Bispidin-9,9-diol Analogues of Cisplatin, Carboplatin, and Oxaliplatin: Synthesis, Structures, and Cytotoxicity

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Supporting Information

INTRODUCTION

Cisplatin represents one of the most important cytostatic drugs currently used in cancer therapy.1,2 However, its administration is associated with many side effects (some serious), a limited activity profile, and the problem of inherent or acquired platinum resistance. To overcome these problems, thousands of other compounds have been tested. From such studies, the present study, it is worth emphasizing that, in cisplatin-type drugs, the amine is considered to be a “carrier ligand”, which remains coordinated at the Pt(II) center during the action of the drug, whereas the anionic ligand (usually chloride, substituted malonate, or oxalate) is split off by hydrolysis.

Although for both cisplatin and carboplatin, the carrier ligand is ammine, in oxaliplatin, it is the organic bidentate primary amine trans-(R,R)-1,2-diaminocyclohexane (DACH). The steric constraint imposed by this chelate ligand appears to impede recognition and repair of DNA damage by specific cell proteins, resulting in reduced platinum resistance, compared to the first- and second-generation drugs. Numerous substituted oxaliplatin derivatives have been investigated.4 So far, relatively little is known about the effect of secondary amines such as cyclic monoamines,5 chelating acyclic diamines,6 and chelating cyclic diamines7 as possible carrier ligands for Pt(II). Based on the established structure–activity relationships (SARs),8,9 Pt(II) complexes with secondary amine ligands are expected to be less potent.

Several years ago, we became aware of the unique ligand properties of bispidines (3,7-diazabicyclo[3.3.1]nonane derivatives).10 As a consequence of the bicyclic structure, the N atoms remain coordinated at the Pt(II) center during the action of the drug, whereas the anionic ligand (usually chloride, substituted malonate, or oxalate) is split off by hydrolysis.

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ABSTRACT: 3,7-Diallyl-bispidin-9-one (6) (bispidin-9-one = 3,7-diazabicyclo[3.3.1]non-9-one) is converted to N-unsubstituted spiro[bispidin-9,2′-[1,3]dioxolane] (12; 35%). The ketal crystallizes in the forms of anhydrous 12a and the dihydrate 12b. The molecules in anhydrous 12a are linked to each other, forming N1–H1···N2–H2···N1* hydrogen-bond chiral helices of alternating chirality. In the dihydrate 12b, the ketal molecules are connected to a central string of water molecules by O3–H···O1 and O4–H···N1 hydrogen bonds, but not to themselves. Reaction of 12 with (1,5-hexadiene)PtCl2 affords almost quantitatively spiro[bispidin-9,2′- [1,3]dioxolane]PtCl2 (13). Cleavage of the ketal to retrieve the ketone produces the geminal diol (bispidin-9,9-diol)PtCl2·2H2O (15b), which can be dehydrated to obtain anhydrous (bispidin-9,9-diol)Pt(cbdca) (15a). Similarly, anhydrous (bispidin-9,9-diol)Pt(oxalate) (16) is obtained. Crystal structures of 14 and 15b reveal association by various forms of hydrogen bonds, but not to themselves. Reaction of 12 with (1,5-hexadiene)PtCl2 affords almost quantitatively spiro[bispidin-9,2′-[1,3]dioxolane]PtCl2 (13). Cleavage of the ketal to retrieve the ketone produces the geminal diol (bispidin-9,9-diol)PtCl2·2H2O (15b), which can be dehydrated to obtain anhydrous (bispidin-9,9-diol)Pt(cbdca) (15a). Similarly, anhydrous (bispidin-9,9-diol)Pt(oxalate) (16) is obtained. Crystal structures of 14 and 15b reveal association by various forms of hydrogen bonds.

Chart 1. Worldwide Approved Platinum Drugs for Cancer Therapy

These modifications have fewer drawbacks, but there is still much room for improvement. In a previous paper, we presented a detailed overview of the properties of the three drugs, their modes of action, and considerations for ongoing research, together with pertinent references.3 In the context of the present study, it is worth emphasizing that, in cisplatin-type drugs, the amine is considered to be a “carrier ligand”, which remains coordinated at the Pt(II) center during the action of the drug, whereas the anionic ligand (usually chloride, substituted malonate, or oxalate) is split off by hydrolysis.

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in bispidines are almost ideally prepositioned for chelating coordination to a metal, to give an adamantane-type structural element comprised of four six-membered rings with shared atoms. This results in a very firm and rigid coordination of a rather strong donor ligand. Until now, a plethora of metal complexes of substituted bispidines has been reported, but very few complexes contain the parent bispidine (1), which can be considered a bicyclic secondary diamine. Disregarding the possible prospect of an unfavorable SAR, but encouraged by our experience with bispidines, we recently investigated the chemical and structural properties of our analogues.3

As a ligand for Pt(II), bispidine 1 is related to the DACH ligand, since both molecules represent chelating organic diamines with the N atoms prepositioned for coordination at Pt(II), with the obvious distinction that bispidine is a secondary and DACH a primary diamine. Although 1 is physically thicker than the relatively flat DACH, it does not appear to be as bulky as other bidentate secondary amines, because of the compression caused by bicyclic structure. Expected possible advantages of the larger 1 over DACH as a possible ligand are the higher selectivity for tumor cells, because of the known wider capillaries of these cells, and lower platinum resistance due to an increased difficulty of the DNA repair enzymes to cope with the DNA damages caused by a drug containing a ligand that is thicker than DACH. In fact, when complexes 2—4 were tested for their cytotoxicity against human cancer cell lines K562 (chronic myeloid leukemia), A2780 (ovarian cancer), and K562 (chronic myeloid leukemia), A2780 (ovarian cancer), and its platinum-resistant subline A2780 CisR, they showed significant cytotoxic activity in the micromolar (μM) concentration range, along with a relatively low platinum resistance factor (for A2780 and A2780 CisR), compared to their parent analogues.3

Encouraged by these results, we set out to modify the bispidine ligand by introducing substituents at the remote 9-position, but otherwise retaining the skeleton. We reasoned that replacing 1 with bispidin-9-one would change the hybridization at 9-C from sp3 to sp2, withdraw electron density from the bispidine skeleton, and probably also induce some steric strain into the ligand, since the added ketone moiety would distort the adamantane-type structure. In addition, the carbonyl group could provide access to further modifications, such as ketal formation by water addition to give the 9,9-dihydroxy derivative. While introduction of hydroxy groups is expected to improve the desired water solubility of the complexes, it remained speculative at this point how such substitutions would affect the biological activity of the platinum compounds.

Here, we report on the synthesis, structural characterization, and antitumor activity of 14—16 (Chart 3), which represent the bispidin-9,9-diol analogues of cisplatin, carboplatin, and oxaliplatin.

Chart 3. 9,9-Dihydroxy Bispidine Analogues 14—16 of Cisplatin, Carboplatin, and Oxaliplatin

- **RESULTS AND DISCUSSION**

**Synthesis of Spiro[bispidin-9,2′-[1,3]dioxolane] (12)**. A “convenient synthesis” of the parent bispidine (1) has been described by Miyahara et al. (eq 1).14b Following the route outlined by Douglass and Ratliff14a the readily accessible N-allyl-4-piperidone (5) was treated with allyl amine and formaldehyde in a double-Mannich condensation to give the bispidin-9-one 6. Without isolation, 6 was subject to Wolff-Kishner reduction to afford 3,7-diallyl bispidine (7) in 51% yield. The N-allyl groups in 7 were cleaved off by treatment with ethyl chloroformate and NaI to afford the bis(ethyl carbamate) (8),15 which, after hydrolysis, afforded parent 1 in a reported overall yield of 37%. Making use of the N-allyl functionality provides a notable improvement in the synthesis of parent bispidine, compared to previous routes. Nevertheless, in the Wolff–Kishner reduction step, about half of 6 is lost. Furthermore, various byproducts are associated with the reaction, and these need to be removed by flash chromatography.13a We found that intermediate 6, previously considered to be unstable, is thermally quite stable, and we have kept samples of 6 under argon at ambient temperature over several months without substantial change. Pure 113 has been used to prepare (C7H14N2)PtCl2 (2).3

In order to make use of the carbonyl function of 6, we converted the bispidin-9-one with glycol in an H2-catalyzed ketal formation into spiro[3,7-diallylbispd-9,2′-[1,3]dioxolane] (9) (eq 2). Compound 9 was purified by flash chromatography to obtain a colorless viscous liquid in 70% yield. We attribute the moderate yield to some loss of 6 due to its lability under acidic conditions. N-allyl cleavage by ethyl
chloroformate/NaI afforded the bis(ethyl carbamate) 11 (75%) together with some incompletely reacted 10 (8%). Pure 11, obtained as an oil, crystallizes upon standing (mp 67 °C). Finally, 11 was hydrolyzed with 10 N aqueous KOH. After azeotropic removal of water with benzene and vacuum sublimation (80 °C), a viscous raw product was obtained that largely solidified upon standing at room temperature to give colorless crystalline spir[bispidin-9,2′-[1,3]dioxolane] dihydrate (12b). Treatment of the reaction solution (before sublimation) with CaH₂ or NaH or a similar treatment of sublimed 12b in ethereal solution gave anhydrous crystalline 12a in 65% yield. The practical overall yield of 12 from 6 is 35% (16% from 5), after reworking 10.

The melting point of the anhydrous bispidine dioxolane 12a was found at 97 °C. Differential scanning calorimetry (DSC), starting at −100 °C and with heating and cooling rates of 5 K min⁻¹, revealed for 12a only a broad intense endothermic effect at 98 °C for the melting (ΔHᵣᵥₓ = 29.5 kJ mol⁻¹, ΔSᵣᵥₓ = 79.5 J mol⁻¹ K⁻¹); recrystallization occurred at 77 °C. This suggests that, up to the melting point, 12a is present in its ordered crystalline phase, in contrast to the situation for parent 1, where its high melting point (190 °C), combined with its ready sublimation, are consistent with a plastically crystalline nature.¹³b

No attempt was made to cleave off the glycolic protecting group from 12 under acidic conditions to yield the N-unsubstituted bispidin-9-one¹⁰ (I, the parent compound to 6) or its hydrate (II). Compounds such as (unprotected) I or II are expected to readily undergo a retro-Mannich reaction, especially under acidic conditions, to generate 4-piperidone, formaldehyde, and ammine. Instead, the ketal 12, representing protected compounds I and II, was directly reacted with a platinum(II) reagent. As shown below, I and II are stable as ligands to Pt(II).

Spectral Characterization of 9–12. ¹H and ¹³C NMR data (25 °C) of the spir[bispidin-9,2′-[1,3]dioxolanes] 9–12 are given in Table S1 (see the Supporting Information). The assignment is based on C,H (HMOC) and H,H correlated spectra and on comparison of the data with those of parent bispidine (1).¹⁵ 3,7-diallylbisp[9-one (6),¹⁵a and 3,7-diallylbisp[9,11 (7).¹⁵a While the data of the N-allyl and N-CO₂Et substituents and the C₆H₄ bridge in 9–12 are unremarkable, interest focuses on the nuclei of the bispidine skeleton. As compared to the situation for the oxygen-free 1 and 7 (δ(C) ≈ 30 for C2 and C3), for 9–12, the spiro C₃ (δ(C) 107–109) uniformly resonates at considerably lower field, as does the bridgehead C2 (δ(C) 38–40), to a lesser extent. Thus, these signals are formally shifted halfway in the direction of the corresponding signals of the ketone 6 (δ(C) 211.5 and 47.4). The NCH₃H₄ resonances of 9 and 12 (no N-CO₂Et substituents; effective C₂ᵥ symmetry of the compounds in solution) correspond to those of the reference bispidines 1, 6, and 7, including a higher field resonance of the axial piperidine protons (H₆) over the equatorial protons (H₄) by ~0.2–0.3 ppm.

More-pronounced spectral changes arise for the N-carboxylates 10 and 11. First, due to partial multiple bond character and hindered rotation of the carbamate N–C bond,¹⁸ the symmetry of the compounds is reduced to C₁ for 10 and C₂ for 11. Hence, for 10, all eight NCH₃H₄ protons and four NC atoms of the piperidine rings are inequivalent, as are the bridgehead H₂a,b and C₂a,b. For 11, the pairwise equivalence of the NCH₃H₄ protons and C atoms and equivalence of the two H₂ and C₂ nuclei are in agreement with the expected C₂ᵥ symmetry of the compound. (For the C₂H₄ protons and C atoms at position 4, the formally full (10) or partial inequivalence (11) is not resolved.) Furthermore, we note that for the carboxylate-substituted piperidine rings in 10 and 11 the NCH₃H₄ ¹H resonances are markedly shifted to lower field and consequently are separated by 0.8–1.0 ppm, whereas the ¹³C resonances are shifted to higher field, by up to 9 ppm (as compared to 9 and 12).

Compound 12 displays for NH a ¹H signal at δ(H) 2.13, which most likely represents the mean of the signals of the protons in exo and endo binding modes rapidly exchanging their bonding situations (eq 3). When cooled to −80 °C, the signal broadens, because of a slowdown of the exchange, and it is shifted to lower field (δ(H) 2.44), which can be attributed to an increased association of the amine. Separate signals for the exo and endo protons are not yet observed at this temperature. The barrier of exchange is likely to correlate with the inversion barrier of the secondary amine N atoms. A similar exchange was established for parent 1¹³b

In the EI mass spectra of all spir[bispidin-9,2′-[1,3]-dioxolanes] 9–12, the molecular ions M⁺ have been observed in high intensities or even as the base ions. Fragmentation of amines is usually initiated by ionization at nitrogen. Subsequently, two independent routes seem possible. For the symmetrically substituted 9 and 11, the prominent ions [M–R]⁺ (where R = allyl, carbamate) can be attributed to immediate cleavage of one N-allyl or N-carboxylate bond. By a further mechanism (eq 4), in line with the previously established behavior of various bispidines and bispidin-9-ones,¹³a ionization at N triggers an α-C–C bond cleavage¹⁷ within the bispidine skeleton. This gives rise to a 3-piperidyl radical having a 5-tethered iminium function. Proton transfer from the 2-position to the iminium affords 2,3-dehydropiperidine having a methyleneamine radical pendant. The ion stabilizes via a second α-C–C bond fission to split into [RN(CH₂)₂CH₃]⁺ and, after loss of a further electron and 6,5-H atom migration, the 2,3,6-dehydropiperidinium cation [(C₆H₄O₂)CH₂NH]⁺. The mixed-substituted 10 and unsubstituted 12 (R = H) also appear to follow this path; however, in these cases, a greater diversity of
ions is observed. In addition, all compounds give rise to a dominant ion at \( m/z = 99 \) (base peak for 9, 11, and 12). This ion can be attributed to further degradation of \([\{(C_2H_4O_2)C_7H_8(NR)\}^+\) to give either \([\{(C_2H_4O_2)C_6H_5\}^+\), retaining the 1,3-dioxolane ring, or, by ethylene oxide elimination, cleavage of N−R, and proton abstraction, to afford the 4-piperidone cation \([OC-(C_6H_5)NH]^+\).

In the ESI+pos mass spectra of compounds 9–12, dissolved in MeOH or THF, the protonated molecular ion \([M+H]^+\) is always base peak, but intense signals for the bimolecular ions \([2M+H]^+\) or \([2M+Na]^+\) are also found.

**Molecular Structure of 12a.** Anhydrous spiro[3,7-diazabicyclo[3.3.1]nonane-9,2′-[1,3]dioxolane] (12a) crystallizes in the orthorhombic crystal system, space group Pca2\(_1\) (No. 29) with four equivalent asymmetric molecules in the unit cell (see Table S2 in the Supporting Information). Diffraction data were collected at 200 K, because the crystals undergo loss of crystallinity on cooling to 100 K.

The geometry of the bispidine skeleton is similar to that of the parent bispidine,\(^\text{13b}\) whereby both piperidine rings adopt a chair conformation, with the N1−H1 proton in an endo orientation and the N2−H2 proton in an exo orientation, with respect to the concave face of the bispidine (see Figure 1a). The endo proton undergoes a strong intramolecular N1−H1···N2 hydrogen bridge bond with a refined N1−H1 bond length of 0.89(3) Å and a N2−H2···N1 distance of 2.22(3) Å; the intramolecular nonbonding N1···N2 distance is 2.824(3) Å (the corresponding values for the parent bispidine are observed at 0.90(1) and 2.26(1) Å, and one parallel to ac. There are no direct bonds between the adjacent helices.

The pads are stacked along the b-axis so that the dioxolane moieties of one pad intermesh with those of the next pad. Each dioxolane moiety displays two pairs of C9\#H9A···O1 (2.568(2) Å) and C9\#H9B···O1 (2.679(2) Å) hydrogen bond contacts to four adjacent dioxolane moieties of the next pad. Corresponding molecules of adjacent pads are related to each other by two additional 2-fold screw axes in the c-direction and using the ac plane as a glide plane.

**Molecular Structure of 12b.** Crystallizing compound 12 from water affords colorless crystals of the dihydrate 12b. The crystals belong to the monoclinic space group P2\(_1\)/c (No. 14). There are four equivalent molecules and four pairs of water molecules in the unit cell (see Table S2 in the Supporting Information, as well as Figure 2a). The four sets of molecules are part of two double-strands that extend along the b-axis.

The geometry of the dioxolane bispidine molecules corresponds to that of anhydrous 12a, including the chair−chair conformation of the two piperidine rings. There is an intramolecular N1−H1···N2 hydrogen bridge for which the N1−H1 and N2−H1 bond lengths are 0.90(1) and 2.26(1) Å, respectively; the nonbonding N1···N2 distance is at 2.830(1) Å.
are linked together by hydrogen bonds. The three O⋯O distances lie within the range of 2.752(1)–2.775(1) Å. Hydrogen atoms within the water chain are disordered over two positions, each with half occupancy.

The O1 and N1 atoms of one bispindic–dioxolane molecule and the O3, O3*, O4, and O4* atoms of four water molecules can be viewed as the vertices of a hexagon with five bridging protons (Figure 2c) in a supramolecular structure. The hexagon adopts a boat conformation with O3 and O4 at the cusps. The bispindic–dioxolane and its hexagon ring are related to the neighboring structural equivalents by inversion centers at the midpoints of O3⋯O3* and O4⋯O4* (four inversion centers for two double-strands). As a consequence, the molecules on the two sides of the double-strands have opposing chirality, affording a mirror-image arrangement.

The double-strands are aligned on both sides to additional double-strands, forming sheets. Neighboring molecules are related by two 2-fold screw axes (along the b-axis), and linkage is given by N2–H2⋯O2* (N2–H2, 0.898(12) Å; H2⋯O2*, 2.317(12) Å; N2–H2⋯O2*, 145.5(8)°) bonding between the peripheral bispindic H2 proton and the dioxolane O2 atom of the neighboring double-strand. The sheets are stacked upon each other in such a way that the molecules of a strand are related to its neighbors to one side by a 2-fold screw axis and to the other side by two inversion centers. Bonding here might involve long C9–H9B⋯O3 hydrogen-bonding interactions between the dioxolane H9B protons and the O3 water molecule (C9–H9B, 0.97 Å; H9B⋯O3, 2.68 Å; C9–H9B⋯O3, 130°).

**Synthesis of the Pt(II) Complexes 13–16.** Heating (1,5-hexadiene)PtCl2 to 100 °C for 2 h gave the spiro[bispindic-dioxolane]-PtCl2 complex 13 as a light yellow precipitate in almost quantitative yield (Scheme 1). In the EI mass spectrum of 13 at an evaporation temperature of 350 °C, the molecular ion m/e = 449 (3%) was observed, which fragments by two successive HCl eliminations. Unfortunately, the complex is practically insoluble in water and common organic solvents, including dimethylformamide (DMF) and dimethylsulfoxide (DMSO), which precludes solution NMR and ESI mass spectral characterization, and it also discourages its application as a possible antitumor drug.

Therefore, we subjected 13 to hydrolytic cleavage of the glycolic protecting group under strongly acidic conditions.21 Heating a suspension of 13 in 6 N HCl to 100 °C for 2 h afforded a clear yellow solution. Vacuum evaporation of all volatiles left a bright yellow powder that was recrystallized from hot water to a light yellow solid. Vacuum evaporation of all volatiles left a bright yellow powder. The complex was stable at room temperature, and its solution in water was stable for longer than 3 months. The complex is moderately soluble in water and DMF.

**Figure 2.** Structure of (C$_4$H$_4$O$_2$)$_2$C$_7$H$_{10}$(NH)$_2$·2H$_2$O (12b) in the crystal. (a) Molecular structure (the selected bond distances and nonbonding distances are N1⋯H1 = 0.90(1) Å, N2⋯H1 = 2.26(1) Å, N2⋯H2 = 0.90(1) Å, and N1⋯N2 = 2.830(1) Å; the selected bond angle is given as N1⋯H1⋯N2 = 121.0(8)°). (b) View of one double-strand (see Figures 2b and 2c). All bispindic molecules on one side of the water string are identical, which includes the same puckering of the five-membered dioxolane ring. For each bispindic–dioxolane molecule, the dioxolane O1 atom is hydrogen-bonded to a proton of the O3 water molecule (O1⋯O3, 2.911(1) Å) and the N1 atom to a proton of the O4 water molecule (N1⋯O4, 2.835(1) Å). The water molecules, O3 and O4, together with symmetry equivalents, O3* and O4*, (12a: 2.824(3) Å, parent bispindic 1: 2.849(2) Å). These data seem typical for N-unsubstituted bispindines.

In the crystal, molecules of 12b are arranged on both sides along a central zigzag-shaped string of water molecules, forming a double-strand (see Figures 2b and 2c). All bispindic molecules on one side of the water string are identical, which includes the same puckering of the five-membered dioxolane ring. For each bispindic–dioxolane molecule, the dioxolane O1 atom is hydrogen-bonded to a proton of the O3 water molecule (O1⋯O3, 2.911(1) Å) and the N1 atom to a proton of the O4 water molecule (N1⋯O4, 2.835(1) Å). The water molecules, O3 and O4, together with symmetry equivalents, O3* and O4*,
stable for a long time. A related displacement occurs, when 14 is dissolved in DMSO (see eq 6a).

The bispidin-9,9-diol analogues of carboplatin and oxaliplatin were synthesized following conventional methods.4,23,24 One can start directly from the Pt(II)-dichloride 14, instead of prior conversion into the Pt(II)-diiodide.23,24 Complex 14 suspended in water reacts with disilver-1,1-cyclobutanedicarboxylate 24 with precipitation of AgCl to a yellow solid. After filtration, a colorless solution from which, at temperatures from 20 °C down to 0 °C, colorless needles of (bispidin-9,9-diol)Pt(II)-(1,1-cyclobutanedicarboxylate) dihydrate (15b) crystallize. Drying 15b under vacuum at 50 °C leaves the anhydrous diol 15a as a white powder in 75% yield (Scheme 1). As the above shows, 15a,b is very soluble in water. High solubility is also given for other solvents such as DMF and DMSO, where 15a partially and reversibly eliminates water to form the corresponding Pt(II)–bispidin-9-one complex 15-ketone (eq 7), featuring the elusive ketone I as a ligand. Dehydration of the 9,9-diols to form the keto complex appears to occur more readily for 15a than for the chloride 14 (in DMF) and the oxalate 16 (in DMSO). The solution behavior of 14 and 15 (see eqs 5–7), as studied by NMR, is described below in more detail.

For the synthesis of the Pt(II)-oxalate 16, we reacted 14 with a substoichiometric amount of AgNO3 (1.9 equiv) in water to afford an aqueous solution of the diaqua complex [(bispidin-9,9-diol)Pt(H2O)2](NO3)2. After removal of the precipitated AgCl, the Pt(II) solution was treated with an aqueous solution of Na2C2O4 to afford (bispidin-9,9-diol)Pt(II)-(oxalate) (16) as a white precipitate in almost quantitative yield (Scheme 1). No solute water is included in 16. Complex 16 is virtually insoluble in DMF and dissolves only poorly in DMSO and water, and so far we have not been able to obtain single crystals of the compound.

**Spectral Characterization of the Pt(II) Complexes 13–16.** The infrared (IR) OH and NH stretching bands are best resolved for the crystalline anhydrous dichloride 14, as it displays, for each, two distinct bands \( \nu(OH) 3394, 3310 \text{ cm}^{-1} \) and \( \nu(NH) 3223, 3180 \text{ cm}^{-1} \) (\( \nu(OD) 2519, 2464 \text{ cm}^{-1} \); \( \nu(ND) 2402, 2376 \text{ cm}^{-1} \)). For the malonate 15 and the oxalate 16, the \( \nu(OH) \) resonances are broad, and the \( \nu(NH) \) bands remain unresolved for 15, while they are split for 16 (3211, 3104 cm\(^{-1}\)). The ketal 13 features a single sharp \( \nu(NH) \) band (3173 cm\(^{-1}\)). See the IR spectra in the Supporting Information.

For the insoluble ketal 13, no solution NMR spectra have been obtained. The 1H and 13C NMR data of the Pt(II)–bispidin-9,9-diol complexes 14–16 and some derivatives formed in solution are listed in Table S3 in the Supporting Information; recording of the 13C NMR spectra required a large number of scans (10,000–200,000). For solutions in D2O, the 1H resonances of OH and NH are absent, because of (slow) H/D exchange; instead, an intense HOD signal is found. A solution of 14 in D2O gives rise to a series of signals indicative of partial and reversal hydrolysis with formation of various aqua complexes (eq 5); these species have not been specifically characterized.

The spectra of the dichloride 14 are best recorded in DMF-d7 as a solvent. When such a solution is left at ambient temperature for several days, an increasing amount of the corresponding bispidin-9-one complex 14-ketone (eq 7) is formed due to slow water elimination (eq 6b). For a solution of 14 in DMSO, one of the chloride ions is replaced by DMSO in an equilibrium reaction to afford the ionic \([(\text{HO})_2C_7H_{10}(\text{NH})_2]\text{Pt(II)} \text{(DMSO)}\text{Cl} (14-DMSO)\) within a few hours (eq 6a). Leaving the solution at ambient temperature for several days gives rise to further signals, attributable to dehydration and the presence
of the bispdin-9-one derivatives 14-ketone and 14-ketone-
DMSO (see eq 6b–d).

In the $^{13}$C NMR spectra of the Pt(II)–cbdc complex 15 in
DMF-d$_7$ or DMSO-d$_6$, two sets of signals with a ratio of ~5:1
are observed. The signals of the major component are assigned
to the 9,9-diol 15. For the minor component, the low-field
signals of the bridging C3 ($\delta(C) \approx 208$) and the bridgehead C2
($\delta(C) \approx 46$) appear to be the most characteristic and can be
attributed to the Pt(II)–bispdin-9-one complex 15-ketone
generated by reversible water elimination from 15 (eq 7). The
NMR spectra of 16, because of its insolubility in DMF, have
been recorded only in DMSO and D$_2$O. For the solutions of 15
and 16 in DMSO and D$_2$O, no displacement of the cbdc and
oxalate ligands is observed.

Specifically, compounds 14–16 in DMF or DMSO solutions
show, for the Pt(II)–bispdin-9-diol entity, a sharp $^1$H NMR
OH resonance of $\delta(H) \approx 6.2$. Since there is also a sharp signal
for incidental water ($\delta(H) 3.45$), arising from partial
dehydration of the diol, the exchange of diol and water protons
must be slow. The lower field NH resonance is broadened; for
the dichloride 14, it is flanked by $J(195$Pt,H) coupling satellites,
similar to those observed for the parent bisp dine complexes.3
Similarly, for 14–16, the axial piperidine ring protons H$a1$
resonate at higher field than their geminal equatorial protons
H$a1$. These axial protons H$a1$ are in an anti position to Pt and
the resonance appears to be flanked by $J(195$Pt,H) coupling
satellites, albeit less distinct than for the parent bisp dine analogues.4
The satellites are best resolved for the D$_2$O solutions of 15 and 16. In the $^{13}$C NMR spectra, the resonance of the
diol quaternary C3 is at $\delta(C) \approx 91$ and that of the
bridgehead C2 at $\delta(C) 37–39$, while the NC1 signal occurs at
$\delta(C) \approx 51$. In the case of the Pt(II)–bispdin-9-one derivatives,
the first two resonances shift to lower field; that is, the carbonyl
C3 resonates at $\delta(C) \approx 208$ and the C2 signal lies at $\delta(C) \approx
46$, as is exemplified for 15-ketone. For the asymmetrically
substituted 14-DMSO, most resonances are doubled, with the
exception of C2H2 and C3.

Molecular Structure of 14. The single-crystal structures of the bispdin-9,9-diol complexes 14 and 15b, analogues of
cisplatin and carboplatin, have been determined by X-ray
crystallography (see Table S2). Unlike the situation for the
parent Pt(II)–dichloride 2, which forms a trihydrate,3 the
yellow needles of the 9,9-diol 14 crystallize from water without
inclusion of water molecules. The molecules exhibit a non-
crystallographic ~2-fold axis of symmetry in the crystal and
pack in the monoclinic space group C2/c (No. 15) with eight
equivalent molecules in the unit cell.

The coordination geometry at the Pt center is square
planar, with typical Pt1–N (2.032(4) Å, mean) and Pt1–Cl
(2.306(12) Å, mean) bond lengths (Figure 3a). The angle
formed by the N donor atoms and Pt1 is normal at 85.29(6)°,
as is the (nonbonding) N1–N2 distance at 2.753(2) Å.3
Further molecular structural details of interest are for the
geminal diol:

- O1–C7–O2 angle: 110.20(13)°
- C2–C7–C5 angle: 106.50(13)°
- (mean) C7–OH bond length: C–O = 1.413(11) Å
- (nonbonding) O1–O2 distance: 2.316(2) Å

The length of the C–O bonds in 14 is slightly smaller than the
standard value of 1.428 Å for a typical C–OH single bond
length. This seems to be in agreement with MO calculations,
which predict a normal C–O bond distance for an unstrained
methane diol moiety having alky1 substituents at carbon.25,26

The two hydroxy groups, the two ammonium N–H groups,
and one chloride in the molecule of 14 undergo hydrogen
bonding in the crystal. Figures 3b and 3c show the relevant
intermolecular interactions. Most prominent of these is the
association of the 9,9-diol moieties of two molecules via a pair of
O1–H1C–O2$^*$ (174°) hydrogen bonds (O1···O2$^*$ = 2.808(2) Å)
around a center of inversion. In addition, O1 acts as a hydrogen
bond acceptor from a neighboring N2–H2 group (N···O, 3.102(2) Å; N–H···O, 140°) and the O2–H$_2$C
hydroxyl group is a hydrogen-bond donor to a neighboring
Cl1 (O···Cl, 3.173(2) Å; O–H···Cl, 145°). The remaining N1–H1
group is directed toward the same Cl1 atom (N···Cl, 3.260(2)
Å; N–H···Cl, 153°). Of the functional groups, only one

Figure 3. Crystal and molecular structure of [(HO)$_2$C$_7$H$_{10}$(NH)$_2$]-
PtCl$_2$ (14). (a) Drawing of the molecule. Selected bond distances and
nonbonding distances: Pt1–N1 = 2.0289(14) Å, Pt1–N2 = 2.0341(15) Å, Pt1–Cl1 = 3.145(5) Å, Pt1–Cl2 = 2.971(5) Å, C7–O1 = 1.405(2) Å, C7–O2 = 1.420(2) Å, N1···N2 = 2.753(2) Å, and
O1···O2$^*$ = 2.808(2) Å; selected bond angles: N1–Pt1–N2 = 85.29(6)°, C11–Pt1–Cl2 = 92.149(16)°, C2–C7–C5 = 106.50(13)°, O1–C7–O2 = 110.20(13)°. (b) Atoms and their intermolecular hydrogen bonding interactions. (c) Association of molecules in the unit cell, viewed along the b-axis.
chloride (Cl2) appears to participate in no significant intermolecular interactions.

**Molecular Structure of 15b.** The Pt(II)–cbdca complex 15b contains two resolved solute water molecules and crystallizes in the tetragonal crystal system, space group P4/n (No. 85). There are eight equivalent molecules in the unit cell and two solvent accessible voids, each with a volume of 58 Å³ (Mercury, probe radius = 1.2 Å, grid spacing = 0.1 Å). Each void occupies the center of a pocket of 16 hydrogen bonded O atoms, comprising the 12 OH groups of neighboring Pt complexes and four solute water molecules. The center of the void lies on a 4-fold rotational axis parallel to the c-axis (C₄ symmetry). There was no significant residual electron density in the voids in the final difference Fourier synthesis in the X-ray analysis. Since the crystals were crystallized from water, the region is probably occupied by disordered water molecules. Based on an average volume of 18 Å³ for each water molecule, one can estimate that there are three to four disordered water molecules in each pocket.

The Pt(II) center in 15b is square planar coordinated by the N atoms of the bispidin-9,9-diol ligand and two carboxylate O atoms of the cbdca ligand (Figure 4a). The Pt–N bond lengths are slightly different, with the Pt1−N2 distance at 2.011(3) Å being shorter than the Pt–N distance in dichloride 14 (2.032(4) Å) and the angle N1−Pt1−N2 at 86.28(12)° is slightly wider than that in 14, resulting in a somewhat increased (nonbonding) N···N distance (2.765(4) Å). These data show that the Pt(II) center in 15b is positioned more closely to the bite of the bispidine than in 14. The 9,9-diol C7–O bonds lengths at 1.422(1) Å (mean) and the O2–C7–O5 angle at 109.1(3)° are very similar those in 14. In the cbdca ligand, the Pt–O bond lengths at a mean distance of 2.029(2) Å are as expected, and the six-membered chelate ring assumes boat conformation, as is typical for Pt(II)–cbdca complexes, giving the entire molecule a curved shape. The main structural features of 15b are very similar to those of the parent 3, with the distinction that the molecules of the latter are completely encapsulated by the water shell.

In the crystal of 15b (Figures 4b and 4c), each Pt complex molecule forms part of a strand of molecules extending along the c-axis. Within each strand, the coordination plane of all molecules (Pt1, N1, N2, O1, O2), together with the C7, O5, and O6 molecules of the bispidine C(OH)₂ group and the O8 molecule of one water molecule lie in the same plane. Within this plane, the molecules are associated with each other both by a simple N1−H1···O4* hydrogen bond (N1···O4* = 2.788(4) Å) to a malonate carbonyl group of the adjacent molecule and a more extended hydrogen bond O3···H8B−O8−H8A···O4* (O3···O8 = 2.807(4) Å, O8···O4* = 2.785(4) Å), in which the malonate groups of the two molecules are bridged by the O8 water molecule. Both types of bridges involve the same O4* anchor atom.

Strands are pairwise aligned with the coordination planes of the molecules above each other (Pt1···Pt1* = 4.258(1) Å) with the cyclobutane rings positioned externally. The complexes in the two strands are related to each other by inversion centers located at the midpoints of the Pt1···Pt1* vectors. The double-strands are held together by a pair of hydrogen bonding interactions, related to each other by inversion and linking the malonate carbonyl O3 and O4* on neighboring molecules in one strand via the O8 in-plane water molecule and an O7 interplane water molecule (O7···O8 = 2.676(5) Å) to the hydroxyl O5** of the pairing strand (O5···O7 = 2.787(4) Å).

![Figure 4. Crystal and molecular structure of {(HO)₅C₆H₆(NH)₅}·Pt{C₆H₄(CO₂)₂}·2H₂O (15b).](image-url)
Association of four adjacent double-strands occurs via four-membered square rings of hydroxy O6 atoms (O6···O6* = 2.860(4) Å) and eight-membered crown rings of alternating hydroxy O5 and water O7 atoms (O5···O7* = 2.609(5) Å and O5···O7* = 2.787(5) Å). The O6 four-membered rings and the O5···O7 eight-membered rings enclose a void, which is probably filled with disordered water molecules (see discussion above). Interestingly, neither N1···H1 of the bispidine, nor O1 and O2 of the malonate groups are involved in hydrogen bonding interactions in the crystal.

**Rationale for the Formation of Pt(II)–bispidin-9,9-diol Complexes 14–16.** From the literature data, one can deduce the following rules concerning the hydration of bispidin-9-ones to form bispidin-9,9-diols (free or as ligands to metals; see the Supporting Information).

(a) The neutral uncoordinated bispidin-9-ones, unless N-keto-substituted, do not add water to form 9,9-diols to a substantial extent.

(b) Bispidin-9-ones, which bear +M-substituents (e.g., aryl, vinyl) in 1,5-position and irrespective of whether or not they are protonated at nitrogen, coordinated to a metal ion, or N-keto-substituted (N-carbamate, N-carboxylate) also do not get hydrated to form 9,9-diols.

(c) The often-given 1,5-di(carboxylate) substitution of bispidin-9-ones for its own is insignificant for bispidin-9,9-diol formation.

(d) Protonation, metal ion coordination, and keto substitution at nitrogen support hydration of bispidin-9-ones to form bispidin-9,9-diols, unless prevented by +M-substituents at 1,5-positions.

These insights allow us to assess the driving force for the formation of the Pt(II)–bispidin-9,9-diol complexes 14–16.

In stark contrast to all previously known derivatives, this paper reports the synthesis and properties of the first C6N-unsubstituted metal-bispidin-9,9-diol complexes. Starting from the isolable secondary diamine spiro[bispidin-9,2′-[1,3]-dioxolane] (12), in which bispidin-9-one I is protected as a ketal, reaction with a suitable Pt(II) source quantitatively provides spiro[bispidin-9,2′-[1,3]-dioxolane]PtCl2 (13). Deprotection of the 9-keto group under aqueous conditions yields (bispidin-9,9-diol)PtCl2 (14), from which (bispidin-9,9-diol)-Pt(bdca) (15) and (bispidin-9,9-diol)Pt(oxalate) (16) are accessible. NMR evidence suggests that the 9,9-diol complexes 14–16, while crystallized from aqueous solutions as stable solids, are in a formal equilibrium with the 9-ketone analogues in solution (eq 7). The same is presumably true for all metal–bispidin-9,9-diol complexes.

There are several conceivable factors that may contribute to stabilization of metal–bispidin-9,9-diol complexes, relative to their bispidin-9-one analogues. Among these are (i) electron withdrawal from nitrogen by the metal ion, which increases the electrophilicity of the entire bispidin-9-one skeleton, including the carbonyl function at 9-C; (ii) reduction of strain in the adamantane-type skeleton due to a relaxation of the hybridization from sp2 to sp3 at 9-C; and (iii) stabilization of the geminal diol by hydrogen bonding of the diol protons to (strong) hydrogen-bond acceptors. In fact, ketone hydration to form the bispidin-9,9-diol is always associated with the simultaneous action of all three effects. Hydrogen bonding by diol self-association (as in 14) and with water (as in 15b) on their own are considered to contribute only secondarily to stabilization of the diols. Similarly, step (ii), which involves the release of strain upon rehybridization from sp2 to sp3 of 9-C, appears unimportant.27 Therefore, it is likely that, in step (i), the increased electrophilicity caused by the divalent metal ion is the most significant contributing factor to the formation of the diols 14–16.

**Cytotoxicity of the Pt(II)–bispidin-9,9-diol Complexes 14–16 in Human Cancer Cell Lines.** The cytotoxicity of the Pt(II)–bispidin-9,9-diol complexes 14–16 and their parental Pt(II)–bispidin complexes 2–4 was determined with a functional MTT assay28 toward the human cancer cell line A2780 (ovarian cancer cell line) and the noncancer cell line HEK293 (embryonic kidney 293). The bispidin complexes 2–4 showed cytotoxicity in the lower micromolar (μM) concentration level, as determined in an earlier study.3 The bispidin-9,9-diol substitution of cisplatin (14), carboplatin (15), and oxaliplatin (16) caused a 2.1-fold to 9.7-fold decrease in cytotoxic activity, in comparison to the correspondent parental complex (see Table 1).29 The reason for the reduced cytotoxicity is seen in the higher hydrophilic properties of the bispidin-9,9-diol complexes, possibly inhibiting cellular uptake.

The analysis of a general cytotoxicity by using the noncancer cell line HEK293 in the MTT assay revealed values in the higher μM range (35, 100, >100 μM) for the platinum bispidine complexes 2–4. Interestingly, the corresponding bispidin-9,9-diol complexes 14–16 showed no cytotoxic activity up to 316 μM toward this cell line, indicating the absence of unspecific cytotoxicity.

**CONCLUSIONS**

In continuation of our previous study3 on the synthesis, structure, and biological properties of the Pt(II)–bispidin analogues 2–4 of cisplatin, carboplatin, and oxaliplatin, we have now synthesized and investigated the Pt(II)–bispidin-9,9-diol derivatives \{(HO)2C7H10(NH)2\}PtCl2 (14), \{(HO)2C7H10(NH)2\}Pt(C5H5(CO2)2) (15a, dihydrate: 15b), and \{(HO)2C7H10(NH)2\}Pt(C6O3) (16). Essential findings from this study are given as follows:

(a) The starting bispidin-9-one 6 has been converted to the diamine 12 (eq 2), which is also a secondary diamine exhibiting an intramolecular N1···H1···N2 hydrogen bond. In the crystal, anhydrous 12a forms parallel helical chains of molecules by intermolecular N2···H2···N1* hydrogen bonding. Adjacent helices alternate in their sense of rotation and these are closed-packed. The crystal of dihydrate 12b is characterized by infinite chains of hydrogen-bonded water molecules, which are
hydrogen-bonded to the free amine and one O atom of the dioxalane moiety of adjacent dioxalane molecules.

(b) Reacting (1,5-hexadiene)PtCl2 with 12 affords the insoluble spiro[bispidin-9,2′-[1,3]dioxalane]PtCl2 ([(C6H10)O- C2H4O(NH)]PtCl2, 13) in quantitative yield. Cleavage of the [1,3]dioxalane in 13 under acidic conditions yields the modestly water-soluble Pt(II)–bispidin-9,9-diol 14 in high yield. In the crystal, the molecules of 14 are alternately hydrogen-bonded to each other head–head via the geminal diol functions and tail–tail via C2 symmetrical N–H–Cl bonding, to each other head–head and tail–tail via the geminal diol functions and C2 symmetrical N–H–Cl bonding, involving the Pt(II) bound amine, to form infinite strands that are linked together by O–H···Cl hydrogen bonds, with the exclusion of solute water.

(c) The dichloride 14 has been converted by conventional routes to the 1,1-cyclobutanedicarboxylate 15, which dissolves well in water, and the poorly soluble oxalate 16. Compound 15 crystallizes from water in form of the dihydrate 15b, in which 15 undergoes extensive hydrogen bonding, with incorporation of disordered solute water in the crystal lattice. Under vacuum, 15b releases water to give anhydrous 15a.

(d) The Pt(II)–bispidin-9,9-diol 14–16 represent the hydridated derivatives of Pt(II)–bispidin-9-ones. Reversible elimination of water from 14–16 with the formation of the ketone can be anticipated, and, for the most soluble 15, signals attributable to the Pt–bispidin-9-one 15-ketone have been detected by NMR in nonaqueous solution (DMF). Isolation of the corresponding Pt–bispidin-9-ones was not considered to be pertinent, since these are expected to rehydrolyze under biological conditions.

(e) The increased stability of the Pt(II)–bispidin-9,9-diol 14–16, with respect to their ketones, can be predominately attributed to an increased electrophilicity of the bispidin-9-one skeleton, because of electron donation from the nitrogen electron pairs to the Pt(II) center.

(f) The cytotoxic potency of the bispidin-9,9-diol compounds 14–16 is discernibly lower than that of the parent bispidine complexes.3 This can be attributed to an increased hydrophilicity and correspondingly reduced lipophilicity of the complexes, which impedes penetration of cell membranes.

These results highlight the need to reconcile the necessity of high hydrophilicity of the complexes to foster water solubility with the demands of high lipophilicity, which favors drug delivery at the active site. To address this problem, we are currently investigating the properties of 9-oxobispdine30 and 9,9-difluorobispdine38 as ligands for Pt(II) complexes.

**Experimental Section**

The reactions were performed under argon with Schlenk-type glassware. (C6H10)PtCl2,20 K2(bdcda),13 and Ag2(bdcda)3,24 were prepared as described. MS data refer to 195Pt and 35Cl isotopes. Na2C2O4 was used as obtained (Aldrich). Elemental analysis was performed at MikroLab Kolbe, Mülheim, Germany (www.mikro-lab.de). For Pt determinations, samples were subjected to acid hydrolysis and analyzed by ASS (PerkinElmer).

**3.7-Diallyl-bispidin-9-one (6)**. A suspension of 4-allylpiperidine (S) (22.12 g, 160 mmol), paraformaldehyde (10.74 g, 340 mmol), and allylamine (9.60 g, 170 mmol) in EtOH (750 mL) was stirred under an inert atmosphere and H2OAc (18.6 mL, 0.34 mol) was added, by cooling with an ice bath. The mixture was heated to 55–60 °C for 5 h, during the course of which the paraformaldehyde dissolved to give a clear amber solution. After recoiling to 0 °C the solution was neutralized with KOH (19.1 g, 0.34 mol) and the solvent was evaporated under reduced pressure. The residue was extracted with dry diethyl ether (3 × 200 mL). Evaporation of diethyl ether left an amber oil, which was purified by flash chromatography (silica gel; ethyl ester/pentane/NEt3 (2:8:0.5)) to give a colorless liquid; yield 15.9 g (45%); C13H12N2O4 (220.3). For NMR data and the EI mass spectrum, see ref 3.

**Spiro[3,7-diallyl-bispidin-9,2′-[1,3]dioxalane] (9).** Compound 6 (9.18 g, 41.7 mmol), ethylene glycol (28 mL, ca. 500 mmol), and p-toluenesulfonic acid monohydrate (19.0 g, 100 mmol) were dissolved in anhydrous benzene (300 mL) in an inert atmosphere. The orange reaction mixture was refluxed for 48 h and water was removed using a Dean–Stark setup. The reaction mixture was treated with 1 M aqueous NaOH (100 mL), the aqueous phase was separated and extracted with ethyl acetate (2 × 50 mL). The organic phases were combined and washed with 1 M NaOH (40 mL). After drying with MgSO4, all volatiles were removed under vacuum, increasing the temperature to 50 °C. The viscous oily raw product was purified using flash chromatography (silica gel, with ethyl acetate/pentane/NEt3 (7:3:0.5) used as an eluent; Rf = 0.20). The product was obtained as colorless viscous liquid; yield 7.8 g (70%). Boiling point (Bp): 115 °C/0.01 mbar. Anal. Calcd for C15H24N2O2 (264.4): C, 68.15; H, 9.15; N, 10.60. Found: C, 67.46; H, 9.57; N, 11.54. EI MS (20 °C): m/e (%) = 264 ([M]+, 77), 223 ([M–C2H4]+, 87), 180 ([C2H4O2]– C2H4NC2H4O2)+, 33), 99 ([C2H4O2]C2H4)+, 100), 84 ([C2H4N– C2H4]+, 54), 41 ([C2H4]+, 100).

**3.7-diallyl-ethoxycarboxylate-bispidin-9,2′-[1,3]dioxalane (11).** To a suspension of NaI (27.46 g, 183 mmol) and freshly distilled ethyl chloroformate (17.5 mL, 183 mmol) in dry CH2CN (150 mL) was added a solution of 9 (8.06 g, 30.5 mmol) in dry CH2CN (20 mL). The mixture was refluxed for 8 h, cooled to room temperature, and filtered; the filtrate then was evaporated under reduced pressure. The residue was dissolved in ethyl acetate, washed with aqueous NaOH, dried over Na2SO4, and purified using flash chromatography (silica gel), with hexane/EtOAc/NEt3 (8:2:0.2) as an eluent; Rf = 0.25 to give a colorless oil, which crystallized upon standing: yield 7.03 g (70%). Melting point (Mp) = 67 °C. C15H24N2O6 (328.4). EI MS (75 °C): m/e (%) = 328 ([M]+, 41), 255 ([M–C2O2]+, 60), 212 ([C2H4O2]– C2H4N(CO2)C2H4)+, 42), 116 ([C2H4O2]N(C2H4)C2H4)+, 13), 99 ([C2H4O2]C2H4)+, 100), ESISp MS (THF): m/e (%) = 615 ([2M+Na]+, 44), 297 ([M+H]+, 100).

**3.7-diallyl-bispidin-9,2′-[1,3]dioxalane (12a,b).** In a 250 mL flask, a solution of 11 (6.57 g, 20.0 mmol) in EtOH (40 mL) and 10 N aqueous KOH (80 mL) was refluxed for 12 h. After distilling off all EtOH, the reaction mixture was refluxed for an additional 20 h. Benzene (100 mL) was added and the reflux condenser was replaced by a Dean–Stark trap. Heating was continued until all H2O was azeotropically removed. After cooling to ambient temperature, the reaction mixture was filtered through a Celite pad. The solvent was evaporated and the residue was subdued at 80 °C/10−3 mbar. The viscous product solidified largely at ambient temperature to give colorless crystals of the dihydrate 12b. Full removal of water is possible by stirring an ethereal solution of the product with CaH2 or NaH.

**Spiro[3,7-diallyl-bispidin-9,2′-[1,3]dioxalane]platinum(II)dichloride (13).** A solution of (C6H10)PtCl2 (3.48 g, 10.0 mmol) and 12a (1.84 g, 10.0 mmol) in 150 mL of DMF was heated to 100 °C for 2 h.
A light yellow precipitate was formed, which after cooling to ambient temperature was isolated by filtration, washed with ethyl ether, and dried under vacuum. Yield: 4.36 g (97%). Anal. Calcd for C_{60}H_{64}Cl_{12}N_{12}O_{12}Pt (450.2): C, 24.01; H, 3.58; Cl, 15.75; N, 6.22; O, 7.11; Pt, 34.33. Found: C, 15.45; N, 6.02; Pt, 42.24. IR (neat): ν = 3173 (NH) cm^{-1}. EL MS (350 °C): m/e (%) = 449 ([M−1]^{+}, 3); 413 ([M−2HCl]^{−}, 3); 377 ([M−2HCl]^{−}, 2), 99 (100). It decomposes above 300 °C without melting. The compound is insoluble in all solvents, including DMSO. No NMR characterization was performed.

**Bispidin-9,9-diol|platinum(ll)|dichloride** (14). A suspension of light yellow 13 (450 mg, 1.00 mmol) in 40 mL of 6 N HCl was heated to 100 °C for 2 h to give a yellow solution. All volatiles were removed in a vacuum to leave a bright yellow residue. This was repeatedly washed with small volumes of cold H2O and cold ethanol to remove any acid and glycol, and the solid was dried again under vacuum. Recrystallization from boiling water and slow cooling afforded yellow needles. Yield: 360 mg (85%); mp 310 °C Dec. IR (neat): ν = 3134 (br, OH), 3121 (br, NH) cm^{-1}. Anal. Calcd for C_{72}H_{36}N_{4}O_{18}Pt (1201.4): C, 16.72; N, 8.10; Pt, 39.38. Found: C, 31.38; H, 4.07; N, 5.65; Pt, 39.07. Anal. Calcd for C_{72}H_{36}N_{4}O_{18}Pt (1201.4): C, 16.72; N, 8.10; Pt, 39.38. Found: C, 31.38; H, 4.07; N, 5.65; Pt, 39.07. 

**Bispidin-9,9-di|platinum(ll)|dicyclohexano|trioxide** (15). A warm (50 °C) solution of 14 (424 mg, 1.00 mmol) in water (40 mL) was added to AgCl (385 mg, 1.00 mmol) suspended in water (10 mL). The reaction mixture was stirred in darkness for 5 h in darkness. The precipitate was immediately gave a colorless precipitate of AgCl. The mixture was stirred for 5 h in darkness. The precipitate was collected by filtration. Recrystallization from hot water afforded a colorless precipitate, which was collected by filtration. Recrystallization from warm water (10 mL) gave a colorless precipitate of AgCl. The mixture was stirred for 5 h in darkness. The precipitate was filtered off and to the filtrate was added Na_{2}C_{6}H_{5}O_{4} (128 mg, 0.95 mmol). The reaction mixture was stirred overnight and the product was obtained as a colorless precipitate, which was collected by filtration. Recrystallization from hot water afforded thin colorless needles. Yield: 400 mg (91 %). mp 310 °C Dec. IR (neat): ν = 3300 (vbr, OH), 3112 (br, NH) cm^{-1}. Anal. Calcd for C_{72}H_{36}N_{4}O_{18}Pt (1201.4): C, 16.72; N, 8.10; Pt, 39.38; C, 31.38; H, 4.07; N, 5.65; Pt, 39.38. Found: C, 31.38; H, 4.07; N, 5.65; Pt, 39.38. 

**Bispidin-9,9-di|platinum(ll)|oxalate** (16). Combining a solution of 14 (424 mg, 1.00 mmol) in warm water (40 mL) with a solution of AgNO_{3} (325 mg, 1.91 mmol) in water (10 mL) immediately gave a colorless precipitate of AgCl. The mixture was stirred for 5 h in darkness. The precipitate was filtered off and to the filtrate was added Na_{2}C_{6}H_{5}O_{4} (128 mg, 0.95 mmol). The reaction mixture was stirred overnight and the product was obtained as a colorless precipitate, which was collected by filtration. Recrystallization from hot water afforded thin colorless needles. Yield: 400 mg (91 %). mp 310 °C Dec. IR (neat): ν = 3300 (vbr, OH), 3112 (br, NH) cm^{-1}. Anal. Calcd for C_{72}H_{36}N_{4}O_{18}Pt (1201.4): C, 16.72; N, 8.10; Pt, 39.38; C, 31.38; H, 4.07; N, 5.65; Pt, 39.38. Found: C, 31.38; H, 4.07; N, 5.65; Pt, 39.38. 

**ASSOCIATED CONTENT**

**Supporting Information**

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.inorgchem.5b02855.

Tables S1–S3, an evaluation of literature data concerning the possible hydration of bispidin-9,9-diols, infrared (IR) spectra for 6, 11, 12a, and 13–16 (PDF)

X-ray crystallographic data (CIF)

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**Notes**

The authors declare no competing financial interest.

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