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Gold(III) complexes with hydroxyquinoline, aminoquinoline and quinoline ligands: Synthesis, cytotoxicity, DNA and protein binding studies☆

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ABSTRACT

In this article, we report on the synthesis and the chemical and biological characterization of novel gold(III) complexes based on hydroxyl- or amino-quinoline ligands that are evaluated as prospective anticancer agents. To gain further insight into their reactivity and possible mode of action, their interactions with model proteins and standard nucleic acid molecules were investigated.

1. Introduction

The therapeutic application of metallic complexes in cancer treatment is one of the main areas of medicinal inorganic chemistry, where cisplatin represents the principal drug in widespread clinical use. In recent years, gold(I) and gold(III) complexes have attracted much attention among medicinal inorganic chemists because of their strong cytotoxicity in vitro and of their different mode of action in comparison to cisplatin [1–12]. Indeed, although platinum(II) and gold(III) complexes are isoelectronic (d^8 configuration) and isostructural (square planar geometry), they were found to show different biological profiles and mechanisms of action [13]. For platinum(II) complexes, DNA is commonly believed to be the primary target while inhibition of a few crucial proteins seems to be the main mechanism of action for cytotoxic gold complexes. In addition, ligand exchange is faster in gold(III) complexes compared to platinum(II) ones. In this sense, the chelation of the metallic centre with multidentate ligands have shown to enhance the stability of the complex, but an excessive stabilization of the gold centre may be detrimental to the biological activity (e.g. Au(cyclam)) [14]. The selection of ligands is also crucial to modulate the oxidizing character of the gold(III) centre and to decrease its pronounced tendency to be reduced to gold(I). In the last few years, new promising antitumor gold(III) complexes containing nitrogen-donor polyaromatic ligands, such as terpyridine and phenanthroline derivatives (see Chart 1) have been reported to control these two features [15,16].

In the context of polyaromatic ligands, hydroxyquinolines were reported to be promising therapeutic agents for Alzheimer's dementia due to strong complexation with copper and zinc ions which are involved in the ß-amyloid peptide aggregation that causes neuronal loss in Alzheimer's disease patients [17–20]. Moreover, hydroxyquinolines are known to exhibit a variety of biological activities [21–25]. In particular, clioquinol (5-chloro-7-iodo-quinolin-8-ol) is currently commercially available as an antifungal and antibacterial drug. Regarding the anticancer activity of the hydroxyquinolines, a number of interesting features were highlighted. They are classified as proteasome inhibitors through complexation with copper ions [26–29]; they induce apoptosis of human cancer cell lines by targeting zinc to lysosomes [30]; they are NF-kappa β inhibitors [31,32], or stimulate macrophages to release tumor necrosis factor alpha [33] among other anticancer activities. All these applications are related to the use of hydroxyquinolines as scavengers of metals involved in the pathogenesis of various diseases. Recently, we have synthesized new platinum complexes [34–36] containing hydroxyquinolines in their structure and could demonstrate high in vitro antitumor activity and their interactions with DNA [37]. Therefore, we considered feasible the synthesis of new gold complexes

Abbreviations: EDTA, Etilendiaminotetraacetic acid; PBS, Phosphate buffered saline; TAE buffer, Tris-acetate–EDTA buffer.

☆ This manuscript is dedicated to Prof. Giovanni Natile.

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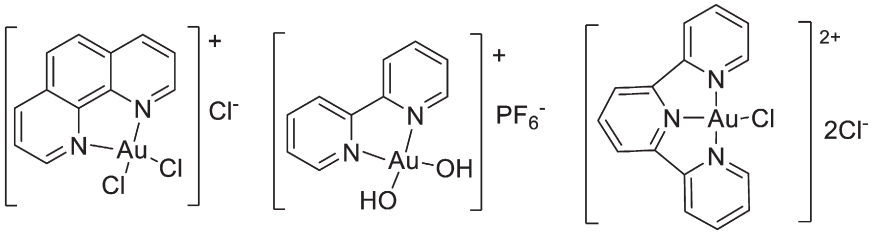


Chart 1. Antitumor active gold complexes containing nitrogen-donor polyaromatic ligands.

analogous to the platinum ones and their possible antiproliferative activity.

In the present study, we report on the synthesis and characterization of new gold(III) complexes containing hydroxyquinolines as ligands (Chart 2, complexes **2**). To explore potential structure-activity relationships, the role of the coordinating atom (oxygen) of the quinoline ligand was investigated by the preparation of one complex with an amino coordinating group (complex **3**). In addition, the synthesis of the quinoline-monocoordinated complex **4** was shown by the chelation effect of the ligand in the cytotoxic activity. The stability and electrochemical properties of the complexes were determined, and the antiproliferative evaluation of the compounds was done in vitro with four human cancer cell lines. Finally, we studied the interactions of these complexes with DNA and with model proteins like cytochrome c to establish adducts formation at the biomolecular level.

2. Experimental

2.1. Material and methods

All reagents and materials were purchased from commercial sources and used without further purification. pBR322 plasmid DNA was purchased from GeneCust-thermo scientific. NMR spectra were acquired on a Bruker 300 spectrometer running at 300, and 75 MHz for ^{1}H, and ^{13}C, respectively. Chemical shifts (δ) are reported in ppm relative to residual solvent signals ($CDCl_3$: 7.26 ppm for ^{1}H NMR, 77.0 ppm for ^{13}C NMR; CD_2Cl_2: 5.32 ppm for ^{1}H NMR, 53.84 for ^{13}C NMR; DMSO-d_6: 2.50 ppm for ^{1}H NMR, 39.52 for ^{13}C NMR). ^{13}C NMR spectra were acquired on a broad band decoupled mode.

2.2. General procedure for the synthesis of complexes **2a–c**, **3** and **4**

To a solution of the corresponding ligand **1** (0.85 mmol) in 5 mL of MeOH was added Na[$AuCl_4$] (0.68 mmol) at rt. The resulting suspension was stirred for 24 h and then the solid product was filtered, washed with cold methanol and cold ether, and dried at 60 °C over 24 h.

2.2.1. [$AuCl_2$(8-O-quinoline)] (**2a**)

Green solid. Yield: 46%. ^{1}H NMR (300 MHz, CD_2Cl_2) δ: 9.14 (dd, J = 5.5, 1.2 Hz, 1H), 8.61 (dd, J = 8.3, 1.2 Hz, 1H), 7.73 (dd, J = 8.4, 5.5 Hz, 1H), 7.65 (t, J = 8.0 Hz, 1H), 7.40 (dd, J = 8.1, 0.7 Hz, 1H), 7.31 (dd, J = 8.0, 0.8 Hz, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 164.7, 145.2, 143.2, 142.6, 131.9, 131.4, 123.0, 117.5, 114.9. MALDI-MS: 411 ($[M]^+$), 376 ($[M\text{-}Cl]^+$), 341 ($[M\text{-}2Cl]^+$). Anal. Calcd. For $C_9H_6AuCl_2NO$ (%): C, 26.24; H, 1.47; N, 3.40. Found (%): C, 26.26; H, 1.61; N, 3.31.

2.2.2. [$AuCl_2$(5-Cl-8-O-quinoline)] (**2b**)

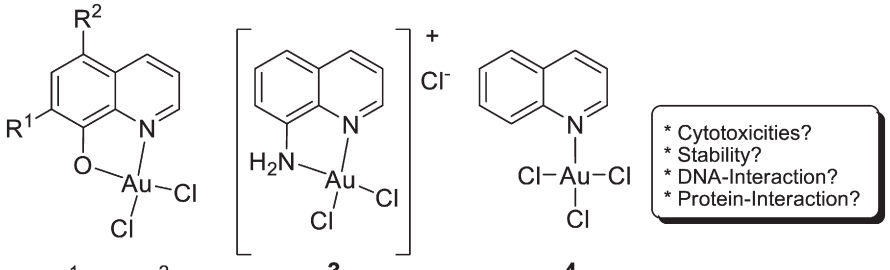
Green solid. Yield: 76%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.25 (dd, J = 5.4, 1.2 Hz, 1H), 8.91 (dd, J = 8.6, 1.2 Hz, 1H), 7.85 (dd, J = 8.6, 5.4 Hz, 1H), 7.72 (d, J = 8.5 Hz, 1H), 7.26 (d, J = 8.5 Hz, 1H). ^{13}C NMR (75 MHz, CD_2Cl_2) δ: 164.7, 145.7, 143.8, 140.9, 131.8, 129.6, 123.2, 120.9, 115.9. ESI + MS (TOF): 444.24 ($[M]^+$). Anal. Calcd. For $C_9H_5AuCl_3NO$ (%): C, 24.21; H, 1.13; N, 3.14. Found (%): C, 24.38; H, 1.29; N, 3.09.

2.2.3. [$AuCl_2$(8-NH_2-quinoline)]Cl (**3**)

Purple solid. Yield: 52%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.37 (dd, J = 5.4, 1.2 Hz, 1H), 8.50 (dd, J = 8.3, 1.2 Hz, 1H), 7.71 (dd, J = 8.3, 5.4 Hz, 1H), 7.51 (t, J = 7.9 Hz, 1H), 7.23 (d, J = 7.6 Hz, 1H), 7.03 (dd, J = 7.8, 0.7 Hz, 1H), 6.50 (brs, 2H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 155.6, 146.0, 143.0, 139.4, 131.7, 131.0, 123.2, 116.2, 112.8. FAB-HRMS: $[M]^+$ calcd. For $[C_9H_8AuCl_2N_2]^+$: 410.9725, found: 410.9717. Anal. Calcd. For $C_9H_8AuCl_3N_2$ (%): C, 24.16; H, 1.80; N, 6.26. Found (%): C, 24.48; H, 1.84; N, 6.52.

2.2.4. [$AuCl_3$(quinoline)] (**4**)

Yellow solid. Yield: 62%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.10 (dd, J = 5.5, 1.3 Hz, 1H), 8.82 (dd, J = 8.5, 0.8 Hz, 1H), 8.65 (d, J = 8.2, 1H), 8.15–8.06 (m, 2H), 7.91–7.84 (m, 1H), 7.80 (dd, J = 8.2, 5.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 152.0, 143.7, 143.0, 134.1, 131.3, 129.7, 129.1, 126.4, 123.1. Anal. Calcd. For $C_9H_7AuCl_3N$ (%): C, 24.99; H, 1.63; N, 3.24. Found (%): C, 24.63; H, 1.73; N, 3.12.



2a (R^1 = H, R^2 = H)
2b (R^1 = H, R^2 = Cl)
2c (R^1 = I, R^2 = Cl)

3 **4**

Chart 2. Gold(III) complexes synthesized and studied in the present work.

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