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A novel aminotriazole-based NHC complex for the design of gold(I) anti-cancer agents: synthesis and biological evaluation

Cite this: DOI: 10.1039/x0xx00000x

Received 00th January 2012,
Accepted 00th January 2012

DOI: 10.1039/x0xx00000x

www.rsc.org/

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Published on 13 May 2015. Downloaded by Yale University Library on 18/05/2015 09:06:32.

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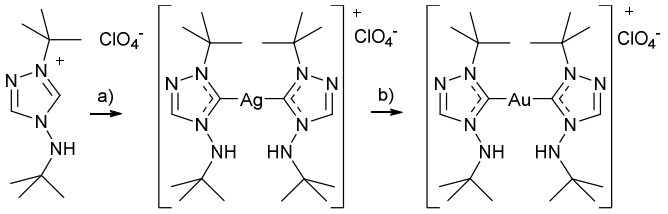
A novel gold(I) complex based on an aminotriazole *N*-heterocylic carbene ligand represents a promising scaffold to design anticancer bioorganometallics. The complex triggered cytotoxic effects in HT-29 and MDA-MB-231 cancer cells, inhibited the activity of the enzyme thioredoxin reductase and showed an effective and fast cellular accumulation.

Besides their frequent and successful application in chemical catalysis, *N*-heterocyclic carbene (NHC) ligands represent a conveniently tunable and very fruitful platform for design of new biologically active metal complexes and, in particular, highly potent gold(I)-based antiproliferative agents.[1] The high biological activities of many gold NHC complexes have been established and their impact on cellular biochemistry and enzyme activities has been studied.[2] Based on the convenient access through standard synthetic methods, the majority of the biologically studied complexes contain NHC ligands obtained from imidazole or benzimidazole, while the biological properties of other types have been explored less intensively. Accordingly, this triggers now an increasing demand on the extension of the structural diversity of the coordinated NHC ligands. Recent examples where this issue has been addressed include bioactive 1,2,3-triazoles-[3], heteroleptic pyrazoles[4], N/S-NHC complexes[5] or several metal-NHC-(bio)conjugates.[2i, 3, 6] With the aim to extend the structure-activity relationships for the gold(I)-NHC pharmacophore, we present here the synthesis and biological evaluation of a novel aminotriazole-based NHC gold(I) complex, namely bis(1-*tert*-butyl-4-(*tert*-butylamino)-1,2,4-triazol-5-ylidene) gold(I) perchlorate (**3** in Scheme 1).



Scheme 1 Synthesis of triazole-based silver(I) and gold(I) NHC complexes; a) Ag_2O, K_2CO_3; b) $(CH_3)_2SAuCl$

The 1,2,4-triazolium perchlorate **1** was synthesized by excessive *tert*-butylation of 4-amino-1,2,4-triazole in acidic media according to a previously reported method.[7] NHC complexes **2** and **3** were obtained using a modified silver(I) oxide procedure proposed by Wang and Lin[8] (see Scheme 1).

According to the literature,[1f, 9] azolium salts containing weakly coordinating counterions such as PF_6^-, BF_4^-, or ClO_4^- often do not react directly with Ag_2O and the presence of an additional base such as NaOH is required. Some reports claim that a source of halide (for instance, trialkylammonium choride) is also necessary for the reaction to proceed.[1f, 9] Due to this fact, a modification of the method by Wang and Lin has been recently proposed by Monkowius et al. allowing smooth generation of $Ag(NHC)_2Y$ (Y = PF_6, SF_6, or ClO_4) from the corresponding imidazolium salt, using AgCl and an excess of KOH.[9b] Referring to the established equilibrium between (NHC)AgX and $[Ag(NHC)_2]AgX_2$ in solution, the authors argued that AgCl was required as a source of chloride ion and postulated formation of (NHC)AgCl species as intermediates. Later, this procedure has been also applied for synthesis of two homoleptic silver(I) carbene complexes derived from 1,2,4-triazolium perchlorate salts.[10]

Similarly to the above mentioned results, we found that the triazolium salt **1** does not react with Ag_2O in DCM solution. However, addition of other bases such as K_2CO_3 or Na_2CO_3 enabled generation of the NHC complex. Particularly, treatment of **1** with Ag_2O in the presence of 2 equiv. K_2CO_3 in dry DCM resulted in formation of **2** with a good yield (88%). Complex **2** was isolated and characterized by elemental analysis, IR and NMR (^{1}H and ^{13}C) spectroscopy.[†] Preparation of single crystals of **2** was impossible due to its sensitivity to light. For this reason, **2** was kept in the dark and utilized for synthesis of the gold(I) complex in a timely manner. Gold(I) NHC complex **3** was obtained from **2** using the standard transmetallation procedure[1g] and $(CH_3)_2SAuCl$ as a source of gold. Its composition and structure was confirmed by elemental analysis, HRESI mass spectrometry, IR and NMR (^{1}H and ^{13}C) spectroscopy, and single crystal X-ray analysis.[††] Results of elemental analyses and HRESI MS are in good agreement with the proposed structures. The ESI$^{(+)}$ mass spectrum of **3** exhibits one intensive peak corresponding to the $[Au(NHC)_2]^+$ ion. Coordination of the NHC ligand was confirmed by ^{1}H and ^{13}C NMR spectra of the complexes (see Figures S1–S4 in ESI). Particularly, ^{1}H NMR of **2** and **3** lack the

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signal of C(5)H proton that is observed at 9.74 ppm in the spectrum of the triazolium salt **1**.[7] Formation of the metal-carbon bond also leads to a significant (up to 38 ppm) downfield shift of C(5) resonances in comparison with the spectrum of the precursor salt (145.3 ppm). The ^{13}C NMR spectrum of **3** displays a singlet resonance at 183.2 ppm, whereas in the spectrum of silver(I) complex **2** the carbene carbon appears as doublet of doublets due to fully resolved coupling to both silver isotopes [$^{1}J(^{13}C–^{107}Ag)$ = 190.3 Hz; $^{1}J(^{13}C–^{109}Ag)$ = 219.5 Hz], which can be quite rarely observed experimentally.[1f, 9a] Besides, the C(3) triazole endocyclic carbon also appears as a doublet due to $^{3}J(C–Ag^{107/109})$ coupling (5.9 Hz). The observed chemical shifts and $^{1}J(C–Ag^{107/109})$ coupling constants fall in the range previously described for $[Ag(NHC)_2]^+$ complexes.[1f, 9a, 10-11]

Complexes **2** and **3** exhibit almost identical *mid*-IR spectra indicating their similar structure. For instance, spectra of both complexes display intensive broad bands at ca. 1100 and 620 cm^{-1} assigned to $\nu_{as}(ClO_4)$ stretching and $\delta(ClO_4)$ deformation vibrations of the uncoordinated perchlorate ion, respectively.[12] Thermal stability of **3** was additionally studied by TG/DSC analysis. The complex was found stable up to 220–230 °C, its melting at 228–229 °C being followed by two-step endothermal decomposition at 250–270 °C. The molecular and crystal structure of **3** was additionally confirmed by single crystal X-ray study, however only with low resolution (see Figure S5 and Tables S1–S3).

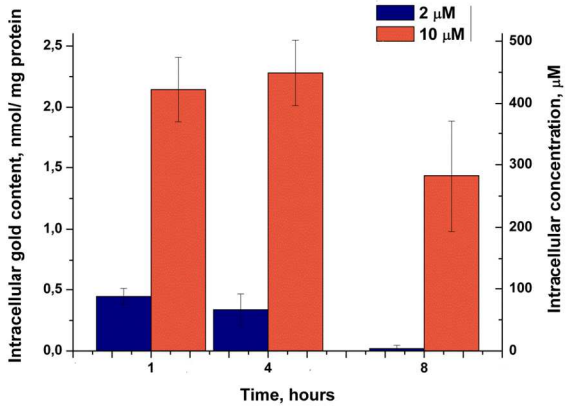

Figure 1: Cellular gold content of HT-29 cells exposed to 2.0 μM or 10 μM of gold(I) complex **3**

Many gold(I) based NHC complexes, both neutral and cationic, are known as effective tumor cell growth inhibitory and pro-apoptotic agents that are able to trigger cell death *via* inhibition of the enzyme thioredoxin reductase (TrxR), induce reactive oxygen species formation, and cause antimitochondrial activities and other antitumoral effects.[1a, 2a-d, 2g, 2h, 2k] In order to evaluate key biological properties of the aminotriazole NHC complex **3**, we determined its antiproliferative effects in two selected cancer cell lines (namely, HT-29 colon carcinoma and MDA-MB-231 breast adenocarcinoma) and its effectivity as an inhibitor of TrxR.

Complex **3** demonstrated good cytotoxic effects in both cell lines with IC_{50} values in the low micromolar range (2.1±0.0 μM in HT-29 and 1.0±0.0 μM in MDA-MB-231 cells). This is in good agreement with previous studies using imidazole- and benzimidazole-based cationic $[Au(NHC)_2]^+$ complexes in the same assay, which afforded IC_{50} values in a comparable range.[13] The precursor triazolium perchlorate **1** was used as a negative control and, as expected, showed no antiproliferative activity in concentrations up to 100 μM. Complex **3** also showed moderate TrxR inhibition activity with an IC_{50} value of 1.2±0.6 μM as measured in the DTNB reduction assay, again comparable with other $[Au(NHC)_2]^+$ complexes.[13] Importantly, TrxR is considered to be one of the most important biological targets of Au^I based drugs.[2a, 2c, 2d, 13a, 14]

Cellular gold uptake was assessed using high resolution continuum source atomic absorption spectroscopy (HR CS AAS) and measured in HT-29 cells exposed to 2.0 μM (approx. IC_{50} value) or 10 μM of **3** for a period of 1, 4 or 8 h. Results of the experiment are given in Figure 1 as nmol Au per mg protein. The respective values of intracellular molar gold concentrations were obtained based on certain biophysical parameters of HT-29 cells.[15] According to the results, complex **3** led to very high cellular gold levels of up to 450 μM upon incubation with 10 μM, corresponding to an approximately 45-fold cellular accumulation with respect to the extracellular medium. Since levels after 1 and 4 hours were comparable, it can be concluded that the complex was quickly taken up into the cells. This was followed by decreased cellular gold levels after 8 h, and this effect was in particular well pronounced with the concentration close to the IC_{50} value of cytotoxicity (2.0 μM). In general, the values are within the same order of magnitude as observed recently with a cationic biscarbene NHC complex, which had reached cellular gold levels (in MCF-7 breast adenocarcinoma cells) in the range of 1.0-1.5 nmol/mg at an exposure concentration of 3.0 μM.[13a] However, in these previous experiments stable gold levels were observed.

Conclusions

Complex **3** was synthesized *via* the silver(I) oxide route and was fully characterized using spectroscopic and structural methods. According to the results of the biological evaluation, it showed marked antiproliferative activity against HT-29 and MDA-MB-231 tumor cell lines with IC_{50} values in low micromolar range (1–2 μM) and good to moderate activity as inhibitor of TrxR. Cellular uptake studies showed a fast and efficient accumulation in HT-29 cells that was followed by decreased gold concentrations after 8 h. This pattern could be attributed to a fast uptake related to the cationic charge and lipophilic nature of **3** and a subsequent excretion of gold, which might be the consequence of active transport processes or metabolism. Of note, the enhanced excretion of gold is less evident at higher concentration above the IC_{50} value of cytotoxicity (10 μM) when cell homeostasis is strongly affected by toxic effects.

The aminotriazole moiety of **3** is of particular interest since it displays certain possible advantages for metallodrug development. First, with its *N*-amino group it represents a comparably hydrophilic NHC core that could be used in the design of novel bioactive gold bioorganometallics and might overcome common solubility issues. Secondly, it could also be speculated that this NH group next to the NHC might facilitate additional interactions with the molecular targets of the complex. And thirdly, in comparison with much more frequently studied imidazole based carbenes, NHC ligands based on other heterocycles, particularly 1,2,4-triazole derivatives, may show altered electronic properties and donor ability.[16]

Concerning structure-activity-relationships the following conclusions can be drawn: 1) the expected impact of the gold center could be clearly established as **3** was active against tumor cell growth in contrast to the metal free **1**, 2) the mode of drug action of **3** is likely dominated by the combination of the gold-based inhibition of TrxR and antimitochondrial effects related to the cationic nature of the compound, as it has also been observed with other complexes of this general type.[1a, 2bg, 13a]

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The postdoctoral fellowships for T.V.S. by DAAD (Deutscher Akademischer Austauschdienst) and Saint Petersburg State University (grant 12.50.1560.2013) is gratefully acknowledged. HRESI MS and X-ray diffraction studies were performed at the Center for Chemical Analysis and Materials Research, and Research Center for X-ray Diffraction Studies of St. Petersburg State University.

Notes and references

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† Synthesis of bis(1-*tert*-butyl-4-(*tert*-butylamino)-1,2,4-triazol-5-ylidene)silver(I) perchlorate (**2**); 0.50 mmol (116 mg) of Ag_2O, 1.0 mmol (296 mg) of **1** and 2 mmol (138 mg) of anhydrous K_2CO_3 were suspended in 20 mL of dry CH_2Cl_2. The suspension was stirred under nitrogen atmosphere at RT for 48 h. Then unreacted Ag_2O was filtered off, and the filtrate was evaporated to dryness. The off-white crystalline residue of **2** was kept in the dark. Yield: 266 mg (88%). *Anal.* Calc. for $C_{20}H_{40}AgClN_8O_4$: C, 40.04; H, 6.72; N, 18.68. Found: C, 40.28; H, 6.91; N, 18.63%. ^{1}H NMR [400 MHz, $CDCl_3$, δ (ppm)]: 8.32 (s, 1H, C(3)H); 5.99 (s, 1H, NH); 1.75 (s, 9H, ^{t}Bu); 1.22 (s, 9H, ^{t}Bu). ^{13}C NMR [100 MHz, $CDCl_3$, δ (ppm), *J* (Hz)]: 179.5(dd, ^1J(C,^{109}Ag) = 219.5, ^1J(C,^{107}Ag) = 190.3, C(5)); 143.1 (d, ^3J(C,Ag) = 5.9, C(3)); 61.4 (s, $\underline{C}(CH_3)_3$); 55.7 (s, $\underline{C}(CH_3)_3$); 30.9 (s, CH_3 from ^{t}Bu); 28.1 (s, CH_3 from ^{t}Bu). FT-IR (ν, cm^{-1}): 3287 (vs), 3156 (m), 3135 (m), 3095 (w), 2968 (vs), 2932 (s), 2906 (s), 2872 (s), 1550 (m), 1467 (s), 1412 (s), 1395 (s), 1366 (s), 1303 (m), 1259 (w), 1229 (m), 1205 (s), 1113 (sh), 1067 (vs br), 971 (m), 932 (w), 874 (s), 821 (w), 772 (w), 713 (s), 648 (s), 622 (vs), 592 (s), 543 (w), 463 (m).

†† Synthesis of bis(1-*tert*-butyl-4-(*tert*-butylamino)-1,2,4-triazol-5-ylidene)gold(I) perchlorate (**3**); 0.41 mmol (247 mg) of **2** and 0.40 mmol (118 mg) of $(SMe_2)AuCl$ were dissolved in 20 mL of dry CH_2Cl_2. The solution was stirred under the nitrogen atmosphere at RT for 24 h. Then the reaction mixture was filtered, and the filtrate was evaporated to dryness to give colorless crystalline product **3**. Single crystals of **3** were obtained from CH_2Cl_2/hexane (1:1, v/v). Yield: 252 mg (91%). *Anal.* Calc. for $C_{20}H_{40}AuClN_8O_4$: C, 34.84; H, 5.85; N, 16.26. Found: C, 35.04; H, 5.72; N, 16.19%. HRMS (ESI$^+$, 100 V, CH_2Cl_2, m/z): 589.3040 $[Au(NHC)_2]^+$, (calcd. 589.3041). DSC/TG: 228–229 °C (mp); 257 °C (T_{max}, endothermal dec.). ^{1}H NMR [400 MHz, $CDCl_3$, δ (ppm)]: 8.38 (s, 1H, C(3)H); 5.95 (s, 1H, NH); 1.84 (s, 9H, ^{t}Bu); 1.24 (s, 9H, ^{t}Bu). ^{13}C NMR [100 MHz, $CDCl_3$, δ (ppm), *J* (Hz)]: 183.2(s, C(5)); 142.9 (s, C(3)); 62.8 (s, $\underline{C}(CH_3)_3$); 56.2 (s, $\underline{C}(CH_3)_3$); 31.2 (s, CH_3 from ^{t}Bu); 28.1 (s, CH_3 from ^{t}Bu). FT-IR (ν, cm^{-1}): 3287 (s), 3138 (m), 3103 (w), 2969 (s), 2935 (m), 2907 (m), 2874 (m), 1553 (m), 1470 (s), 1413 (s), 1397 (s), 1367 (s), 1307 (m), 1261 (w), 1230 (m), 1203 (s), 1116 (sh), 1067 (vs br), 978 (m), 934 (w), 872 (s), 821 (m), 773 (w), 713 (m), 653 (s), 620 (vs), 592 (s), 547 (w), 465 (m).

Electronic Supplementary Information (ESI) available: [materials and methods, examples of NMR spectra, crystallographic results, Figures S1–S5 and Tables S1–S3]. See DOI: 10.1039/c000000x/

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