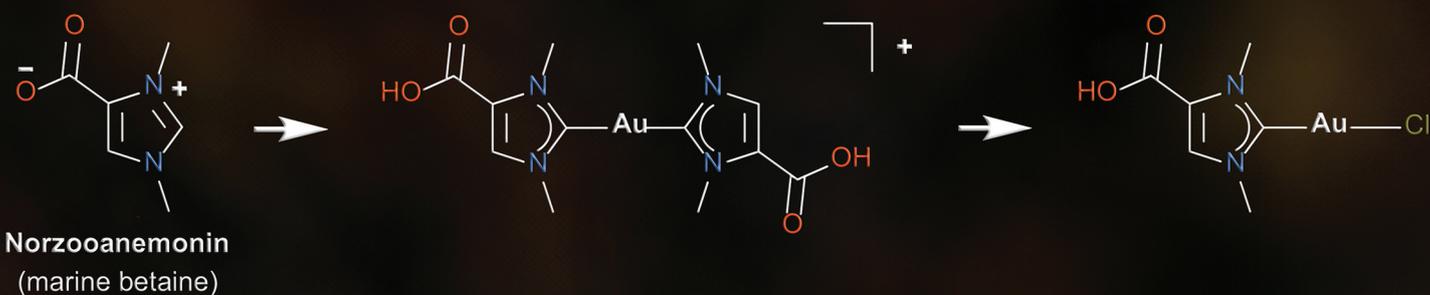


# Dalton Transactions

An international journal of inorganic chemistry

rsc.li/dalton



ISSN 1477-9226



Cite this: *Dalton Trans.*, 2024, **53**, 1942

Received 11th December 2023,  
Accepted 2nd January 2024

DOI: 10.1039/d3dt04135b

rsc.li/dalton

## Synthesis of N-heterocyclic carbene gold(i) complexes from the marine betaine 1,3-dimethylimidazolium-4-carboxylate†

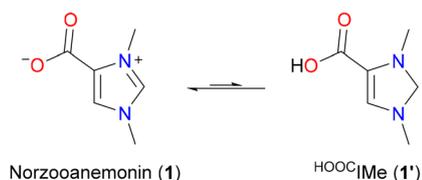
Seyedeh Mahbobeh Mahdavi,<sup>a</sup> Dirk Bockfeld,<sup>a</sup> Rolf Büssing,<sup>b</sup> Bianka Karge,<sup>c</sup> Thomas Bannenber,<sup>a</sup> René Frank,<sup>a</sup> Mark Brönstrup,<sup>c</sup> Ingo Ott<sup>b</sup> and Matthias Tamm<sup>†a</sup>

The marine natural product norzooanemonin (1,3-dimethylimidazolium-4-carboxylate) has been used to prepare a series of carboxyl- or carboxylate-functionalized N-heterocyclic carbene (NHC) gold(i) complexes from [(Me<sub>2</sub>S)AuCl] in the presence of potassium carbonate. The potential of the resulting mono- and dicarbene complexes to act as cytotoxic or antibacterial drugs was investigated.

Norzooanemonin (1,3-dimethylimidazolium-4-carboxylate, **1**) is a naturally occurring betaine that has been isolated from various marine invertebrates.<sup>1</sup> Its synthesis has been described several times,<sup>2</sup> and it has also been observed as a by-product in the preparation of imidazolium-2-carboxylates.<sup>2b,3</sup> Compounds of the latter type are usually referred to as “normal” N-heterocyclic carbene-carbon dioxide adducts (NHC·CO<sub>2</sub>) and have been used extensively, particularly as masked carbenes and carbene transfer reagents.<sup>4</sup> In contrast, **1** has received little attention in NHC chemistry, although its potential to transfer the corresponding “abnormal” carbene, 1,3-dimethylimidazolin-4-ylidene, to organic substrates *via* decarboxylation has been demonstrated.<sup>2c</sup> In addition, there are a few reports describing the use of **1** as a zwitterionic carboxylate ligand in some cobalt, copper, and lanthanide complexes, in which **1** is bound through one or two oxygen atoms.<sup>5</sup> Surprisingly, however, the possibility of using **1** *via* its tautomeric N-heterocyclic carbene form **1'** (<sup>H</sup>OOC|Me)<sup>6</sup> for the synthesis of carboxyl functionalized NHC metal complexes has, to the best of our knowledge, not yet been investigated

(Scheme 1). According to our initial calculations, the tautomer **1'** is only slightly higher in energy than **1** ( $\Delta G_{298\text{ K}} = +4.0$  kcal mol<sup>-1</sup>); given the strength of metal–NHC bonds,<sup>7</sup> a significant stabilization of this tautomeric form by metal coordination can be expected (see ESI† for further details).

The use of norzooanemonin (**1**) as an NHC precursor would provide direct access to carboxyl- or carboxylate-functionalized NHC metal complexes, since the few existing examples of NHC metal complexes with COO or COOH groups directly attached to the 4-position of the N-heterocycle were prepared by template synthesis through “post-coordination backbone functionalization”.<sup>8</sup> Thus, the manganese(i) complex [Cp(IMes)Mn(CO)<sub>2</sub>] (IMes = 1,3-bis(2,4,6-trimethylphenyl)imidazolin-2-ylidene, Cp = η<sup>5</sup>-C<sub>5</sub>H<sub>5</sub>) was treated with *n*-butyl lithium (*n*-BuLi) followed by CO<sub>2</sub> and HCl to afford [Cp(<sup>H</sup>OOCIMes)Mn(CO)<sub>2</sub>]. This complex was further used to prepare polymetallic complexes containing the corresponding ambidentate NHC-carboxylate ligand <sup>OOC</sup>IMes.<sup>8</sup> Another approach to site-specific carboxylation of NHCs was realized by deprotonation of NHCs such as IDipp (1,3-bis(2,6-diisopropylphenyl)imidazolin-2-ylidene) with *n*-BuLi. The resulting lithium salt Li(<sup>OOC</sup>IDipp) could serve as a carbene transfer reagent, but this has not been further investigated.<sup>9</sup> The latter approach corresponds in principle to the construction of anionic N-heterocyclic carbenes with a fluoroborate unit in the 4-position, which have



**Scheme 1** Norzooanemonin (1,3-dimethylimidazolium-4-carboxylate, **1**) and its tautomeric N-heterocyclic carbene (NHC) form <sup>H</sup>OOC|Me (**1'**),<sup>6</sup> the energy difference between the tautomers is  $\Delta G_{298\text{ K}} = +4.0$  kcal mol<sup>-1</sup> (see the ESI† for details).

<sup>a</sup>Institut für Anorganische und Analytische Chemie, Technische Universität Braunschweig, Hagenring 30, 38106 Braunschweig, Germany. E-mail: m.tamm@tu-bs.de

<sup>b</sup>Institute of Medicinal and Pharmaceutical Chemistry, Technische Universität Braunschweig, Beethovenstraße 55, 38106 Braunschweig, Germany

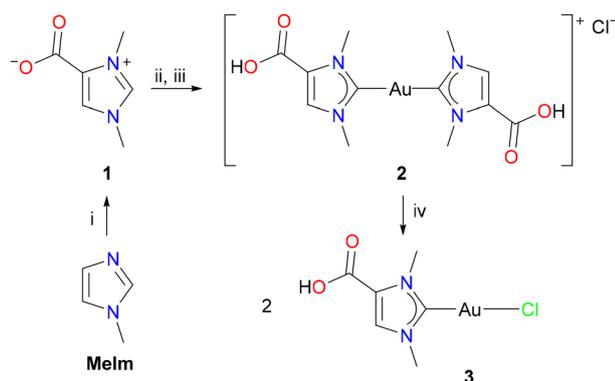
<sup>c</sup>Department of Chemical Biology, Helmholtz Centre for Infection Research GmbH, Inhoffenstrasse 7, 38124 Braunschweig, Germany

† Electronic supplementary information (ESI) available. CCDC 2310639–2310645. For ESI and crystallographic data in CIF or other electronic format see DOI: <https://doi.org/10.1039/d3dt04135b>

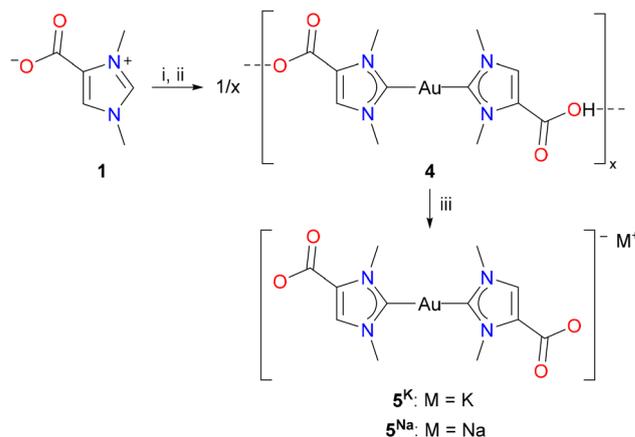


found widespread application in transition metal and main group element chemistry as well in homogeneous catalysis.<sup>10</sup>

Norzooanemonin (**1**) was prepared from 1-methylimidazole (**MeIm**) and dimethyl carbonate according to a slightly modified version of a previously reported protocol (Scheme 2).<sup>2b</sup> The white solid (m.p. = 235.5 °C) crystallized as the mono- and dihydrates **1**·H<sub>2</sub>O and **1**·2H<sub>2</sub>O from aqueous solutions or as the solvate **1**·CH<sub>3</sub>OH from methanol, and their crystal structures were determined by X-ray diffraction analysis (see Fig. S15, S16, Tables S1 and S2, ESI†).<sup>11</sup> Since gold NHC complexes are important for both catalytic and medical applications,<sup>12</sup> our initial goal was to prepare a monocarbene gold(i) complex derived from **1**. Among many other approaches toward the synthesis of late transition metal NHC complexes,<sup>13</sup> [(NHC)AuCl] complexes were recently obtained by reliable and scalable protocols from imidazolium salts with [(Me<sub>2</sub>S)AuCl] in the presence of potassium carbonate as a suitable base.<sup>14</sup> However, our initial efforts to prepare the monocarbene complex [(<sup>HOOC</sup>Ime)AuCl] (**3**) failed, and the reactions between **1**, K<sub>2</sub>CO<sub>3</sub>, and [(Me<sub>2</sub>S)AuCl] in methanol yielded only mixtures of mono- and dicarbene species. Similar observations have also been made for water-soluble gold(i) NHC complexes with pendant sulfonate groups.<sup>15</sup> Therefore, we first turned our attention to the synthesis of dicarbene complexes, and [(Me<sub>2</sub>S)AuCl] was treated with two equivalents each of **1** and K<sub>2</sub>CO<sub>3</sub> in methanol (Scheme 2). After evaporation, the resulting white powder proved to be very soluble in water, which prevented the separation of the anionic dicarbene complex K[(<sup>HOOC</sup>Ime)<sub>2</sub>Au] (**5<sup>K</sup>**, see below, Scheme 3) from potassium chloride and bicarbonate. For this purpose, an aqueous solution of the product mixture was treated with hydrochloric acid (2 N HCl) until a pH of 1–2 was reached, resulting in the precipitation of the cationic dicarbene complex [(<sup>HOOC</sup>Ime)<sub>2</sub>Au]Cl (**2**) as a white solid, which was isolated in 60% yield by filtration. The monocarbene complex **3** was then prepared by a comproportionation reaction of **2** with another equivalent of [(Me<sub>2</sub>S)AuCl] in



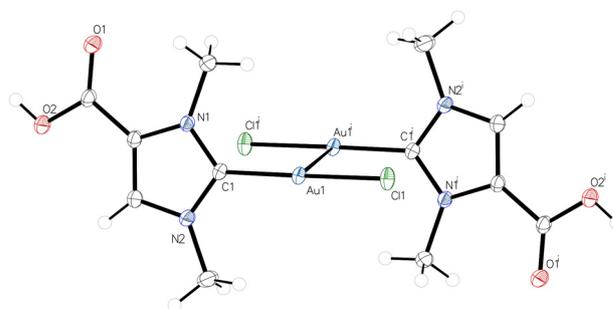
**Scheme 2** Preparation of di- and monocarbene gold(i) complexes from norzooanemonin (**1**); reagents and reaction conditions: (i) 1 equiv. dimethyl carbonate, bomb flask, 8 h, 140 °C; (ii) 1 equiv. K<sub>2</sub>CO<sub>3</sub>, 0.5 equiv. (Me<sub>2</sub>S)AuCl, MeOH, 12 h, rt; (iii) 1 equiv. HCl (2 N), pH = 1–2, H<sub>2</sub>O, rt; (iv) 1 equiv. (Me<sub>2</sub>S)AuCl, MeOH, 4 h, rt.



**Scheme 3** Preparation of dicarbene gold(i) complexes from norzooanemonin (**1**); reagents and reaction conditions: (i) 1 equiv. K<sub>2</sub>CO<sub>3</sub>, 0.5 equiv. (Me<sub>2</sub>S)AuCl, MeOH, 12 h, rt; (ii) 1 equiv. HI (2 N), pH = 6–7, H<sub>2</sub>O, rt; (iii) 1 equiv. KOH or NaOH, H<sub>2</sub>O, rt.

methanol, affording [(<sup>HOOC</sup>Ime)AuCl] (**3**) as a white solid in 85% yield (step iv, Scheme 2).

The NMR spectra of **2** and **3** were recorded in CD<sub>3</sub>OD. Three <sup>1</sup>H NMR signals are observed at 8.01, 4.17, and 3.95 ppm for **2** and at 7.92, 4.07, and 3.84 ppm for **3**. These signals can be assigned to the CH and the two CH<sub>3</sub> groups, respectively, while the COOH proton is exchanged in methanol solution. The <sup>13</sup>C{<sup>1</sup>H} NMR spectra show low-field signals at 189.7 ppm (**2**) and 176.1 ppm for the carbene carbon atoms, which are in the expected ranges for gold(i) NHC complexes.<sup>16</sup> The <sup>13</sup>C{<sup>1</sup>H} NMR signals for the COOH group appear at 161.3 ppm (**2**) and 161.9 ppm (**3**). The molecular structures of **2** and **3** were determined by X-ray diffraction analysis; the structure of the monocarbene complex **3** is shown in Fig. 1, while the structure of the dicarbene complex **2** is discussed in a later section. **3** crystallizes in the monoclinic space group *P*2<sub>1</sub>/*c* with one molecule **3** in the asymmetric unit. The C1–Au–Cl angle of 176.50(4)° is consistent with the expected nearly linear two-coordinate environment around the gold atom, and the Au–C1 and Au–Cl bond lengths of 1.9849(12) Å and 2.2908(3) Å are in the range reported for other [(NHC)AuCl] complexes.<sup>17</sup> **3** forms centrosymmetric dimers in the solid with an



**Fig. 1** Molecular structure of **3**; a dimeric centrosymmetric unit is shown with an Au–Au' distance of 3.23241(11) Å.



Au–Au' distance of 3.23241(11) Å, which is well within the typical range expected for aurophilic interactions (*ca.* 2.8–3.50 Å).<sup>18</sup> The dimeric units are in turn linked to form chains by hydrogen bonding between the carboxyl groups, with the typical pattern of two O–H...O hydrogen bonds between each pair of COOH groups, see Fig. S17 (ESI†) for a packing diagram. Accordingly, **3** represents a nice example of complementarity between aurophilic and conventional hydrogen bonding interactions in the supramolecular assembly of gold(I) compounds.<sup>19</sup>

The successful isolation of the cationic dicarboxyl-dicarbene complex  $[(^{\text{HOOC}}\text{IME})_2\text{Au}]$  (**2**) raised the question of whether this complex could be used as a starting material for the synthesis of the corresponding anionic dicarboxylate-dicarbene complexes  $\text{M}[(^{\text{OOC}}\text{IME})_2\text{Au}]$  ( $5^{\text{K}}$ , M = K;  $5^{\text{Na}}$ , M = Na) by treatment with potassium or sodium hydroxide. However, their high solubility in water, as described above for  $5^{\text{K}}$  (Scheme 2), would probably again prevent their isolation and separation from KCl or NaCl. Considering the better solubility of the corresponding iodides, KI and NaI, in organic solvents, we adapted the protocol for the synthesis of dicarbene-gold(I) complexes from **1**, and the resulting mixture of  $5^{\text{K}}$ , KCl, and  $\text{KHCO}_3$  was treated with hydroiodic acid (2 N HI). We found that a white solid precipitated already at pH of 6–7, and the neutral complex  $[(^{\text{HOOC}}\text{IME})\text{Au}(^{\text{OOC}}\text{NHC})]$  (**4**) was isolated in 52% yield by filtration (Scheme 3). Interestingly, complex **4** did not precipitate upon treatment with HCl, although both HCl and HI are strong acids in aqueous media. Treatment of this complex **4** with one equivalent of either potassium or sodium hydroxide afforded the desired dicarboxylate-dicarbene complexes  $5^{\text{K}}$  and  $5^{\text{Na}}$  in >90% yield after washing with acetone to remove any traces of KI or NaI. Both complexes are highly water soluble, and their NMR spectra were recorded in  $\text{D}_2\text{O}$ . In the  $^1\text{H}$  NMR spectra, the three CH and  $\text{CH}_3$  signals are all shifted to slightly lower field compared to **2** (in  $\text{CD}_3\text{OD}$ ); the  $^{13}\text{C}\{^1\text{H}\}$  NMR exhibit signals at *ca.* 189 and 167 ppm for the carbene and carboxylate carbon atoms, respectively.

The molecular structures of the dicarbene complexes **2**, **4**, and  $5^{\text{K}}$  were confirmed by X-ray diffraction analysis. Complex **2**, as well as the complexes **4** and  $5^{\text{K}}$  crystallized as solvates, namely  $2\cdot\text{H}_2\text{O}$ ,  $4\cdot 6\text{H}_2\text{O}$ ,  $5^{\text{K}}\cdot 4\text{H}_2\text{O}$  and  $5^{\text{K}}\cdot 2\text{H}_2\text{O}\cdot\text{MeOH}$ , the latter structure suffering from poor data quality.  $5^{\text{K}}\cdot 4\text{H}_2\text{O}$  and  $5^{\text{K}}\cdot 2\text{H}_2\text{O}\cdot\text{MeOH}$  are isostructural and crystallize in the triclinic space group  $P\bar{1}$  with one centrosymmetric molecule of  $5^{\text{K}}$  in the unit cell, and both structures differ significantly only in the arrangement of the solvate molecules. Therefore, the following discussion is limited to the structures of  $2\cdot\text{H}_2\text{O}$ ,  $4\cdot 6\text{H}_2\text{O}$ , and  $5^{\text{K}}\cdot 4\text{H}_2\text{O}$ . As observed for  $5^{\text{K}}$ , **2** and **4** are centrosymmetric and crystallize with one half molecule in the asymmetric unit in the monoclinic space groups  $P2_1/c$  ( $2\cdot\text{H}_2\text{O}$ ) and  $P2_1/n$  ( $4\cdot 6\text{H}_2\text{O}$ ), respectively. The molecular structure of the anion  $[(^{\text{OOC}}\text{IME})_2\text{Au}]^-$  in  $5^{\text{K}}\cdot 4\text{H}_2\text{O}$  is shown in Fig. 2, while the structures of  $2\cdot\text{H}_2\text{O}$  and  $4\cdot 6\text{H}_2\text{O}$  are presented in the ESI section.† The gold atoms in all structures exhibit perfectly linear coordination spheres with C1–Au–C1' angles of 180°, resulting from the fact that the gold atoms in all structures are

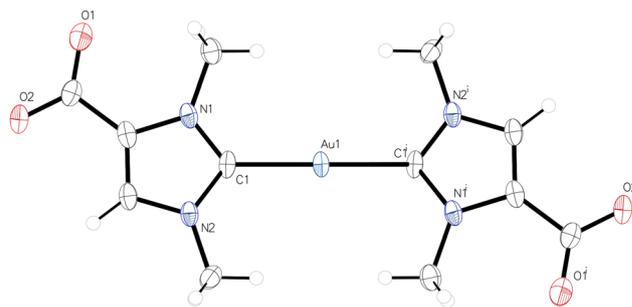


Fig. 2 Molecular structure of the anionic dicarbene-gold unit in  $5^{\text{K}}\cdot 4\text{H}_2\text{O}$ .

located on inversion centers. The Au–C1 bond lengths are 2.010(10) ( $2\cdot\text{H}_2\text{O}$ ), 2.027(8) ( $4\cdot 6\text{H}_2\text{O}$ ), and 2.027(7) Å ( $5^{\text{K}}\cdot 4\text{H}_2\text{O}$ ) and are within the range observed for related dicarbene gold(I) complexes containing  $[(\text{NHC})_2\text{Au}]^+$  cations (Table 1).<sup>20</sup>

In contrast to the hydrogen bonding pattern observed between the carboxyl groups in the monocarbene complex **3**, the OH groups in the dicarbene complex **2** in  $2\cdot\text{H}_2\text{O}$  form hydrogen bonds with the chloride counterions with OH...Cl contacts of 2.102(15) Å. The chloride ion again forms a hydrogen bond with the water molecule (Cl...HOH 2.167(15) Å). Both the chloride ion and the water molecule reside in approximately the same position, each 50% occupied, and are connected by an inversion center. The water molecule forms another hydrogen bond to the OH groups in the neighbouring dicarbene complex (O...HO 1.87(4) Å). The  $[(^{\text{HOOC}}\text{IME})_2\text{Au}]^+$  cations stack along the *a* axis, resulting in Au–Au distances of 3.6946(5) Å, just outside the range expected for unambiguous aurophilic interactions.<sup>18</sup> In  $4\cdot 6\text{H}_2\text{O}$ , both the gold and the hydrogen atoms at the carboxyl groups are located on inversion centers, linking the neutral dicarbene gold units  $[(^{\text{HOOC}}\text{IME})\text{Au}(^{\text{OOC}}\text{IME})]$  to chains parallel to the *ac* plane. These chains are further connected through hydrogen bonds with the solvate water molecules. The anionic dicarbene gold units  $[(^{\text{OOC}}\text{IME})_2\text{Au}]^-$  in  $5^{\text{K}}\cdot 4\text{H}_2\text{O}$  are connected *via* contacts between the carboxylate groups and the potassium atoms, which suffer from disorder and are located above and below the NHC planes, resulting in a corrugated plane parallel to the *a* axis and to a diagonal of the *bc* plane (see ESI† for further details and presentation of packing diagrams for all gold complexes).

All gold complexes were tested for cytotoxicity and antibacterial activity. The minimum inhibitory concentrations (MICs)

Table 1 Selected bond lengths [Å] and angles [°] in the mono- and dicarbene gold(I) complexes **2–5**

Complex	Au–C1	C1–Au–C1'/Cl	N1–C1–N2
<b>2</b>	2.010(10)	180.0	104.5(8)
<b>3</b>	1.9849(12)	176.50(4)	105.95(11)
$4\cdot 6\text{H}_2\text{O}$	2.027(8)	180.0(10)	105.6(7)
$5^{\text{K}}\cdot 4\text{H}_2\text{O}$	2.021(7)	180.0(2)	105.0(6)



against six pathogenic bacterial strains, two Gram-positive (*Enterococcus faecium*, methicillin-resistant *Staphylococcus aureus* (MRSA)) and four Gram-negative (*Acinetobacter baumannii*, *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*) were determined by a curve-fitting method. In general, the NHC–Au(I) complexes displayed moderate to low activities (Table 2 and ESI†). Complex 4 was the most potent analog, with activity against *A. baumannii* (MIC = 16  $\mu$ M), *E. coli* (MIC = 32  $\mu$ M), *K. pneumoniae* (MIC = 32  $\mu$ M), *P. aeruginosa* (MIC = 32  $\mu$ M), while it was poorly active against MRSA (MIC = 65  $\mu$ M) and inactive against *E. faecium* (MIC > 100  $\mu$ M). Inhibition of thioredoxin reductase has been reported as the antibacterial mechanism of the gold lead compound auranofin as well as gold mono- and bis-NHC complexes.<sup>21</sup> In fact, complex 3 showed good activity in an inhibition assay of the TrxR from *E. coli*, with IC<sub>50</sub> values of 0.786  $\pm$  0.118 [ $\mu$ M] (Table 3), while complexes 2, 4 and 5 were inactive (IC<sub>50</sub> values > 50  $\mu$ M). The observed pattern of activity (high TrxR inhibition by the monocarbene complex 3 and low TrxR inhibition by the dicarbene complexes 2, 4 and 5) is in excellent agreement with our previous reports.<sup>21b,c</sup> Preliminary cytotoxicity experiments in several cancer cell lines revealed very low antiproliferative effects for 3 (Table 3), while 2, 4 and 5 were inactive (IC<sub>50</sub> values >100  $\mu$ M). It can be concluded that while the overall cellular potency of the gold–NHC compounds is moderate, the preference for Gram-negative bacteria is surprising and warrants further investigation. To this end, the possibility of

specifically functionalizing the novel gold complexes *via* the carboxyl function offers an interesting opportunity to optimize their activity. Furthermore, we see the potential to use these gold complexes for the synthesis of water-soluble nanoparticles<sup>22</sup> or as building blocks in supramolecular chemistry,<sup>19</sup> which seems very promising due to their easy accessibility from the marine natural product norzooanemonin (1), as described above.

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

Financial support by the Lower Saxony Ministry for Science and Culture for the doctoral program “Drug Discovery and Cheminformatics for New Anti-Infectives (iCA)” and technical support by Petra Lippmann are gratefully acknowledged.

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**Table 2** Antibacterial activities of complexes 2–5

Compound	E.f.	MRSA	A.b.	E.c.	K.p.	P.a.
2	>100	>100	31	62	62	62
3	>100	>100	43	86	43	>100
4	>100	64	16	32	32	32
5 <sup>K</sup>	>100	>100	>100	>100	>100	>100
5 <sup>Na</sup>	>100	>100	>100	>100	>100	>100
Auranofin	0.3	0.4	55	46	81	>100
Antibiotic <sup>a</sup>	9.5	4.7	1	0.1	0.2	7

Minimal inhibitory concentrations (MIC) are given in  $\mu$ M. E.f. = *Enterococcus faecium* DSM20477, MRSA = methicillin-resistant *Staphylococcus aureus* DSM 11822, A.b. = *Acinetobacter baumannii* DSM30007, E.c. = *Escherichia coli*, K.p. = *Klebsiella pneumoniae* DSM111678, P.a. = *Pseudomonas aeruginosa* DSM 24068. <sup>a</sup>As positive control antibiotics, amikacin (P.a.), linezolid (MRSA) and ciprofloxacin (all other strains) have been used.

**Table 3** Results of the cytotoxicity tests and the TrxR inhibition assay for monocarbene gold(I) complex 3

Compound	A549	HT-29	MCF-7	MDA-MB-231	TrxR ( <i>E. coli</i> )
Auranofin	4.24 $\pm$ 0.61	2.71 $\pm$ 0.29	2.13 $\pm$ 0.47	1.21 $\pm$ 0.34	0.210 $\pm$ 0.30
3	60.0 <sup>a</sup>	63.9 <sup>a</sup>	53.4 <sup>a</sup>	76.1 <sup>a</sup>	0.786 $\pm$ 0.118

Half maximal inhibitory concentration IC<sub>50</sub> values are given in  $\mu$ M ( $n$  = 3). <sup>a</sup>Half maximal inhibitory concentration IC<sub>50</sub> values are given in  $\mu$ M ( $n$  = 1). For experimental procedures see ref. 21a.



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