Dalton Transactions

Cite this: *Dalton Trans.*, 2012, **41**, 5925

www.rsc.org/dalton

PAPER

Synthesis, structural characterization, antimicrobial and cytotoxic effects of aziridine, 2-aminoethylaziridine and azirine complexes of copper(II) and palladium(II)†‡

E. Budzisz,*[a] R. Bobka,[b] A. Hauss,[b] J. N. Roedel,[b] S. Wirth,[b] I.-P. Lorenz,*[b] B. Rozalska,[c] M. Więckowska-Szakiel,[c] U. Krajewska[d] and M. Rozalski[d]

Received 4th November 2011, Accepted 8th March 2012
DOI: 10.1039/c2dt12107g

The synthesis, spectroscopic and X-ray structural characterization of copper(II) and palladium(II) complexes with aziridine ligands as 2-dimethylaziridine $HNCH_2CMe_2$ (**a**), the bidentate *N*-(2-aminoethyl)aziridines $C_2H_4NC_2H_4NH_2$ (**b**) or $CH_2CMe_2NCH_2CMe_2NH_2$ (**c**) as well as the unsaturated azirine NCH_2CPh (**d**) are reported. Cleavage of the cyclometallated Pd(II) dimer [μ-Cl($C_6H_4CHMeNMe_2$-*C*,*N*)Pd]$_2$ with ligand **a** yielded compound [Cl($NHCH_2CMe_2$)($C_6H_4CHMe_2NMe_2$-*C*,*N*)Pd] (**1a**). The reaction of the aziridine complex *trans*-[$Cl_2Pd(HNC_2H_4)_2$] with an excess of aziridine in the presence of AgOTf gave the ionic chelate complex *trans*-[($C_2H_4NC_2H_4NH_2$-*N*,*N*′)$_2$Pd](OTf)$_2$ (**2b**) which contains the new ligand **b** formed by an unexpected insertion and ring opening reaction of two aziridines ("aziridine dimerization"). $CuCl_2$ reacted in pure HNC_2H_4 or $HNCH_2CMe_2$ (**b**) again by "dimerization" to give the tris-chelated ionic complex [Cu($C_2H_4NC_2H_4NH_2$-*N*,*N*′)$_3$]Cl_2 (**3b**) or the bis-chelated complex [CuCl($C_2H_2Me_2NC_2H_2Me_2NH_2$-*N*,*N*′)$_2$]Cl (**4c**). By addition of 2*H*-3-phenylazirine (**d**) to $PdCl_2$, *trans*-[Cl_2Pd(NCH_2CPh)$_2$] (**5d**) was formed. All new compounds were characterized by NMR, IR and mass spectra and also by X-ray structure analyses (except **3b**). Additionally the cytotoxic effects of these complexes were examined on HL-60 and NALM-6 human leukemia cells and melanoma WM-115 cells. The antimicrobial activity was also determined. The growth of Gram-positive bacterial strains (*S. aureus, S. epidermidis, E. faecalis*) was inhibited by almost all tested complexes at the concentrations of 37.5–300.0 μg mL^{-1}. However, MIC values of complexes obtained for Gram-negative *E. coli* and *P. aeruginosa*, as well as for *C. albicans* yeast, mostly exceeded 300 μg mL^{-1}. The highest antibacterial activity was achieved by complexes **1a** and **2b**. Complex **2b** also inhibited the growth of Gram-negative bacteria.

Introduction

The high interest that the chemistry of aziridines attracts is generated by the manifold applications of these smallest saturated azaheterocycles.[1–3] Aziridines are not only used as reactive synthons in organic synthesis, in the synthesis of peptides and natural products,[4,5] but also as monomeric units in polymerization reactions[6] or as natural and synthetic pharmaceuticals.[7–9] Though the parent aziridine C_2H_4NH is classified as mutagenic,[10,11] there are some aziridine-containing natural compounds known to be useful as chemotherapeutics to combat cancer targeting biochemical processes. Good examples are the family of mitomycins and acinomycins.[12–14] Their physiological effect relies on their poor stability towards ring opening followed by alkylation and cross-linking to form DNA interstrands. This leads to the inhibition of DNA replication and to cell death. There are also some man-made aziridine derivatives with similar antitumor capabilities based on the exact same cytotoxic effect, *e.g.* some aziridinylbenzoquinones,[15,16] TEM,[17] or thioTEPA.[18] This ring-opening reaction of aziridines by nucleophilic attack is very similar to that of isoelectronic oxiranes and thiiranes. With regard to coordination chemistry, however, the reactivity of nucleophilic aziridines towards electrophilic transition metal centers differs strongly from those of oxiranes and thiiranes with a only few exceptions.[19–21] While the latter act as oxidizing agents towards organometallic complexes resulting in the formation of oxo- or thiocomplexes *via* ethene

[a]*Department of Cosmetic Raw Materials Chemistry, Faculty of Pharmacy, Medical University of Lodz, Muszynski Str. 1, 90-151 Lodz, Poland. E-mail: elzbieta.budzisz@umed.lodz.pl*
[b]*Department of Chemistry, Ludwig-Maximilians-University, Butenandtstr. 5-13 (D), D-81377 Munich, Germany. E-mail: ipl@cup.uni-muenchen.de*
[c]*Department of Immunology and Infectious Biology, University of Lodz, Banacha 12/16, 90-237 Lodz, Poland*
[d]*Department of Pharmaceutical Biochemistry, Medical University of Lodz, Muszynski Str. 1, 90-151 Lodz, Poland*
† Dedicated to Prof. Dr Wolfgang Beck on the occasion of his 80th birthday.
‡ CCDC 849020–849023. For crystallographic data in CIF or other electronic format see DOI: 10.1039/c2dt12107g

elimination,[22–26] aziridines usually remain intact and prefer metal coordination *via* the nitrogen atom. Therefore, only one example of two-fold breakage of C–N bonds, elimination of ethene and formation of an imido complex is known in the literature.[26] However, many aziridine complexes of a variety of transition metals with up to four aziridine ligands are currently known, most of which have been published by us.[27–41] Ring opening reactions especially with functionalized metal carbonyls have also been reported, *e.g.* with hydrido carbonyl complexes to form β-aminoacyl complexes *via* M–C addition[42–46] or with halogenido carbonyl complexes to form five-membered aminooxycarbene complexes.[47,48]

Transition metal-mediated ring opening reactions of aziridine ligands yielding aminoethylaziridine-*N*,*N*′ complexes by "aziridine dimerization" was first observed by Beck *et al.*[49] and Fritz *et al.*[50] The first examples of such an aziridine dimer template have been structurally characterized by X-ray determination in the case of a cationic Co(III) complex bearing two dimerized 2-methylaziridine ligands.[51] We later reported further examples of analogous complexes with dimerized aziridine ligands.[52,53] Furthermore, most recently a novel route to *N*-(2-aminoethyl)aziridines was developed based on the one reported by Beck *et al.*[49] utilizing a Cu(II)-mediated template dimerization of aziridine ligands.[53]

In this paper we report on the synthesis and characterization of new palladium(II) and copper(II) complexes with dimerized aziridine ligands as well as of palladium(II) complexes with one *N*-bound aziridine ligand and two azirine ligands, respectively. Hitherto, only a few azirine complexes of transition metals are known.[54,55] Usually they undergo ring-opening or rearrangement reactions in the presence of transition metals.[56,57] Because of the successful employment of aziridine-containing mitomycin derivatives in cancer therapy, some of their transition metal complexes have been synthesized, which did not show significant differences in biological activity compared to the uncoordinated compounds.[58] The *cis*-bisaziridine Pt(II) complex[59,60] analogous to cisplatin showed no better activity, but had higher selectivity. Therefore all the synthesized complexes here have been investigated for their biological activity.

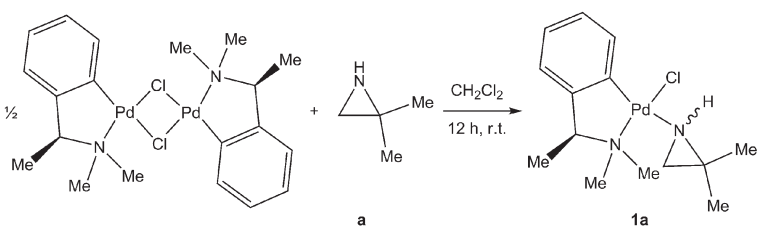
Results and discussion

Synthesis of the complexes 1a, 2b, 3b, 4c and 5d

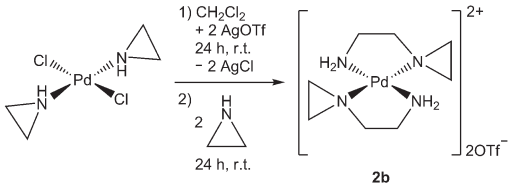
The cleavage reaction of the chlorido-bridged dimer bis[μ-Cl(*S*)-2-{1-(dimethylamino)ethyl}phenyl-*C*,*N*-palladium(II)][61] with an excess of 2,2-dimethylaziridine (**a**) in CH_2Cl_2 affords the square planar palladium(II) complex Cl($C_6H_4CHCH_3NMe_2$-*C*,*N*)-($NHCH_2CMe_2$)Pd (**1a**) (Scheme 1). Light yellow **1a** is obtained with 50% yield, and is air-stable, soluble in polar solvents (CH_2Cl_2), but insoluble in non-polar solvents (n-pentane). The spectroscopic characterization showed the evidence of *S*,*S* and *R*,*R* enantiomers due to *N* chirality at the aziridine nitrogen.

The starting material for the synthesis of complex **2b** is the bisaziridine complex *trans*-[$Cl_2Pd(NHC_2H_4)_2$].[62] When it is treated with at least 3 equivalents of aziridine HNC_2H_4 and 2 equivalents of AgOTf in CH_2Cl_2 at r.t., the cationic square planar palladium(II) complex [($C_2H_4NC_2H_4NH_2$-*N*,*N*′)$_2$Pd]-($OTf)_2$ (**2b**) with 2 OTf^- as counteranions is formed (Scheme 2). As already published by us in the case of copper(II) complexes, the bidentate β-aminoethylaziridine ligand **b** is formed by a metal-induced dimerization reaction. Hitherto, this unusual reaction was only observed for HNC_2H_4[52] and its mono- and dimethyl derivatives $HNCH_2CHMe$[51] and $HNCH_2CMe_2$[63] as is also shown in the following syntheses of complexes **3b** and **4c**. Thus, it seems that this "aziridine dimerization" is limited by steric reasons. Yellow **2b** is soluble in polar solvents, even methanol, but insoluble in non-polar solvents such as n-pentane, and under argon it can be stored indefinitely.

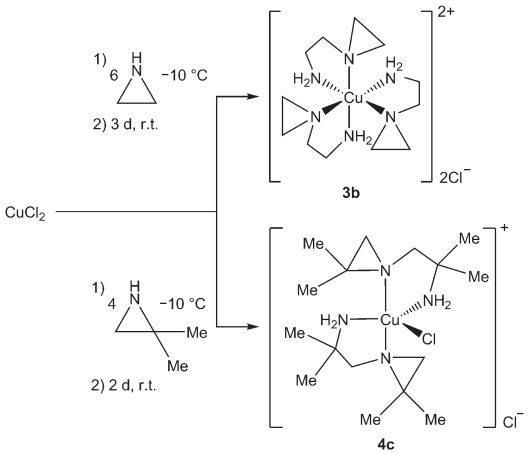
The first aziridine complexes of copper(II) have been published by Edwards *et al.* in 1961[64,65] and by Beck *et al.* in 1973,[49] but without any structural characterization. Beck *et al.* also observed the first "aziridine dimerization" induced by metal coordination.[49] This has been recently proven by our own results with some aziridine complexes of copper(II). In most cases, however, several derivatives of aziridines kept intact and coordinated as ligands in 1 : 2, 1 : 3 and 1 : 4 molar ratios to Cu(II) centers.[53,66,67] To increase this stoichiometry and to obtain hexaaminecopper(II) analogous complexes, we decided to use a large excess of aziridine and to avoid using any solvent. Therefore, anhydrous $CuCl_2$ was added directly to the liquid aziridines C_2H_4NH or CH_2CMe_2NH (**a**), respectively. As shown in Scheme 3, two different ionic complexes with different stoichiometry and coordination geometry were obtained depending on the substituents. In the case of aziridine, C_2H_4NH, the tris-chelated octahedral complex [($C_2H_4NC_2H_4NH_2$-*N*,*N*′)$_3$Cu]Cl_2 (**3b**) resulted and in the case of the 2,2-dimethylderivative the bis-chelated trigonal bipyramidal complex [($CH_2CMe_2NCH_2C$-Me_2NH_2-*N*,*N*′)ClCu]Cl (**4c**). Both complexes, however, again contain the corresponding "dimerized" aziridines as ligands **b** and **c**. Our attempts to obtain single crystals of **3b** by recrystallisation were not successful, because it was destroyed by any longer attack of polar solvents. Using methanol for instance, caused the formation of the bis-chelated complex *trans*-[($C_2H_4NC_2H_4NH_2$-*N*,*N*′)$_2$($HOMe)_2$Cu]Cl_2 with two MeOH ligands in axial positions as proven by X-ray structural



Scheme 1 Synthesis of the neutral palladium(II) complex **1a** with ligand 2,2-dimethylaziridine (**a**).



Scheme 2 Synthesis of the ionic palladium(II) complex **2b** with ligand *N*-(2-aminoethyl)aziridine (**b**) formed by metal-induced "aziridine dimerization" of C_2H_4NH.



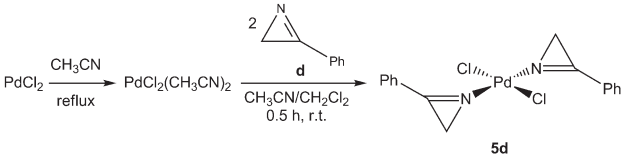
Scheme 3 Synthesis of the ionic copper(II) complexes **3b** and **4c** with ligands *N*-(2-aminoethyl)aziridine (**b**) and *N*-(2-amino-2-methylpropyl)-2,2-dimethylaziridine (**c**) both again formed by metal-induced "aziridine dimerization".

analysis.[53] **4c** is soluble in slightly polar solvents such as acetone or dichloromethane, insoluble in non-polar solvents such as n-pentane. Both complexes are air-stable.

Azirine ligands were mentioned in palladium(II) complexes by several groups in 1978.[54–56] One of them presented with *trans*-[(2*H*-3-tolylazirine)$_2$Cl$_2$Pd] the only example structurally characterized by diffraction studies.[55] The syntheses of azirine complexes turned out to be difficult because of subsequent rearrangement reactions in the presence of metal complexes and too long reaction times. If the reaction can be stopped, however, it is possible to isolate some palladium(II) complexes of the type *trans*-[(2*H*-3-arylazirine)$_2$Cl$_2$Pd] (aryl = C_6H_5 (**d**), C_6H_4Cl, C_6H_4Br) by the reaction of $PdCl_2$ and 2*H*-3-arylazirine in acetonitrile.[66] Here we only present the synthesis and structural characterization of the phenyl derivative **5d** (Scheme 4), once formed and isolated, stable enough for the implemented analytical and biological studies in low concentration. **5d** is obtained as air-stable orange yellow powder in 65% yield and is soluble in CH_2Cl_2 and $CHCl_3$, but insoluble in n-hexane.

Spectroscopic characterization

All the complexes have been characterized by their ^{1}H and ^{13}C NMR, IR and mass spectra with the exception of the copper(II) complexes **3b** and **4c**, where characterization by NMR



Scheme 4 Synthesis of the neutral palladium(II) complex **5d** with ligand 2*H*-3-arylazirin (**d**).

spectroscopy was not possible because of their paramagnetic properties.

The IR spectrum of **1a** shows ν(NH) absorptions slightly shifted by coordination to lower frequencies at about 3100 cm^{-1}. Somewhat lower are found the ν(CH) bands (2971–2833 cm^{-1}). Two striking absorptions between 1600 and 1500 cm^{-1} are assigned to ν(C=C) of the *N*,*N*-dimethylbenzylamine moiety. In the IR spectrum of **2b**, analogous absorptions for ν(NH) and ν(CH) are found in the same region as for **1a**. Besides this, a weak band for $\delta(NH_2)$ at 1608 cm^{-1} is observed. Additionally, the typical strong bands of the triflate anion appear in the region 1280–1030 cm^{-1} for the $\nu(CF_3)$ and $\nu(SO_3)$ vibrations. The IR spectra of the ionic copper complexes **3b** and **4c** are very similar to each other and similar to that of **2b**. The ν(NH) and ν(CH) absorptions are found at 3240–3100 and 3000–2870 cm^{-1} respectively, as well as the $\delta(NH_2)$ at 1604 (**3b**) and 1602 cm^{-1} (**4c**). The azirine complex **5d** shows only the ν(CN) absorption at 1771 cm^{-1} as significant, besides the expected ones for ν(CH) and ν(C=C).

The ^{1}H and ^{13}C NMR spectra of **1a** point to the evidence of the intact *N*-bound aziridine ligand **a**. The CH_3 and CH_2 proton signals show the typical low field shifts caused by metal coordination. The CH_3 signals are found at 1.53 and 1.52 ppm instead of 0.96 ppm for free **a**, the CH_2 signals lie at 2.50 and 2.09 ppm (1.26 ppm free **a**). Analogously, the signals of the C_q and CH_2 carbon atoms appear about +8 and +4 ppm further downfield than those of free **a** (C_q 31.0 ppm, CH_2 33.3 ppm). Concerning the CH_3 carbon signals, complexation causes only slight shifts of about 0.3 and 1.0 ppm. It should be mentioned that both the ^{1}H and ^{13}C NMR spectra of **1a** show a pair for each signal (which overlap in some cases) suggesting the presence of diastereomers in **1a**, which contains an asymmetric carbon and nitrogen atom. Starting off enantiomerically pure (*S*,*S*)-[$C_6H_4CHCH_3NMe_2PdCl]_2$, the coordination of the incoming bridge-splitting aziridine **a** is completely regioselective. This is caused by the known electronic directing effect of Pd–Cl bonds[68–70] to yield pure (S_C,S_N) and (S_C,R_N)–**1a** with the az-*N* taking up the position *trans* to the NMe_2 group. As the corresponding proton signals of both diastereomers are finely separated, especially at the chiral amine ligand, the integration of the signals of $C_6H_4CHMeNMe_2$ delivers a ratio of about 40 : 60 (S_C, S_N) : (S_C,R_N) enantiomers. The new dimerized ligand **b** can be well observed in its ^{1}H and ^{13}C NMR spectra by the signals of the ethane bridge. They are shifted downfield to 2.34 and 2.90 ppm or 42.87 and 62.56 ppm, respectively compared to the C_2H_4 signals of the aziridine ring (1.40 and 1.87 ppm or 28.30 and 33.98 ppm, respectively). The protons of the NH_2 group could not be detected clearly as they are shifted to low field and overlayed by the signals of the C_2H_4 bridge.

The azirine ligand in **5d** shows a low field shift in the ^{1}H and ^{13}C NMR spectra compared to free ligand **d** only for the methylene protons. Because both ligands **d** are chemically equivalent, only one signal for CH_2 at 20.9 ppm (**d**: 19.2 ppm) is observed. While the azirine C_q signal of **5d** is slightly shifted to lower field at 166.8 ppm (**d**: 165.3 ppm), the C_q signal of the phenyl ring is found at higher field (121.6 ppm, **d**: 125.1 ppm). In both spectra of **5d** the three types of protons and C atoms appear separately and can be easily identified (see Experimental part).

The mass spectrum (FAB$^+$) of **1a** features the parent peak with m/z = 362 for [M$^+$] at relatively low intensity (22%) with the typical isotope pattern. In the further fragmentation, first the loss of Cl (m/z = 325, 100%) and then of aziridine **a** with m/z = 254 (13%) occurs. In the mass spectrum of **2b** not only the parent signal for the cation with m/z = 277 (80%) [M$^+$] and one at m/z = 191 (48%) [M^{2+} − **b**] after elimination of one ligand **b** was detected, but also a signal at m/z = 427 (93%) [M^{2+} + OTf] with one triflate still attached to the complex.

The mass spectra of both copper(II) complexes **3b** and **4c** show the cation parent peaks at m/z = 321 (4%) and m/z = 383 (67%). For **3b** a signal at higher mass at m/z = 356 for [M^{2+} + Cl] is observed as well as the corresponding signals after fragmentation of n **b** ligands (n = 1, 2). The mass spectrum of **4c** shows the expected fragmentation pattern with signals at m/z = 348 (30%) [M$^+$ − Cl], 240 (100%) [M$^+$ − **c**] and 205 (74%) [M$^+$ − Cl − **c**]. In the case of the azirine complex **5d** the parent signal [M$^+$] was not detected, but there was a signal at m/z = 377 (100%) [M$^+$ − Cl].

In the UV/Vis spectra of both Cu(II) complexes **3b** and **4c** a broad, unstructured absorption is observed with a maximum at 721 nm (**3b**, ε = 279 L mol^{-1} cm^{-1}) and 796 nm (**4c**, ε = 380 L mol^{-1} cm^{-1}). In spite of the low symmetry caused by the chelating ligands, no shoulder or splitting is observable. The measured values, however, correspond to those of similar Cu(II) complexes with coordination numbers of five and six.[71,72]

Molecular structures of 1a, 2b, 4c and 5d

Single crystals of the complexes were grown from their solutions in CH_2Cl_2 (**1a**, **4c** and **5d**) or CH_3OH (**2b**) by isothermic diffusion of n-pentane. Their solid-state structures have been solved by X-ray diffraction and are shown in Fig. 1–4 together with selected bond lengths and bond angles. The crystallographic data are summarized in Table 1.

As expected for the 4d^8 configuration, **1a** exhibits a slightly distorted square planar geometry at palladium(II) with a small tilt from planarity of only 4.43° between the C5–Pd1–N2 and Cl1–Pd1–N1 planes (Fig. 1). The *cis* angles at the Pd1 center range between 81° and 96°. The five-membered dimethyl-1-phenylethaneamine-2-*C*,*N* chelate ring adopts the envelope conformation with palladium and the three carbon atoms C5, C10 and C11 being essentially coplanar (dihedral angle Pd1–C5–C10–C11 = 1.57°). The nitrogen atom of NMe_2 lies 0.726 Å off this plane. The aziridine ring is almost an equilateral triangle as its C–C and C–N bond lengths (1.476(5) Å and 1.483(4)/1.495(4) Å, respectively) and angles (59.4(2)–60.6(2)°) differ only slightly from those for free aziridine in the solid state.[73] It is noteworthy that the Pd1–N2 bond (2.099(3) Å) is somewhat longer than that of Pd1–N1 (2.047(3) Å). All other Pd1–X distances (X = C5: 1.983(3) Å, X = Cl: 2.4326(8) Å) lie in the expected range.

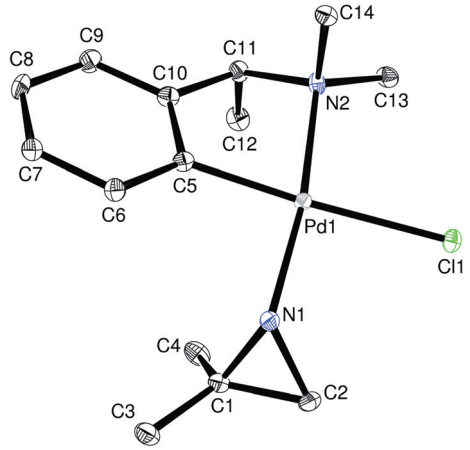


Fig. 1 Molecular structure of complex **1a** with selected bond lengths (Å) and angles (°). S_c,R_N isomer, only one of the four independent molecules in the asymmetric unit is shown. Thermal ellipsoids are drawn at the 30% probability level, H atoms are omitted for clarity. Pd1–N1 2.047(3), Pd1–N2 2.099(3), Pd1–C5 1.983(3), Pd1–Cl1 2.4326(8), N1–C1 1.495(4), N1–C2 1.483(4), C1–C2 1.476(5), C1–C3 1.521(5), C1–C4 1.506(4); C5–Pd1–N1 90.94(12), C5–Pd1–N2 81.41(12), N1–Pd1–Cl1 91.75(8), N2–Pd1–Cl1 96.06(7), N1–Pd1–N2 171.67(10), C5–Pd1–Cl1 176.06(10), C2–C1–N1 59.9(2), C1–C2–N1 60.7(2), C2–N1–C1 59.4(2).

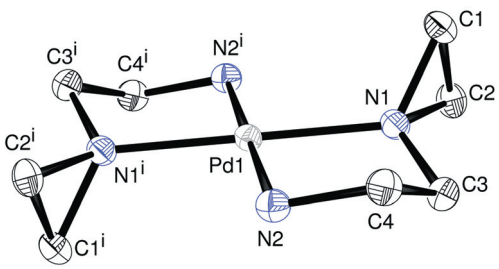


Fig. 2 Molecular structure of complex **2b** with selected bond lengths (Å) and angles (°). H atoms and anions (triflate) are omitted for clarity. Thermal ellipsoids are drawn at the 30% probability level. Pd1–N1 2.0339(16), Pd1–N2 2.0458(18), N1–C1 1.487(3), N1–C2 1.478(3), C1–C2 1.477(3), C3–C4 1.499(3); N1–Pd1–N2 82.71(7), N1–Pd1–N2^i 97.29(7), N1–Pd1–N1^i 180.0, N2–Pd1–N2^i 180.0, N1–C1–C2 59.82 (13), N1–C2–C1 60.44(13), C1–N1–C2 59.74(14).

The cation of compound **2b** has an inversion center at the Pd(II) center surrounded by four nitrogen atoms in a square planar geometry (Fig. 2). The *trans* N–Pd1–N angles are exactly 180°, while the *cis* N–Pd1–N angles vary between 82.7° and 97.3° because of the five-membered chelating ligand in a *twist* configuration. Both of the intact aziridine rings are orientated almost vertical (81.54°) to the molecular square plane. The Pd1–N2 bond length (2.0458(18) Å) is only slightly longer than that of Pd1–N1 (2.0339(16) Å). The same is observed for the C–C bonds of the ethane bridge (C3–C4 1.499(3) Å) and of the aziridine ring (1.477(3) Å). The C–N bonds (1.476(3)/1.485(3) Å) and all angles of the aziridine ring (59.74(14)–60.44(13)°) show similar values to those in **1a**.

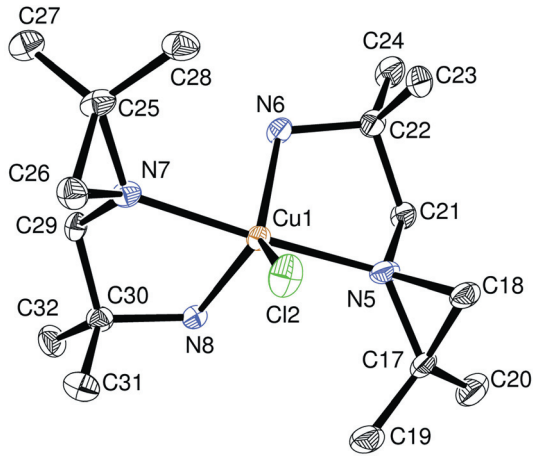


Fig. 3 Molecular structure of complex **4c** with selected bond lengths (Å) and angles (°). Thermal ellipsoids are drawn at the 30% probability level, H atoms, anions (chlorine) and a second molecular unit are omitted for clarity. Cu1–Cl2 2.309(2), Cu1–N5 2.066(7), Cu1–N6 2.105 (5), Cu1–N7 2.074(6), Cu1–N8 2.145(6), N5–C17 1.517(8), N5–C18 1.495(8), C17–C18 1.513(10), N5–C21 1.484(8), N6–C22 1.467(9), C21–C22 1.540(8); N5–Cu1–N7 172.8(2), N6–Cu1–N8 96.5(2), N6–Cu1–Cl2 136.80(19), N8–Cu1–Cl2 126.67(15), N5–Cu1–N6 83.0(2), N5–Cu1–N8 94.5(2), N5–Cu1–Cl2 94.7(2), N7–Cu1–N6 90.6(2), N7–Cu1–N8 82.8(2), N7–Cu1–Cl2 92.30(15), N5–C17–C18 59.1(4), N5–C18–C17 60.5(4), C17–N5–C18 60.3(4).

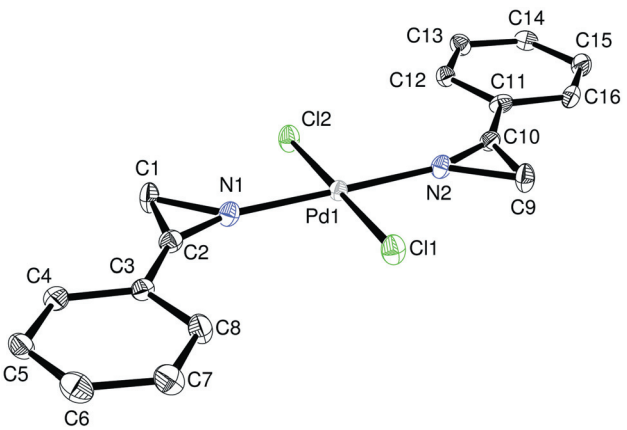


Fig. 4 Molecular structure of complex **5d** with selected bond lengths (Å) and angles (°). Thermal ellipsoids are drawn at the 30% probability level, H atoms are omitted for clarity. Pd1–N1 1.994(4), Pd1–N2 1.973 (4), Pd1–Cl1 2.3009(15), Pd1–Cl2 2.2957(15), N1–C1 1.504(7), N1–C2 1.245(6), C1–C2 1.463(7); N1–Pd1–N2 179.3(3), N1–Pd1–Cl1 92.09 (14), N1–Pd1–Cl2 87.89(15), Cl1–Pd1–Cl2 179.38(5), C1–N1–Pd1 137.5(3), C1–N1–C2 63.5(3), N1–C1–C2 49.6(3), N1–C2–C1 66.9(3).

In the unit cell of complex **4c** are two independent molecular units with only a few slight differences in their structural parameters. Therefore, only one is discussed and shown in Fig. 3. The Cu(II) center shows a distorted trigonal bipyramidal geometry surrounded by four nitrogen atoms and one chlorido ligand. This and both NH_2 groups lie within the equatorial plane, while both aziridine N atoms occupy the *trans*-axial positions. The equatorial angles differ greatly because of the steric demand of the chlorido ligand (N6–Cu1–Cl2 136.80(19)°, N8–Cu1–Cl2 126.67(15)° and N6–Cu1–N8 96.5(2)°). The *trans*-axial angle N5–Cu1–N7 (172.8(2)°) is also affected. The angles between equatorial and axial ligands show values larger than 90° (90.6–94.7°) with the only exception of those two (N5–Cu1–N6 83.0(2)°, N7–Cu1–N8 82.8(2)°) caused by both five-membered chelate systems in *twist* conformation. All structural parameters of both aziridine rings range within normal values and correspond to those in **1a** and **2b**.

Analogous trigonal bipyramidal Cu(II) complexes are rarely found in the literature. Normally, analogous geometries can be formed by multidentate ligands, *e.g.* $[(Cu(tren)NH_3)ClO_4]_2$[74] or by special polyhedral structures, *e.g.* in the tetrameric adamantane-analogous μ_4-oxo-complex $[(\mu_4\text{-}O)(\mu_4\text{-}Cl)(C_2H_4NHCu)_4]$.[75]

The square planar azirine complex of palladium(II) **5d** (Fig. 4) is slightly distorted because of the two different ligands, two chlorido ligands and two azirine-N atoms each in *trans* positions (N1–Pd1–N2 179.3(3)°, Cl1–Pd–Cl2 179.38(5)°). The planes of the azirine rings form different small angles to the equatorial PdN_2Cl_2 plane (Δ_1 = 2.56 and 3.78°) as well as to the phenyl plane (Δ_2 = 4.48 and 5.63°). Therefore, one can say that the whole molecule is nearly planar. Both Pd–Cl1/Cl2 and Pd–N1/N2 bond lengths are nearly equal, the latter ones of course are shorter because of their sp^2-hybridized *N*-atoms than those in the aziridine complexes mentioned above. This is also observed in the structural parameters of the unsaturated azirine ring (N1–C1 1.504(7), N1–C2 1.245(6) and C1–C2 1.463(7) Å; C1–N1–C2 63.5(3), N1–C1–C2 49.6(3) and N1–C2–C1 66.9(3)°) which differ significantly from those of the saturated aziridine rings.

Biological studies

The cytotoxicity of the complexes **1a**, **2b**, **3b**, **4c** and **5d** was assayed against human HL-60 and NALM-6 leukemia cells and melanoma WM-115 cells. During these tests no signs of decomposition were noticed. Cisplatin and carboplatin were used as reference compounds. Cells were exposed to a broad range of drug concentrations (10^{-7} to 10^{-3} M) for 48 h and cell viability was analyzed by MTT assay. IC_{50} values are presented in Table 2. The complexes **2b**, **3b** and **5d** exhibited the highest cytotoxic activity for HL-60 and NALM-6 cell lines, with IC_{50} values in the range of 1.5–8.2 μM. Interestingly, compound **3b** was even more effective then reference drug cisplatin in the case of human skin melanoma WM-115 cells.

It was found that the growth of Gram-positive bacterial strains (*S. aureus*, *S. epidermidis* and *E. faecalis*) was inhibited by almost all tested complexes at the concentrations of 37.5–300.0 μg mL^{-1} (Table 3). On the other hand, MIC values of complexes obtained for Gram-negative *E. coli* and *P. aeruginosa*, as well as for *C. albicans* yeast, exceeded 300 μg mL^{-1}. The exception was activity of **2b** against *E. coli* and *P. aeruginosa* (at 75.0 μg mL^{-1}) and **1a** with the MIC for *E. coli* equal to 150.0 μg mL^{-1}. In general, the highest activity was achieved by **2b**. MICs of this complex were relatively low: 37.5 μg mL^{-1} for *S. aureus* and 18.75 μg mL^{-1} for *S. epidermidis*. The second complex with noticeable antimicrobial activity was **1a**. It inhibited growth of Gram-positive cocci (*S. aureus*, *S. epidermidis* and *E. faecalis*) at a concentration range of 75.0–150.0 μg mL^{-1}.

Table 1 Crystallographic data for complexes **1a**, **2b**, **4c** and **5d**

Compound	**1a**	**2b**	**4c**	**5d**
Formula	$C_{14}H_{23}ClN_2Pd$	$C_8H_{20}N_4Pd$, 2 (CF_3O_3S)	$C_{16}H_{36}ClCuN_4$, Cl	$C_{16}H_{14}Cl_2N_2Pd$
FW	361.22	576.83	418.94	411.62
T/K	200(2)	200(2)	200(2)	200(2)
Wavelength/Å	0.71073	0.71073	0.71073	0.71073
Crystal system	Monoclinic	Monoclinic	Orthorhombic	Orthorhombic
Space group	$P2_1$	$P2_1/c$	$Pna2_1$	$Pca2_1$
a/Å	10.7546(5)	11.6261(3)	24.9994(5)	21.4333(5)
b/Å	26.4634(11)	9.8324(2)	9.0537(1)	5.6449(1)
c/Å	11.0319(4)	9.8676(2)	18.8146(3)	12.6506(3)
α/°	90	90	90	90
β/°	92.912(3)	111.658(2)	90	90
γ/°	90	90	90	90
V/Å^3	3135.6(2)	1048.36(4)	4258.44(12)	1530.58(6)
Z	8	2	8	4
ρ_c/g cm^{-3}	1.53036	1.82736	1.3069	1.78631
μ/mm^{-1}	1.340	1.170	1.281	1.554
F(000)	1472	576	1784	816
Crystal size/mm	0.34 × 0.24 × 0.15	0.14 × 0.10 × 0.04	0.16 × 0.04 × 0.03	0.18 × 0.05 × 0.02
θ range/°	3.78 to 27.62	3.99 to 27.52	3.2 to 26.00	3.61 to 27.48
Index range	$-13 \le h \le 14$ $-34 \le k \le 23$ $-14 \le l \le 14$	$-15 \le h \le 15$ $-12 \le k \le 12$ $-12 \le l \le 12$	$-30 \le h \le 30$ $-11 \le k \le 11$ $-23 \le l \le 23$	$-27 \le h \le 27$ $-7 \le k \le 7$ $-16 \le l \le 16$
Refls. collected	18 229	4640	7966	3291
Independent refls.	10 459	2400	4295	3291
R_{int}	0.0295	0.0142	0.0275	0.041
Completeness to θ	99.4%	99.5%	99.4%	99.7%
Data/restraints/parameters	10 459/1/649	2400/0/169	4295/1/416	3291/1/191
S on F^2	1.001	1.104	1.021	1.049
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0221$, wR_2 = 0.0494	$R_1 = 0.0228$, wR_2 = 0.0523	$R_1 = 0.0465$, wR_2 = 0.1204	$R_1 = 0.0322$, wR_2 = 0.0730
R indices (all data)	$R_1 = 0.0247$, wR_2 = 0.0504	$R_1 = 0.0278$, wR_2 = 0.0546	$R_1 = 0.0692$, wR_2 = 0.1352	$R_1 = 0.0473$, wR_2 = 0.0808
Absolute structure parameter	0.021(14)	–	0.29(6)[a]	0.47(7)[a]
Largest difference peak/hole [e Å^{-3}]	0.483/−0.550	0.605/−0.552	1.208/−0.366	2.186/−0.618
CCDC	849020	849021	849022	849023

[a] Structures **4c** and **5d** refined as twins (twinned by inversion) yielding BASF 0.2926 (**4c**) and 0.4697 (**5d**). The determination of the absolute structures is not possible.

Table 2 IC_{50} values (in μM) for complexes **1a**, **2b**, **3b**, **4c** and **5d**

Compounds	HL-60	NALM-6 IC_{50} [a]	WM 115
1a	56.4 ± 2.3	48.7 ± 1.0	62.4 ± 3.4
2b	8.2 ± 0.3	7.2 ± 0.5	47.6 ± 1.0
3b	1.53 ± 0.30	0.58 ± 0.10	5.9 ± 0.9
4c	50.3 ± 2.8	48.1 ± 3.0	51.4 ± 3.9
5d	4.6 ± 0.7	5.8 ± 1.1	84.6 ± 2.8
Cisplatin	0.8 ± 0.1	0.7 ± 0.3	18.2 ± 4.3
Carboplatin	4.3 ± 1.3	0.7 ± 0.2	422.2 ± 50.2

[a] IC_{50} – concentration of a tested compound required to reduce the fraction of surviving cells to 50% of that observed in the control, non-treated cells. Data represents the mean value of at least three experiments, each performed at five repeats ± S.D.

Table 3 Antimicrobial activity of complexes. MIC values (μg mL^{-1}) were determined by broth microdilution assay, according to CLSI recommendations

	MIC (μg mL^{-1})				
Microorganism	**1a**	**2b**	**3b**	**4c**	**5d**
S. aureus (ATCC 29213)	**150.0**	**37.5**	300.0	>300.0	300.0
S. epidermidis (ATCC 12228)	**75.0**	**18.75**	300.0	>300.0	300.0
E. faecalis (ATCC 29212)	**150.0**	**150.0**	300.0	>300.0	300.0
E. coli (NCTC 8196)	**150.0**	**75.0**	>300.0	>300.0	>300.0
P. aeruginosa (NCTC 6749)	>300.0	**75.0**	>300.0	>300.0	>300.0
C. albicans (ATTC 10231)	>300.0	>300.0	>300.0	300.0	>300.0

Conclusion

In the present paper the synthesis, characterization and crystal structures of three square planar palladium(II) complexes (**1a**, **2b** and **5d**) containing the ligands 2-dimethylaziridine-*N* (**a**), *N*-(2-aminoethyl)aziridine-*N*,*N*′ (**b**) and 2*H*-3-phenylazirine (**d**) as well as of two copper(II) complexes (octahedral **3b** and trigonal bipyramidal **4c**), where ligands **b** and **c** are dimers of the parent aziridine C_2H_4NH and its 2-dimethyl derivative **a**, are reported.

This unexpected dimerization occurs *via* insertion and ring opening reaction of two aziridines by metal-induced activation. Though aziridines are considered to be highly mutagenic, all the complexes have been examined for cytotoxic and antimicrobial properties. To the best of our knowledge this is the first time such directed investigations have been carried out. All the novel

aziridine-containing complexes are promising compounds with high antitumor activity and two of them, **1a** and **2b**, also show remarkable antibacterial activity. Many natural or synthetic compounds show activity against Gram-positive bacteria but not against Gram-negative species or fungi, which have evolved significant permeability barriers. Thus, it is worth emphasizing that in our experiments the Gram-negative bacteria were susceptible to damage by one of complexes used (**2b**). It suggests that this compound may easily penetrate biological membranes probably without any help of active transport mechanisms and may be promising as a future therapeutic agent and alternative to antibiotics. However, on the basis of this study it is difficult to predict its mechanisms of action.

Experimental

Materials and methods

All experiments were performed under a dry argon atmosphere using Schlenk line techniques. The separation of phases in heterogeneous reaction mixtures was carried out by centrifugation with subsequent pipetting or by filtration. Reagents were commercially available and used without further purification. The starting complexes [μ-Cl(C_6H_4CHMeNMe_2-*C*,*N*)Pd]$_2$[61] and *trans*-[C_2H_4NHPdCl]$_2$[62] were prepared according to literature methods. The solvents were purified by standard procedures; CH_2Cl_2 was distilled from calcium hydride, n-pentane from lithium aluminium hydride and methanol from MgH_2. All dried solvents were stored under a dry Ar atmosphere with 3 Å molecular sieves. NMR spectra were recorded using a Jeol Eclipse 270 or a Jeol Eclipse 400 spectrometer operating at 270 MHz (^{1}H) and 68 MHz (^{13}C) or 400 MHz (^{1}H) and 100 MHz (^{13}C), respectively. The ^{1}H and ^{13}C chemical shifts were determined relative to TMS as an internal standard. IR spectra were recorded using a Perkin Elmer Spectrum One FT-IR-Spectrometer in the range of 4000–400 cm^{-1}. UV/visible (UV/Vis) data were recorded with a Varian Cary 50 UV/Vis spectrophotometer at room temperature. Mass spectra were obtained with a JEOL MStation MS-700, NBA matrix (FAB). Multi-isotope containing fragments refer to the isotope with the highest abundance. Elemental analyses were performed by the Microanalytical Laboratory of the Department of Chemistry, LMU Munich, using a Heraeus Elementar Vario El. Single crystal X-ray data were collected with a Nonius Kappa CCD diffractometer (**2b**, **4c**, **5d**) equipped with a rotating anode generator or an Oxford Diffraction XCalibur diffractometer (**1a**), both using graphite-monochromated Mo-K$_\alpha$ radiation (λ = 0.71073 Å). Structures were solved by direct methods using the SHELXS software and refined on F^2 by full-matrix least-squares with SHELXL-97.[76] CCDC numbers in Table 1 contain the supplementary crystallographic data for this paper.‡

Synthesis of the palladium(II) and copper(II) complexes 1a, 2b, 3b, 4c and 5d

Chlorido-(2,2-dimethylaziridine)-[2-{1-(dimethylamino)ethyl}-phenyl-*C*,*N*]-palladium(II) (1a). 6 equivalents of 2,2-dimethylaziridine (**a**) (66.1 μL, 0.732 mmol) were added to a solution of bis[μ-chlorido-[(*S*)-2-{1-(dimethylamino)ethyl}phenyl-*C*,*N*-palladium(II)][61] (71 mg, 0.122 mmol) in 5 mL CH_2Cl_2. After 12 h of stirring at r.t., the solvent was removed *in vacuo* and the residue was purified by stirring in dry n-heptane (10 mL) for 12 h at r.t. Yield 44 mg (0.122 mmol, 50%), light grey powder, m.p. 157 °C. Elemental analysis: Found: N, 7.72; C, 46.58; H, 6.45. Calc. for $C_{14}H_{23}ClN_2Pd$ (361.22 g mol^{-1}): N, 7.76; C, 46.55; H, 6.42%. IR: ν_{max}/cm^{-1} (KBr) 3139vs (NH), 3105s, 2971s (CH), 2912m (CH), 2856m (CH), 2833w (CH), 2788w, 1579w, 1458s, 1446s, 1384s, 1370m, 1340s, 1290w, 1251w, 1175w, 1175w, 1146m, 1114s, 1062w, 1030w, 1011m, 981w, 939s, 921s, 812s, 786w, 756vs, 729s, 661w, 557w. ^{1}H NMR (270.17 MHz, CD_2Cl_2): δ = 7.00–6.82 (m, 4H, Ar-CH), 3.62 and 3.53 (two signals for *S*,*S* and *S*,*R* enantiomer, quartet, $^3J_{H-H}$ = 6.5 Hz, 0.4H and 0.6H, C*H*Me), 2.75 and 2.59 (s, 1.5H each, NCH_3), 2.63 and 2.56 (s, 1.5H each, NCH_3), 2.50 (d, br, $^3J_{H-NH}$ = 5.9 Hz, 1H, az-CH_2), 2.09 (d, br, $^3J_{H-NH}$ = 7.4 Hz, $^2J_{H-H}$ = 2.1 Hz, 1H, az-CH_2), 1.53 (s, 3H, az-CH_3), 1.52 (s, 3H, az-CH_3), 1.46 and 1.42 (s, $^3J_{H-H}$ = 6.5 Hz, 1.5H each, CHCH_3). ^{13}C NMR, DEPT: (67.93 MHz, CD_2Cl_2): δ = 154.0 and 153.6 (Ar-C_q), 147.5 and 147.2 (Ar-C_q-Pd), 131.6 (Ar-*C*H), 124.5 and 124.8 (Ar-*C*H), 124.2 and 124.1 (Ar-*C*H), 122.1 and 122.0 (Ar-*C*H), 76.2 and 75.6 (>*C*HCH$_3$), 52.2 and 51.9 (>NCH$_3$), 48.0 and 47.2 (>NCH$_3$), 38.9 and 38.7 (az-C_q), 37.5 and 37.4 (az-*C*H$_2$), 25.8 and 25.5 (az-*C*H$_3$), 25.4 and 25.0 (az-*C*H$_3$), 20.9 and 19.2 (>CH*C*H$_3$). MS (FAB$^+$): *m*/*z* (%) = 362 (22) [M$^+$], 325 (100) [M$^+$ − Cl], 254 (13) [M$^+$ − Cl − **a**], 211 (11) [Pd + Cl + **a**].

[Bis(*N*-(2-aminoethyl)aziridine-*N*,*N*′)palladium(II)]bis(trifluormethansulfonate) (2b). To a suspension of 100 mg (0.380 mmol) *trans*-[bis(aziridine)dichloridopalladium(II)] ($(C_2H_4N)_2Cl_2Pd$)[62] in 20 mL CH_2Cl_2, 205 mg (0.797 mmol) AgOTf was added. After stirring at r.t. for 24 h the precipitate of AgCl was separated by centrifugation. The resulting solution was combined with 61.4 μL (1.14 mmol) aziridine C_2H_4NH, whereby it become clouded. After stirring again at r.t. for 24 h the solvent was removed *in vacuo*. The crude residue was purified by stirring in n-hexane and separation by pipetting two times; afterwards it was dried *in vacuo*. Yield 108 mg (0.187 mmol, 50%), light yellow solid, m.p. 176 °C (dec.). Elemental analysis: Found: C, 21.09; H, 3.88; N, 9.15. Calc. for $C_{10}H_{20}F_6N_4O_6PdS_2$ (576.83 g mol^{-1}): C, 20.82; H, 3.49; N, 9.71%. IR: ν_{max}/cm^{-1} (KBr) 3252m, 3154w, 2926w, 1608w, 1448w, 1280s, 1246s, 1166s, 1032s, 990w, 957w, 906w, 829w, 805w, 750w, 639s, 574w, 517m, 408w. ^{1}H NMR (399.78 MHz, CD_3OD): δ = 2.90 (t, ^3J = 5.6 Hz, 4H, en-CH_2), 2.34 (t, ^3J = 5.6 Hz, 4H, en-CH_2), 1.87 (t, ^3J = 2.2 Hz, 4H, az-CH_2), 1.40 (t, ^3J = 2.2 Hz, 4H, az-CH_2). ^{13}C NMR (100.53 MHz, CD_3OD): δ = 121.83 (q, $^1J_{C-F}$ = 319 Hz, *C*F$_3$), 62.56 (en-*C*H$_2$), 42.87 (en-*C*H$_2$), 33.98 (az-*C*H$_2$), 28.30 (az-*C*H$_2$). MS (FAB$^+$): *m*/*z* (%) = 427 (93) [M^{2+} + OTf], 277 (80) [M^{2+}], 191 (48) [M^{2+} − **b**].

[Tris(*N*-(2-aminoethyl)aziridine-*N*,*N*′)copper(II)]dichloride (3b). The aziridine C_2H_5NH (8 mL, 149 mmol) was cooled down to −10 °C. Then anhydrous $CuCl_2$ (1.55 g, 11.5 mmol) was added in small portions while stirring for 4 h. After warming up to r.t. the blue mixture was stirred for 3 d and then the excess of C_2H_5NH was removed *in vacuo*. The residue was purified by stirring in n-hexane overnight and dried *in vacuo* after separation from n-hexane by pipette. Yield 4.35 g (11.0 mmol, 96%), blue

powder, m.p. 111 °C (dec.). Elemental analysis: Found: C, 36.65; H, 7.67; N, 21.12. Calc. for $C_{12}H_{30}Cl_2CuN_6$ (392.86 g mol^{-1}): C, 36.69; H, 7.70; N, 21.39%. UV/Vis: $\lambda_{max}(CH_2Cl_2)$/nm 721 (ε/L mol^{-1} cm^{-1} 279). IR: ν_{max}/cm^{-1} (KBr) 3192s, 3101s, 2995w, 2966w, 2882m, 1660w, 1602m, 1448m, 1359w, 1323w, 1293w, 1259m, 1222w, 1152m, 1097w, 1063m, 1008s, 936s, 902w, 861s, 834w, 816w, 787w, 755m, 708w, 553w, 450w. MS (FAB^+): *m*/*z* (%) = 356 (5) [M^{2+} × Cl], 321 (4) [M^{2+}], 270 (100) [M^{2+} + Cl − **b**], 240 (31) [M^{2+} − **b**], 184 (36) [M^{2+} + Cl − 2**b**].

[Bis{*N*-(2-amino-2-methylpropyl)-2,2-dimethylaziridine-*N*,*N*′} chlorido-copper(II)]chloride (4c). The synthesis of **4c** takes place analogously to that of **3b**: Cooling of aziridine CH_2CMe_2NH (1 mL, 11.1 mmol), slowly adding 130 mg (0.967 mmol) anhydrous $CuCl_2$, reaction time 2 days and the same procedure of purification. Yield 388 mg (0.930 mmol, 96%), turquoise powder, m.p. 174 °C (dec.). Elemental analysis: Found: C, 45.93; H, 8.71; N, 13.42. Calc. for $C_{16}H_{36}Cl_2CuN_4$ (418.94 g mol^{-1}): C, 45.87; H, 8.66; N, 13.37%. UV/Vis: $\lambda_{max}(CH_2Cl_2)$/nm 796 (ε/L mol^{-1} cm^{-1} 380). IR: ν_{max}/cm^{-1} (KBr) 3239s, 3136s, 2992m, 2968s, 2878m, 2734w, 1604m, 1476m, 1461m, 1393m, 1382s, 1373m, 1348m, 1338m, 1282w, 1236m, 1199m, 1151m, 1111m, 1067w, 1024w, 999m, 948m, 932m, 924m, 867m, 812s, 773m. MS (FAB^+): *m*/*z* (%) = 383 (67) [M^+], 348 (30) [M^+ − Cl], 240 (100) [M^+ − **c**], 205 (74) [M^{2+} − Cl − **c**].

Following the suggestion of a reviewer that the dinuclear Cu(II) complex $[(\mu\text{-Cl})(CH_2CMe_2NH)_2ClCu]_2$ (synthesized from $CuCl_2$ in CH_2Cl_2 solution)[67] could be a possible intermediate in the formation of **4c**, we repeated the synthesis of **4c** as described above with this complex instead of $CuCl_2$. Indeed we were able to detect **4c** in the products of this reaction with MS (FAB^+) but further purification was not possible.

***trans*-Bis[(2*H*-phenylazirine)dichlorido]palladium(II) (5d).** 193 mg (0.744 mmol) of $PdCl_2$ in 20 mL of CH_3CN was heated to reflux until it dissolved. Small amounts of insoluble components were filtered off and the solvent distilled off *in vacuo*. The orange yellow residue was dissolved in a mixture of 30 mL CH_2Cl_2 and 10 mL CH_3CN. The resulting solution was combined with 174 mg (1.488 mmol) 2*H*-3-phenylazirine **d** and stirred at r.t. for 0.5 h. The solvent was removed *in vacuo*. Yield 200 mg (0.419 mmol, 65%), yellow-orange powder, m.p. 154 °C (dec.). Elemental analysis: Found: C, 46.22; H, 3.26; N, 6.70. Calc. for $C_{16}H_{14}Cl_2N_2Pd$ (411.62 g mol^{-1}): C, 46.69; H, 3.43; N, 6.81%. IR: ν_{max}/cm^{-1} (KBr) 3049w, 1777vs, 1597w, 1491w, 1450m, 1326w, 1308w, 1265w, 1185w, 1132w, 1020s, 874m, 767s, 699m, 682s, 543m. ^1H NMR (399.78 MHz, $CDCl_3$): δ = 8.37–8.34 (m, 4H, C*H*), 7.75–7.71 (m, 2H, C*H*), 7.65–7.61 (m, 4H, C*H*), 2.23 (s, 4H, CH_2). ^{13}C NMR (100.53 MHz, $CDCl_3$): δ = 166.8 (C_q), 133.6 (*C*H), 132.4 (*C*H), 129.3 (*C*H), 121.6 (C_q), 20.9 (CH_2). MS (FAB^+): *m*/*z* (%) = 377 (100) [M^+ − Cl].

Cell and cytotoxicity assay

Cell cultures. Human skin melanoma WM-115 cells as well as human leukemia promyelocytic HL-60 and lymphoblastic NALM-6 cell lines were used. Leukemia cells were cultured in RPMI 1640 medium supplemented with 10% fetal bovine serum and antibiotics (100 μg mL^{-1} streptomycin and 100 U mL^{-1} penicillin). For melanoma WM-115 cells Dulbecco's minimal essential medium (DMEM) instead of RPMI 1640 was used. Cells were grown in 37 °C in a humidified atmosphere of 5% CO_2 in air.

Cytotoxicity assay by MTT. Cytotoxicity of complexes **1a**, **2b**, **3b**, **4c**, **5d**, cisplatin and carboplatin was determined by the MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide, Sigma, St. Louis, USA) assay as described.[77] Briefly, after 46 h of incubation with drugs, the cells were treated with the MTT reagent, and incubation was continued for 2 h. MTT–formazan crystals were dissolved in 20% SDS and 50% DMF at pH 4.7 and absorbance was read at 562 nm on an ELISA-plate reader (ELX 800, Bio-Tek, USA). The values of IC_{50} (the concentration of the tested compound required to reduce the cells survival fraction to 50% of the control) were calculated from concentration–survival curves and used as a measure of cellular sensitivity to a given treatment. Complexes, cisplatin and carboplatin were tested for their cytotoxicity in final concentrations from 10^{-7} to 10^{-3} M. As a control, cultured cells were grown in the absence of drugs. Data points represent means of 3–4 experiments, each performed at five repeats ± S.D.

Antibacterial activity

Microorganisms. Gram-positive bacteria: *Staphylococcus aureus* ATCC 29213; *S. epidermidis* ATCC 12228; *Enterococcus faecalis* ATCC 29212; two Gram-negative bacteria: *Escherichia coli* NCTC 8196; *Pseudomonas aeruginosa* NCTC 6749, and yeast *Candida albicans* ATCC 10231, were used. The organisms were stored in TSB with 15% glycerol at −70 °C, and in each experiment cultures were established from the original stock.

Antibacterial activity testing. The susceptibility of microorganisms to complexes was determined by the standard CLSI (Clinical and Laboratory Standards Institute) broth microdilution method. Sterile stock solutions of each compound at the concentration of 60.0 mg mL^{-1} were prepared in DMSO. The agent concentration range used in the antimicrobial tests was 0.29–300.0 μg mL^{-1} prepared for bacteria in Mueller–Hinton broth (Difco, USA), and for yeast in RPMI-1640 medium supplemented with L-glutamine and $NaHCO_3$ (Biomed, Poland). Since stock solutions of chemicals were prepared in DMSO, this solubilizer alone was used as a control. To specify the minimal inhibitory concentrations (MIC), turbidometric (OD_{600}) studies were carried out using the multifunction counter Victor2 (Wallac, Finland). MIC was estimated as the lowest concentration of antimicrobial agent which gave drop in OD_{600} equal to the medium negative control (below 0.05), after 24 h at 37 °C of co-incubation.

Acknowledgements

This work was supported by grants from the Medical University of Lodz No. 503/3-066-02/503-01 (to E. Budzisz) and No. 503/3-015-02/503-01 (to M. Rozalski and U. Krajewska). We thank Dr Karin Lux for the assistance in crystal structure solution.

Notes and references

1 J. B. Sweeney, *Chem. Soc. Rev.*, 2002, **31**, 247–258.
2 I. D. Watson, L. Yu and A. K. Yudin, *Acc. Chem. Res.*, 2006, **39**, 194–206.
3 D. M. Noll, T. M. Mason and P. S. Miller, *Chem. Rev.*, 2006, **106**, 277–301.
4 B. M. Trost and D. R. Fandrick, *Org. Lett.*, 2005, **7**, 823–826.
5 V. K. Yadav and V. Sriramurthy, *J. Am. Chem. Soc.*, 2005, **127**, 16366–16367.
6 O. Ihata, Y. Kayaki and T. Ikariya, *Macromolecules*, 2005, **38**, 6429–6434.
7 J. A. Katzenellenbogen, K. E. Carlson, D. F. Heiman, D. W. Robertson, L. L. Wei and B. S. Katzenellenbogen, *J. Biol. Chem.*, 1983, **258**, 3487–3495.
8 B. S. Iyengar, S. M. Sami, S. E. Tarnow, W. A. Remers, W. T. Bradner and J. E. Schurig, *J. Med. Chem.*, 1983, **26**, 1453–1457.
9 G. Sosnovsky and M. Konieczny, *Synthesis*, 1978, 583–585.
10 R. Kho, J. A. Hodges, M. R. Hansen and H. O. Villar, *J. Med. Chem.*, 2005, **48**, 6671–6678.
11 S. R. Rajski and R. M. Williams, *Chem. Rev.*, 1998, **98**, 2723–2796.
12 M. M. Paz, G. Suresh Kumar, M. Glover, M. J. Waring and M. Tomasz, *J. Med. Chem.*, 2004, **47**, 3308–3319.
13 K. Yokoi, K. Nagaoka and T. Nakashima, *Chem. Pharm. Bull.*, 1986, **34**, 4554–4561.
14 S. C. Schold Jr., J. E. Herndon, P. C. Burger, E. C. Halperin, N. A. Vick, J. G. Cairncross, D. R. Macdonald, E. J. Dropcho, R. Morawetz and D. D. Bigner, *et al.*, *J. Clin. Oncol.*, 1993, **11**, 77–83.
15 Y.-C. Peng, H.-S. Kuo, H.-D. Tsai, Y.-P. Yang and Y.-L. Lin, *Bioorg. Med. Chem.*, 2006, **14**, 263–272.
16 M. J. v. Maanen, C. J. M. Smeets and J. H. Beijnen, *Cancer Treat. Rev.*, 2000, **26**, 257–268.
17 Y. Palom, M. F. Belcourt, S. M. Musser, A. C. Sartorelli, S. Rockwell and M. Tomasz, *Chem. Res. Toxicol.*, 2000, **13**, 479–488.
18 I.-P. Lorenz and J. Kull, *Angew. Chem.*, 1986, **98**, 276–278.
19 J. Amarasekera, T. B. Rauchfuss and S. R. Wilson, *J. Am. Chem. Soc.*, 1988, **110**, 2332–2334.
20 R. F. Heck, *J. Am. Chem. Soc.*, 1963, **85**, 1460–1463.
21 D. Milstein and J. C. Calabrese, *J. Am. Chem. Soc.*, 1982, **104**, 3773–3774.
22 I.-P. Lorenz, J. Messelhäuser, W. Hiller and K. Haug, *Angew. Chem.*, 1985, **97**, 234–235.
23 I.-P. Lorenz, J. Messelhäuser, W. Hiller and M. Conrad, *J. Organomet. Chem.*, 1986, **316**, 121–138.
24 M. Herberhold and B. Schmidkonz, *J. Organomet. Chem.*, 1988, **358**, 301–320.
25 G. Beuter, S. Drobnik, I.-P. Lorenz and A. Lubik, *Chem. Ber.*, 1992, **125**, 2363–2366.
26 L. M. Atagi, D. E. Over, D. R. McAlister and J. M. Mayer, *J. Am. Chem. Soc.*, 1991, **113**, 870–874.
27 C. A. Root and J. W. Allison, *Inorg. Chem.*, 1970, **9**, 2791–2792.
28 D. V. Lefemine, M. Dann, F. Barbatschi, W. K. Hausmann, V. Zbinovsky, P. Monnikendam, J. Adam and N. Bohonos, *J. Am. Chem. Soc.*, 1962, **84**, 3184–3185.
29 J. C. Barnes, J. Iball and T. J. R. Weakley, *Acta Crystallogr., Sect. B: Struct. Crystallogr. Cryst. Chem.*, 1975, **31**, 1435–1437.
30 F. Porta, M. Pizzotti, G. La Monica, L. A. Finessi, S. Cenini, P. L. Bellon and F. Demartin, *J. Chem. Soc., Dalton Trans.*, 1984, 2409–2414.
31 V. B. Ukraintsev, S. V. Yakovlev and Y. N. Kukushkin, *Zh. Obshch. Khim.*, 1987, **57**, 1906–1907.
32 V. B. Ukraintsev, S. V. Yakovlev and Y. N. Kukushkin, *Russ. J. Gen. Chem.*, 1987, **57**, 1704–1705.
33 D. C. Ware, B. G. Siim, K. G. Robinson, W. A. Denny, P. J. Brothers and G. R. Clark, *Inorg. Chem.*, 1991, **30**, 3750–3757.
34 D. C. Ware, D. S. Mackie, P. J. Brothers and W. A. Denny, *Polyhedron*, 1993, **12**, 1371–1376.
35 W. R. Cantrell Jr, G. B. Richter-Addo and J. A. Gladysz, *J. Organomet. Chem.*, 1994, **472**, 195–204.
36 D. C. Ware, D. S. Mackie, P. J. Brothers and W. A. Denny, *Polyhedron*, 1995, **14**, 1641–1646.
37 S. v. Beckerath, I.-P. Lorenz, R. Fawzi and M. Steimann, *Z. Naturforsch., B: Chem. Sci.*, 1996, **51b**, 959–962.
38 R. B. Cheikh, R. Chaabouni, M. C. Bonnet and F. Dahan, *Polyhedron*, 1998, **17**, 185–192.
39 R. Wilberger, H. Piotrowski, M. Warchhold and I.-P. Lorenz, *Z. Anorg. Allg. Chem.*, 2003, **629**, 2485–2492.
40 R. Wilberger, C. Krinninger, H. Piotrowski, P. Mayer, M. Ossberger and I.-P. Lorenz, *Z. Anorg. Allg. Chem.*, 2004, **630**, 1495–1500.
41 I.-P. Lorenz, C. Krinninger, R. Wilberger, R. Bobka, H. Piotrowski, M. Warchhold and H. Nöth, *J. Organomet. Chem.*, 2005, **690**, 1986–1993.
42 W. Beck, W. Danzer and R. Höfer, *Angew. Chem.*, 1973, **85**, 87–88.
43 W. Beck, W. Danzer, A. T. Liu and G. Huttner, *Angew. Chem.*, 1976, **88**, 511–512.
44 A. T. Liu, W. Beck, G. Huttner and H. Lorenz, *J. Organomet. Chem.*, 1977, **129**, 91–96.
45 W. Danzer, R. Hoefer, H. Menzel, B. Olgemoeller and W. Beck, *Z. Naturforsch., B: Chem. Sci.*, 1984, **39b**, 167–179.
46 M. M. Singh and R. J. Angelici, *Inorg. Chem.*, 1984, **23**, 2691–2698.
47 M. M. Singh and R. J. Angelici, *Inorg. Chem.*, 1984, **23**, 2699–2705.
48 R. Wilberger, *Ph.D. Thesis*, LMU, Munich, 2002.
49 R. Höfer, W. Beck and A. Engelmann, *Chem. Ber.*, 1973, **106**, 2590–2600.
50 H. P. Fritz and G. Hierl, *Z. Naturforsch., B: Chem. Sci.*, 1971, **26b**, 476.
51 M. Kojima, A. Sakurai, M. Murata, K. Nakajima, S. Kashino and Y. Yoshikawa, *J. Coord. Chem.*, 1997, **42**, 95–106.
52 C. Krinninger, *Ph.D. Thesis*, LMU, Munich, 2005.
53 R. Bobka, *Ph.D. Thesis*, LMU, Munich, 2007.
54 K. Dietliker, U. Schmid, G. Mukherjee-Mueller and H. Heimgartner, *Chimia*, 1978, **32**, 164–166.
55 A. Hassner, C. A. Bunnell and K. Haltiwanger, *J. Org. Chem.*, 1978, **43**, 57–61.
56 P. F. Dos Santos Filho and U. Schuchardt, *J. Organomet. Chem.*, 1984, **263**, 385–393.
57 H. Alper and J. E. Prickett, *Inorg. Chem.*, 1977, **16**, 67–71.
58 T. Izumi and H. Alper, *Organometallics*, 1982, **1**, 322–325.
59 B. S. Iyengar, T. Takahashi, W. A. Remers and W. T. Bradner, *J. Med. Chem.*, 1986, **29**, 144–147.
60 M. Galanski and B. K. Keppler, *Pharm. Unserer Zeit*, 2006, **35**, 118–123.
61 S. B. Wild, *Coord. Chem. Rev.*, 1997, **166**, 291–311.
62 J. N. Roedel, R. Bobka, M. P. Pfister, M. Rieger, B. Neumann and I.-P. Lorenz, *Z. Naturforsch., B: Chem. Sci.*, 2007, **62b**, 1095–1101.
63 R. Bobka, J. N. Roedel, B. Neumann, T. Nigst and I.-P. Lorenz, *Polyhedron*, 2008, **27**, 955–961.
64 T. B. Jackson and J. O. Edwards, *J. Am. Chem. Soc.*, 1961, **83**, 355–360.
65 T. B. Jackson and J. O. Edwards, *Inorg. Chem.*, 1962, **1**, 398–401.
66 J. N. Roedel, *Ph.D. Thesis*, LMU, Munich, 2008.
67 J. N. Roedel, R. Bobka, B. Neumann, B. Weber, P. Mayer and I.-P. Lorenz, *Z. Anorg. Allg. Chem.*, 2007, **633**, 1171–1177.
68 P. H. Leung, A. C. Willis and S. B. Wild, *Inorg. Chem.*, 1992, **31**, 1406–1410.
69 B.-H. Aw, T. S. A. Hor, S. Selvaratnam, K. F. Mok, A. J. P. White, D. J. Williams, N. H. Rees, W. McFarlane and P.-H. Leung, *Inorg. Chem.*, 1997, **36**, 2138–2146.
70 P.-H. Leung, K.-H. Ng, Y. Li, A. J. P. White and D. J. Williams, *Chem. Commun.*, 1999, 2435–2436.
71 A. B. P. Lever, *Inorganic Electronic Spectroscopy*, Elsevier, Amsterdam, 2nd edn., 1984.
72 G. A. McLachlan, G. D. Fallon, R. L. Martin and L. Spiccia, *Inorg. Chem.*, 1995, **34**, 254–261.
73 N. W. Mitzel, J. Riede and C. Kiener, *Angew. Chem.*, 1997, **109**, 2299–2300, (*Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 2215–2216).
74 M. Duggan, N. Ray, B. Hathaway, G. Tomlinson, P. Brint and K. Pelin, *J. Chem. Soc., Dalton Trans.*, 1980, 1342–1348.
75 S. Putzien, S. Wirth, J. Nicolas Roedel and I.-P. Lorenz, *Polyhedron*, 2011, **30**, 1747–1751.
76 G. M. Sheldrick, *Acta Crystallogr., Sect. A*, 2008, **64**, 112–122.
77 E. Budzisz, U. Krajewska, M. Rozalski, A. Szulawska, M. Czyz and B. Nawrot, *Eur. J. Pharmacol.*, 2004, **502**, 59–65.