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Benzyl-substituted carbene–metal complexes: Potential for novel antibiotics and anticancer drugs?

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ABSTRACT

Benzyl-substituted metallocarbene compounds synthesized by our group and others during the past 5 years give a new perspective on their activity as antibiotic and antitumoral drugs. *N*-Heterocyclic carbene (NHC) containing Au and Ru compounds have shown promising anticancer activity *in vitro* and the Cu derivative WBC4 showed strong cytotoxic efficacy *in vivo* xenograft studies against difficult to treat renal cell cancer. While the carbene–silver acetate derivative SBC1 failed *in vivo* as an anticancer drug the antibacterial derivative SBC3 convinced *in vivo* and this compound may lead the way towards novel injectable emergency antibiotics against resistant bacteria and fungi.

Introduction

Groundbreaking research by Wiley J. Youngs and coworkers established the synthesis and medicinal use of covalently bonded silver in NHC–silver acetate compounds [1]. One derivative called SCC1, which is derived from caffeine, became the antibiotic lead compound [2]; the synthesis and molecular structure of SCC1 is shown in Fig. 1. This bioorganometallic molecule enables antibiotic treatment of pneumonia when used in a suitable formulation [3]. In the meantime several research groups worldwide have taken up the topic of synthesis and medicinal application of NHC–metal complexes and recent review articles show the progress [4–9].

Anticancer activity

The Tacke group contribution started with the idea to make carbene–metal complexes more lipophilic than SCC1 by introducing benzyl groups onto the imidazole nitrogen atoms and add extra stability by substituting the imidazole ring in the 4,5 positions with aryl groups [10–22]. Systematic synthesis and biological testing against human renal cell cancer (CAKI-1) and partly against human breast cancer (MCF-7) led to two preferred structural motifs for further drug development [23,24]; benzimidazoles and 4,5-diphenyl-imidazoles carrying at least one *N*-benzyl group, which can be seen in Fig. 2.

Relatively early, the research group identified (1-methyl-3-(4-cyanobenzyl) benzimidazole-2-ylidene) silver(I) acetate (SBC1) as the silver-based anticancer lead compound showing an IC50 value of 1.2 μM against CAKI-1 [13]. SBC1 was also tested at the NCI 60 cell line panel, where it showed good activity against breast, prostate and renal cell cancer. More detailed studies against resistant cancer lines exhibit that SBC1 is able to break platinum-resistance in UKF-NB-3 (neoblastoma) and HCT8 (colon cancer) as well as paclitaxel-resistance in PC3 (prostate cancer) cells [25]. The molecular structure of SBC1 is shown in Fig. 3.

In a fluorescence assay SBC1 is well able to bind to albumin, which is a potential way for SBC1 of selective delivery into cancer cells [25]. Furthermore, melting curve experiments and CD spectroscopy reveal that SBC1 targets DNA in cancer cells [25] without being able to say, whether this is the main mechanism of apoptosis induction. Here, results from Gaultier and Roland indicate that carbene–silver complexes induce caspase-independent apoptosis via the mitochondrial pathway and AIF release by forming lipophilic metallocarbene cations as the reactive species [26]. This group also reports that carbene–silver complexes do not produce significant ROS concentrations and do not modify the cell-cycle distribution of HL60 cells, which implies that these compounds are therefore not genotoxic [26].

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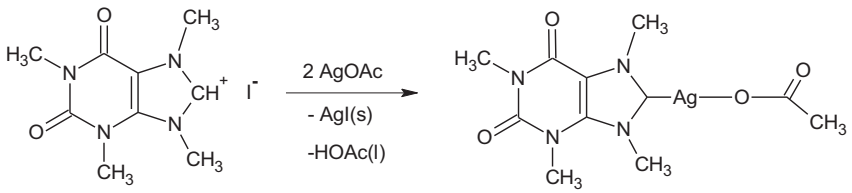

Fig. 1. Synthesis and molecular structure of the NHC–silver acetate derivative SCC1.

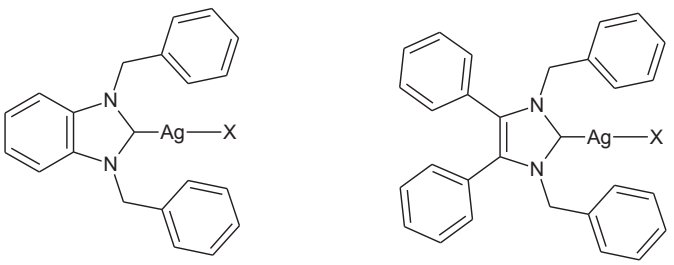

Fig. 2. Preferred NHC–AgX structures for further drug development.

All these positive *in vitro* properties of SBC1 encouraged *in vivo* testing in mice. In a first experiment non-tumor bearing nude mice were treated with increasing doses of SBC1 and 50 mg/kg were determined as the maximum tolerable dose. In a second experiment CAKI-1 tumors were inoculated under the skin of immune-deficient nude mice and after these tumors reached palpable size the mice were treated with 25 or 50 mg/kg of SBC1 for 5 times, while a control cohort received no treatment. Surprisingly, no tumor reduction effect could be seen between the treatment and the control groups [25]; the tumor volume graph can be seen in Fig. 4.

This rather unexpected and disappointing *in vivo* testing of SBC1 led to a change in direction and the best carbene ligands were transmetallated from Ag to other metals with promising anticancer properties. So, imidazolium bromides were reacted with silver oxide in DCM and dimeric (*p*-cymene)$RuCl_2$ was added to the intermediate carbene–silver bromide [20]. The resulting carbene–Ru(*p*-cymene)Cl_2 could be isolated in 40–76% yield and the crystal structure shows the expected pseudo tetrahedral Ru complex with two chloride and two organometallic ligands [20]. The best derivative, which is shown in Fig. 5, exhibits good activity against the human breast cancer cell line MCF-7 with an IC50 value of 2.4 ± 0.7 μM.

A similar synthetic strategy is applied for gold; here the intermediate carbene–silver bromide is reacted with dimethylsulfido gold monochloride and delivers carbene–gold chloride derivatives in yields ranging from 49 to 83%, which are shown in Fig. 6. Further reactions with silver acetate can exchange the anion and results in carbene–gold acetates in yields ranging from 53 to 69%. The crystal

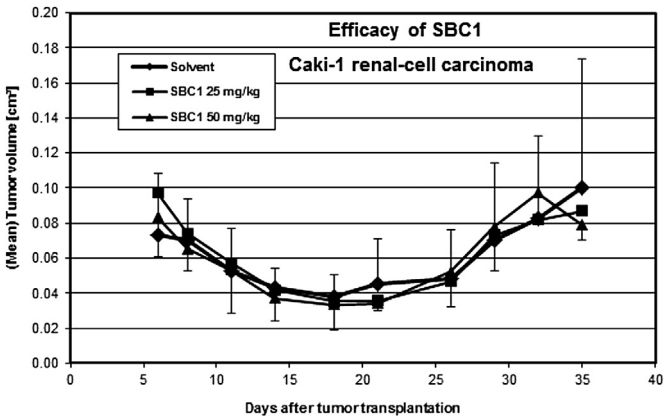

Fig. 4. Tumor growth curves of CAKI-1 xenografts in nude mice comparing two SBC1 treated cohorts against a control cohort (from Ref. [25]).

shows a linear carbene–Au–Cl moiety with a short C–Au bond of 199 pm and a longer Au–Cl bond of 229 pm [20].

Further anion exchange experiments with tetraacetato thioglucose led to carbene–gold thioglucoside derivatives [20]. Such compounds are seen as biocompatible and they might even benefit form overexpressed glucose transporters in cancer cells, which can lead to selective uptake. The gold derivative with the highest anticancer activity is made from 1,3-dibenzyl-4,5-diphenyl-imidazolium and shows good activity against the human breast cancer cell line MCF-7 with an IC50 value of 6.1 ± 1.5 μM [20]; its synthesis and structure is shown in Fig. 7.

In a similar synthesis the intermediate carbene–silver bromide is able to transmetallate its carbene ligand to copper when dimethylsulfido copper monobromide is used. The resulting carbene–copper bromide derivatives are isolated in yields ranging from 32 to 74% and the best derivative WBC4 shows impressive nanomolar activity against Caki-1 (0.60 ± 0.09 μM) and MCF-7 (0.65 ± 0.08 μM) [22]. The synthesis and molecular structure of WBC4, which is isostructural to the silver and gold derivatives, is shown in Fig. 8.

Cytotoxicity of chemotherapeutic agents in the upper nanomolar region is generally seen as ideal and WBC4 was therefore

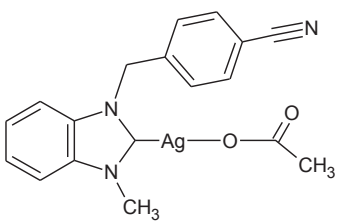

Fig. 3. Molecular structure of the NHC–silver acetate derivative SBC1.

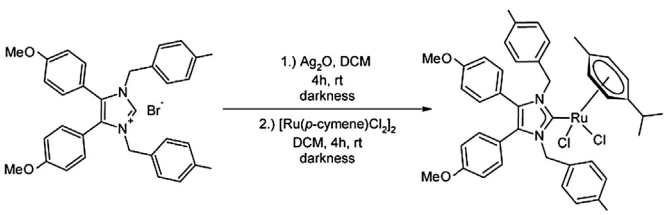

Fig. 5. Synthesis and structure of the most promising NHC–Ru(*p*-cymene)Cl_2 derivative.