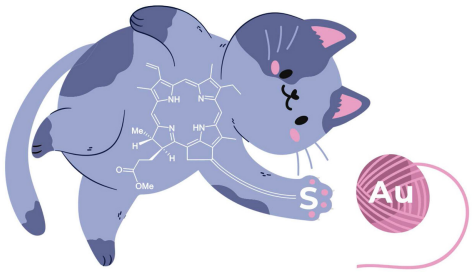
An original synthesis of methyl ester of 13[1]-thioketone pyropheophorbide *A* containing a gold(I) complex at the periphery of the macrocycle (at the E exocycle) *via* the formation of an S–Au bond is performed. The stability of this complex in aqueous solutions at various pH values as well as the effectiveness of its binding to DNA are evidenced.

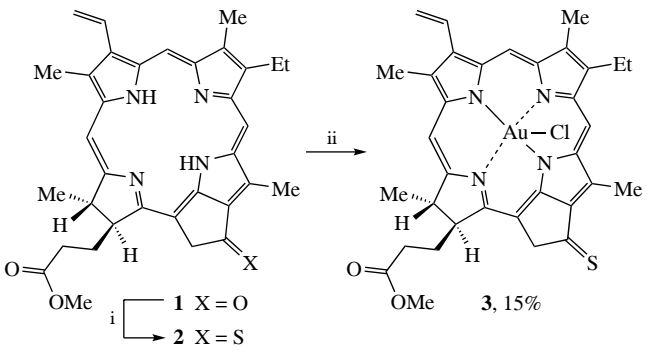


Keywords: pheophorbide, chlorophyll *A*, thiocarbonyl compounds, sulfur-containing compounds, gold(I) complexes, combined action.

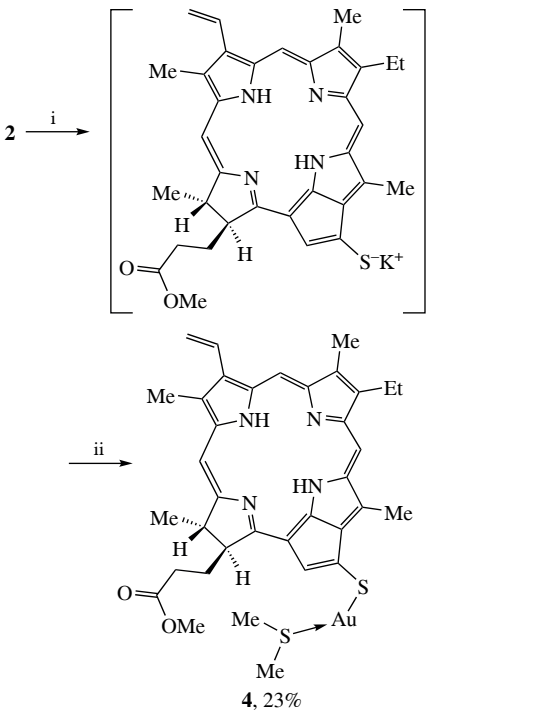
Thionation of carbonyl compounds plays an important role in the synthesis of pharmacologically active compounds, since the replacement of an oxygen atom with sulfur causes an increase in the specific activity, stability of the latter, as well as optimization of the hydrophilic–hydrophobic balance of the target molecules.[1–4] Previously, in our research group thio derivatives of natural chlorins were obtained by various methods, including the use of the Lawesson's reagent.[5–7] However, the resulting thioketone functional group turned out to be unstable as it underwent hydrolysis under physiological conditions. The production of a chlorin metal complexes[8,9] in which the nucleophilic thioketone sulfur atom is coordinated to an Au^{I} complex promotes the stabilization of the thioketone function and facilitates its photodynamic and chemotherapeutic potential for use in oncology. The main application of gold complexes in medicine today is oncology, but there are many studies of their antiviral, antimicrobial and other activities.[10,12]

The metal complexes were obtained using several methods. The conventional one (Scheme 1)[13–15] involves the reaction of chloro(dimethyl sulfide)gold(I) $(Me_2S)AuCl$ with a 13[1]-thiocarbonyl derivative of pyropheophorbide *A* **2** in toluene with triethylamine. During the reaction, instead of the expected addition at the thiocarbonyl group, the gold disproportionation occurs, the precipitation of free metal Au^0 is observed and a chloride metal complex containing Au^{3+} in the center of macrocycle **3** is formed.

The second synthetic approach includes the activation of the thiocarbonyl group of thione **2** by *in situ* formation of potassium thioenolate and the reaction of the latter with $(Me_2S)AuCl$ (Scheme 2). In this way, the target complex **4** is obtained.



Scheme 1 *Reagents and conditions*: i, Lawesson's reagent, toluene, Et_3N, 35 °C, Ar; ii, toluene, $(Me_2S)AuCl$, Ar, dark.



Scheme 2 *Reagents and conditions*: i, KOH, EtOH, 15 min; ii, $(Me_2S)AuCl$, 48 h, Ar, dark.

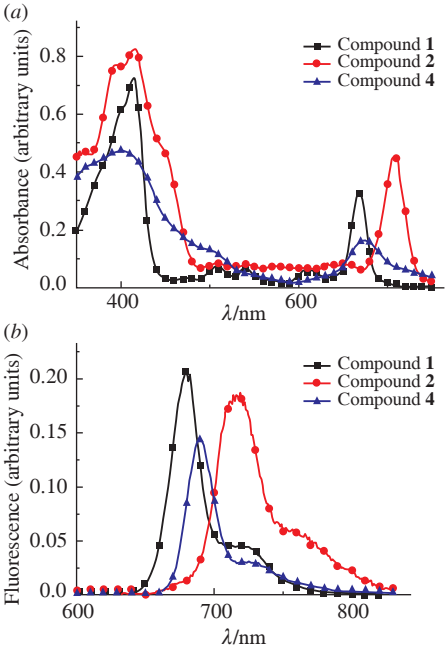


Figure 1 (*a*) Electronic absorption and (*b*) fluorescence spectra of the methyl ester of pyropheophorbide *A* **1**, methyl ester of 13[1]-thioketone pyropheophorbide *A* **2**, metal complex of methyl ester of 13[1]-thioketone pyropheophorbide *A* with Au^I **4**. Absorption and fluorescence spectra were obtained at the same concentration using dichloromethane as a solvent.

For compound **4**, a bathochromic shift of absorption and fluorescence maxima compared to the initial methyl ester of pyropheophorbide *A* **1** by 14 nm was detected (Figure 1). As noted earlier, the thiocarbonyl derivative of chlorin **2** in aqueous solutions is unstable and would hydrolyze to form pyropheophorbide **1**, while compound **4** exhibits varying stability depending on the pH of the medium (see Online Supplementary Materials, Table S1). At pH 7, it is stable for the first four hours, and at pH 9, there is a slight decrease in its stability during the first 4 h and subsequent stabilization up to 24 h. At pH 4, compound **4** undergoes rapid degradation, which is monitored by an 8-fold decrease in absorption intensity. The addition of 0.1% Twin 80 significantly increases the stability of the compound in aqueous solutions for up to 24 h at various pH values.

Gold(I) metal complexes are promising chemotherapeutic agents, one of whose mechanisms of action is binding to DNA.[16–19] To predict the activity of the obtained complex, docking was performed using the HEX 8.0.0 program,[20–22] and visualization of the obtained data was implemented using the BIOVEA Discovery Studio program.[23,24] The data in Table 1 show an increase in the binding energy to DNA when moving from compound **1** to gold complex **4**. Absorption spectroscopy in the UV-visible region of the spectrum was used to evaluate the interaction of single-stranded DNA (SS-DNA) with compounds **1** and **4**.[25–27] From the results presented in Table 1, it follows that conjugate **4** with a gold atom on the periphery of the macrocycle binds to DNA 3.5 times more efficiently than the parent compound, which correlates with the predicted docking results.

Table 1 Calculated total interaction energy and experimentally obtained binding constant and Gibbs energy for compounds **1** and **4**.

Compound	Docking	DNA binding test	
	Total interaction energy/kJ mol^{-1}	Binding constant *K*/ $\times 10^6$ dm^3 mol^{-1}	Gibbs energy/ kJ mol^{-1}
1	–313	2.7	–11.3
4	–324	6.4	–36.8

To summarize, a synthetic route was developed for the metal complex of methyl ester of 13[1]-thioketone pyropheophorbide *A* with Au^I on the macrocycle periphery, with the 'S–Au' bond formation conferring a unique structure and promising functionalities. The metal complex demonstrated high stability in aqueous media across a wide pH range and exhibited efficient DNA-binding, suggesting potential applications in biomedicine and coordination chemistry.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.71267/mencom.7810.

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