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# A glucose derivative as natural alternative to the cyclohexane-1,2-diamine ligand in the anticancer drug oxaliplatin?

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*Having oxaliplatin as archetype, several platinum complexes with a carbohydrate moiety resembling the cyclohexane-1,2-diamine ligand of oxaliplatin have been prepared. As leaving groups, the anionic ligands iodide, oxalate, and malonate were utilized, and for comparison purposes the chloro complex was employed. All compounds were characterized by elemental analysis, nuclear magnetic resonance spectroscopy, and electrospray mass spectrometry. The crystal structure of (SP-4-3)-diiodo(2,3-diamino-2,3-dideoxy-D-glucose-κ²N,N′)platinum(II) was determined by X-ray diffraction. The affinity toward dGMP was assayed by capillary electrophoresis, revealing that the chloro complex shows the highest reactivity, followed by the iodo complex. In contrast, the binding kinetics of the dicarboxylato complexes are slower, with the malonato complex being the least reactive. Reactivity to dGMP in the cell-free system correlates with cytotoxicity in two of four human cancer cell lines as determined by means of the MTT assay. In three of the four cell lines, the chloro and the malonato complex are the most and the least active of the carbohydrate-Pt complexes, respectively, with $IC_{50}$ values differing only by factors of up to 3.2. Cytotoxicity of the chloro complex is one to two orders of magnitude lower than that of oxaliplatin, but still comparable to that of carboplatin in two of the four cell lines.*

## Introduction

Platinum complexes belong to the most widely used anticancer drugs in clinical practice, with the development of cisplatin (Figure 1) by Rosenberg and co-workers in the 1960's being a milestone in modern anticancer treatment.[1, 2] As a result of its activity and application in the treatment of many tumor types, in particular it is effective for treating solid tumors such as testicular and ovarian cancers, the WHO included cisplatin in its list of the 17 essential anticancer drugs[3] necessary to treat the 10 most common cancers (or category 1 or 2 cancers).[4] The second and third generation platinum-based drugs comprise some of the most active and successful chemotherapeutic agents available.

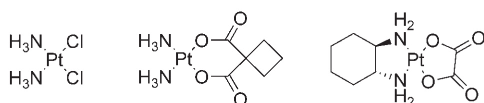

**Figure 1.** Platinum complexes in worldwide clinical use: cisplatin (left), carboplatin (middle), and oxaliplatin (right).

The third generation platinum-based anticancer drug oxaliplatin, (*SP*-4-2)-[(1*R*,2*R*)-cyclohexane-1,2-diamine-κ²*N*,*N*′)(oxalato-κ²*O*,*O*′)platinum(II)], exhibits no cross-resistance in certain cisplatin-resistant tumors.[5] In contrast to cisplatin, a more efficient incorporation of intracellular platinum into DNA was reported for oxaliplatin.[6] In general the cyclohexane-1,2-diamine ligand makes platinum-DNA adducts more cytotoxic, in line with a stronger hindrance of replication.[7, 8] Whereas cisplatin-induced DNA adducts are detected by mismatch repair proteins, those induced by oxaliplatin are not recognized.[9–11] Note that an even lower level of DNA adducts, compared to cisplatin, results in a similar cytotoxicity which indicates a higher cytotoxicity of the DNA lesions produced by oxaliplatin.[12] The cyclohexane ring appears to be an essential structural requirement for the high cytotoxicity of oxaliplatin and also for its different pharmacodynamic properties in comparison to the diammine complexes cisplatin and carboplatin. It is reasonable to assume that the steric demand of the cyclohexane ring is responsible for the strong replication-inhibiting properties of oxaliplatin. Increasing this steric demand is a promising strategy to improve activity.[13]

Warburg and colleagues were among the first to discover that cancer cells have a fundamentally different energy metabolism compared to healthy cells.[14] That is, the upregulation of glycolytic activity, one of the fundamental metabolic alterations in cancer cells.[15, 16] Solid tumors are known to be hypoxic because of an insufficient blood supply, drawing their energy

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mainly from glycolysis. Note that in many tumors, even in the presence of oxygen, glucose is converted to lactate to generate ATP. The transport of glucose through the membrane occurs by transport proteins utilizing the diffusional gradient or by pumping glucose into cells against its concentration gradient.[17] In most primary and metastatic human cancers, increased glucose uptake is accompanied by an upregulation of glucose transporters.[18]

The carbohydrates are one of the major classes of biomolecules: they provide energy for animals and plants, are an important form of stored energy, serve as structural material, as a component of the energy transporting ATP, as recognition sites on cell surfaces, and are one of three essential components of DNA and RNA. Exciting developments in carbohydrate science over the past 20 years have revealed that they are involved in an enormous range of very precise and sophisticated processes.[19–21] Carbohydrate–platinum complexes were shown to have considerable anticancer activity. In vivo experiments of several platinum(II) sugar complexes demonstrated that the compounds are capable of inhibiting the growth of transplanted tumors in mice.[19–21]

In the present study, the carbohydrate 2,3-diamino-2,3-dideoxy-D-glucopyranose was chosen as a ligand to resemble the oxaliplatin-structure, and the respective platinum complexes with iodide **2**, oxalate **3**, and malonate **4** as leaving groups were synthesized and characterized by NMR, MS, and elemental analysis. The complexes were evaluated for their affinity toward dGMP by capillary electrophoresis (CE) and for their in vitro cytotoxicity by a colorimetric microculture assay [MTT (3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2*H*-tetrazolium bromide) assay] in the human cancer cell lines HeLa (cervix carcinoma), CH1 (ovarian carcinoma), SW480 (colon carcinoma), and U2OS (osteosarcoma). The crystal structure of (*SP*-4-3)-[(2,3-diamino-2,3-dideoxy-D-glucose-$\kappa^2$*N,N'*)diiodoplatinum(II)] has been determined by X-ray diffraction.

## Results and Discussion

Following a synthetic scheme (see Figure 2) proposed by Meyer zu Reckendorf,[22, 23] the ligand 2,3-diamino-2,3-dideoxy-D-glucose hydrochloride **1i** was obtained by an improved multistep synthesis with regard to an overall higher yield. Commercially available 2-amino-2-deoxy-D-glucose hydrochloride **1a** was converted with acetic anhydride into 2-acetamido-2-deoxy-D-glucose **1b**. In the next step, the addition of benzyl alcohol in high excess improved the yield of benzyl-2-acetamido-2-deoxy-$\alpha$-D-glucopyranoside **1c** by about 20%. As previously described,[24] ultrasonification was beneficial in obtaining benzyl-2-acetamino-4,6-*O*-benzylidene-2-deoxy-$\alpha$-D-glucopyranoside **1d** and also in the reaction of **1c** with benzaldehyde/$ZnCl_2$. Mesylation in pyridine and transformation into the corresponding allo-derivate, followed by another mesylation and displacement of the mesyl group by azide gave rise to benzyl-2-acetamido-3-azido-4,6-*O*-benzyliden-2,3-dideoxy-$\alpha$-D-glucopyranoside **1g**. To obtain benzyl-2,3-diacetamido-2,3-dideoxy-$\alpha$-D-glucopyranoside **1h**, the benzylidene group was removed under acetic conditions and the azide function was converted after hydrogenation on Pd/C under gentle conditions into an acetamide rest. In contrast to the reported method,[22] the cleavage of the acetyl and benzyl groups was done in a one pot procedure by hydrogenolysis on Pd/C (10% Pd) at 5 bar in 6N hydrochloric acid for 18 h and finally resulted in the desired 2,3-diamino-2,3-dideoxy-D-glucopyranose hydrochloride **1i**. The modifications increased the overall yield to about 12%.

The square-planar $[PtCl_2(L)]$ complex **1** was synthesized from $K_2[PtCl_4]$ and the ligand **1i** following the route of Appleton and Hall.[25] The very good solubility of the dichloro complex in water hampered the isolation of the product (yield 10%). Therefore, $K_2[PtCl_4]$ was replaced by $K_2[PtI_4]$ which was obtained in situ by mixing aqueous solutions of $K_2[PtCl_4]$ and KI. Addition of an excess of 2,3-diamino-2,3-dideoxy-D-glucopyranose hydrochloride in an aqueous KOH solution to $K_2[PtI_4]$ provided the yellow diiodo complex **2**, which precipitated from the reaction mixture. The precipitation was completed at $+4\,^{\circ}C$ overnight and complex **2** was obtained after recrystallization from water (yield 73%).

For syntheses of the oxalato and malonato complexes, **2** was activated in aqueous solution with 2.0 mol of $AgNO_3$. The precipitated AgI was removed by centrifugation and the diaqua complex was reacted with 0.8 mol of freshly mixed solutions of sodium hydroxide and oxalic acid. After stirring for 12 h at room temperature, (*SP*-4-3)-(2,3-diamino-2,3-dideoxy-D-glucose-$\kappa^2$*N,N'*)(oxalato-$\kappa^2$*O,O'*)platinum(II) **3** was precipitated from the reaction mixture by the addition of acetone. The analogous malonato complex **4** was synthesized in a similar manner from the activated complex **1** and sodium malonate.

All compounds were fully characterized by $^1H$ and $^{13}C$ NMR spectroscopy. 2D $^1H,^1H$ and $^{13}C,^1H$ NMR spectroscopy were utilized for the assignment of

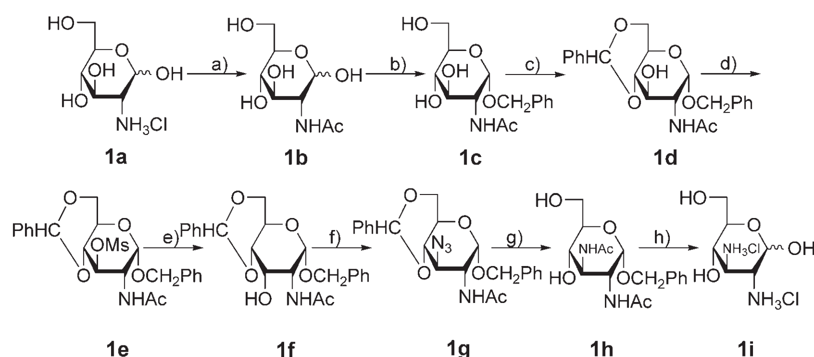


**Figure 2.** The synthetic route to 2,3-diamino-2,3-dideoxy-D-glucopyranose dihydrochloride; a) NaOMe, $Ac_2O$, RT, 18 h; b) $PhCH_2OH$, HCl, reflux, 30 min; c) PhCHO, $ZnCl_2$, 60 °C, 30 min, ultrasonification; d) MsCl, Py, 0 °C, 17 h; e) $CH_3CO_2Na$, $CH_3OCH_2CH_2OH$, reflux, 48 h; f) MsCl, Py, 0 °C, 18 h; $NaN_3$, DMSO, 150 °C, 1 h; g) AcOH, 90 °C, 2 h; Pd/C, $H_2$, MeOH, RT, 4 h; $Ac_2O$, MeOH, RT, 3 h; h) Pd/C, $H_2$, HCl, RT, 18 h; HCl, 90 °C, 1 h.

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the signals. The vicinal proton–proton coupling constants for H2, H3, H4, and H5 of the glucose moiety were within 9.5–12.5 Hz, which indicates that the pyranose ring is present in $^4C_1$ conformation.

The NMR spectra of the aminosugar **1i** and the Pt complexes **1**–**4** (see Figure 3 for **1**–**4**) show two sets of signals corresponding to the α and β anomers, for example the $^{195}$Pt NMR spectra of complex **4** showed two singlets at $\delta =$ −274 ppm and −285 ppm, respectively. Coordination resulted in a shift of the signal of H2 (C2) and H3 (C3) of **1i** in complexes **1**–**4** of about 0.8 ppm in $^1$H and of 10 ppm in $^{13}$C NMR spectra. Exchanging iodide to carboxylates did not induce significant changes in NMR spectra. As reported earlier,[26] the protons of the $CH_2$ group of the malonate moiety in complex **4** undergo a rapid H-D exchange with $D_2O$ and are therefore not visible in the $^1$H NMR spectrum.

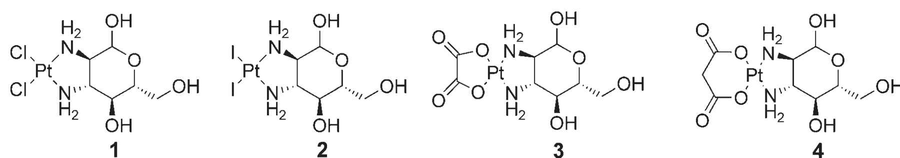


**Figure 3.** Synthesized platinum(II) carbohydrate complexes, (*SP*-4-3)-dichloro(2,3-diamino-2,3-dideoxy-D-glucose-κ$^2$*N,N'*)platinum(II) **1**, (*SP*-4-3)-diiodo(2,3-diamino-2,3-dideoxy-D-glucose-κ$^2$*N,N'*)platinum(II) **2**, (*SP*-4-3)-(2,3-diamino-2,3-dideoxy-D-glucose-κ$^2$*N,N'*)(oxalato-κ$^2$*O,O'*)platinum(II) **3**, and (*SP*-4-3)-(2,3-diamino-2,3-dideoxy-D-glucose-κ$^2$*N,N'*)(malonato-κ$^2$*O,O'*)platinum(II) **4**.

The positive ion ESI mass spectra of compounds **1**–**4** showed the pseudomolecular ions $[M+Na]^+$ at *m/z* 467, 650, 484, and 498, respectively. The observed isotopic patterns in the mass spectra were in good agreement with the calculated isotopic distribution.

The result of the X-ray diffraction study of complex **2** is shown in Figure 4. Selected bond lengths and angles are given in the legend to Figure 4. The platinum(II) atom has a square-planar coordination geometry and is coordinated by two nitrogen atoms of the diaminoglucose moiety and two iodo ligands in *cis*-arrangement [Pt1-N1 2.069(2), Pt1-N2 2.061(3), Pt1-I1 2.5801(3), Pt1-I2 2.5762(2) Å]. The Pt1–N distances are significantly longer than in [$PtCl_2$(methyl 2,3-diamino-2,3-dideoxy-α-D-mannopyranoside)]·$H_2O$[27, 28] at 2.02(1) and 2.03(1) Å because of the stronger *trans*-influence of iodo ligands compared to chloro ones. The glucose ring adopts a chair conformation with the two amino groups in equatorial positions. The chelate ring Pt1N1C1C2N2 has a *synclinal* (gauche) conformation, the torsion angle $\Theta_{N2\text{-}C2\text{-}C1\text{-}N1}$ being at 54.9(3)°. In contrast to [$PtCl_2$(3,4-diamino-2,3,4,6-tetradeoxy-α-L-*lyxo*-hexopyranoside)]·$C_2H_5OH$,[29] no short Pt–Pt contacts have been found in complex **1**·$CH_3OH$.

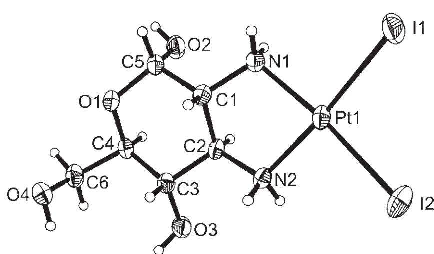


**Figure 4.** ORTEP view of the complex (*SP*-4-3)-diiodo(2,3-diamino-2,3-dideoxy-D-glucose-k$^2$*N,N'*)platinum(II): The displacement ellipsoids are drawn at 50% probability level; the solvate methanol molecule is not shown. Selected bond distances [Å] and angles [deg] Pt–N1 2.069(2), Pt–N2 2.061(3), Pt–I1 2.5801(3), Pt–I2 2.5762(2), C1–N1 1.477(4), C2–N2 1.480(3), C1–C2 1.527(4); N1-Pt-N2 83.00(10), N1-Pt-I1 91.92(7), N1-Pt-I2 173.31(3), N2-Pt-I1 174.90(6), N2-Pt-I2 90.32(6), I1-Pt-I2 94.764(10), C1-N1-Pt 107.33(16), C2-N2-Pt 110.09(16), C2-C1-N1 108.1(2), C1-C2-N2 106.5(2).

To estimate the reactivity of the synthesized compounds toward DNA, which is considered the critical cellular target for platinum complexes, a comparative study on the affinity toward the model nucleotide dGMP was conducted. The DNA building block guanosine (and to a lesser extent adenosine) is suited for modeling the interaction as it was shown to be the preferred binding site for transition metal complexes on DNA[30]—adduct formation takes place primarily at the N7 atom of the nucleotide. CE has already been applied frequently in the field of metallodrug research (for reviews see [31–33]). It was proven to be a valuable tool in characterizing metallocomplex–biomolecule interactions, being a rapid, inexpensive, and reliable technique and thus, superior to chromatography.

The complexes under investigation were incubated at molar ratios of complex:dGMP of 1:2, and the reactivity toward dGMP was found to decrease in the following order (based on the half-lives of the dGMP peaks and the pseudo rate constants): dichloro **1** > diiodo **2** > oxalato **3** > malonato **4** (Table 1). The binding curves of the coordination compounds toward dGMP illustrate that the dichloro complex **1** shows very similar binding kinetics to cisplatin (Figure 5). It is probable that the reaction also follows the same mechanism, that is, exchange of the chloro ligands with water and subsequently,

**Table 1.** Summary of pseudo rate constants $k_{bind}$[a] and graphically assessed half-lives $\tau_{1/2}$ for the dGMP binding of the studied platinum compounds.[b]

| Compd | $k_{bind}$ (mol$^{-1}$ h$^{-1}$) | $R$ | $\tau_{1/2}$ [h] |
|---|---|---|---|
| **1** | 0.0849 | 0.9980 | 8.1 ± 0.1 |
| **2** | 0.0151 | 0.9991 | 26.6 ± 0.3 |
| **3** | 0.0138 | 0.9995 | 35.8 ± 0.9 |
| **4** | 0.0070 | 0.9990 | 69.3 ± 2.1 |
| Cisplatin | 0.0602 | 0.9983 | 8.8 ± 0.7 |
| Carboplatin[c] | | | 420 |
| Oxaliplatin[c] | | | 65 |

[a] In mol$^{-1}$ h$^{-1}$ with correlation coefficents *R*. [b] Compared to values obtained from the literature for carboplatin and oxaliplatin. [c] Taken from [44]. Samples were incubated under different conditions (1 mM phosphate, 4 mM NaCl) and can therefore not be compared without restrictions.

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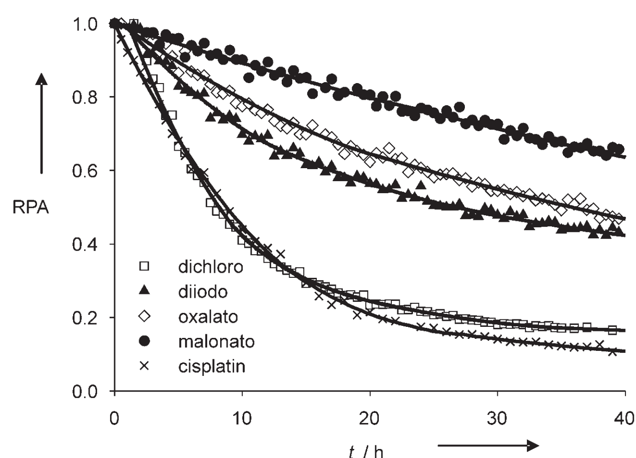


**Figure 5.** Time courses of the dGMP (RPA, Relative Peak Area) binding reaction for the carbohydrate–Pt complexes and cisplatin.

dGMP-binding. The diiodo complex **2** exhibits higher stability as evidenced by much slower binding to the model nucleotide (slower decrease in the dGMP peak area). For complexes **3** and **4** the stability of the dicarboxylato ligands leads to a significant decrease in the binding kinetics and also to a different binding mechanism: apparently, breaking of the first bond results in an immediate labilization and cleavage of the second—therefore, the two biomolecules bind almost concurrently. This hypothesis is verified by the electrophoretic data: the dGMP peak area decreases twice as fast as the complex peak area, the major peaks corresponding to bisadducts—still, the reaction kinetics follow pseudo first order.

When taking a closer look at the electropherograms (see Figure 6), two peaks can be observed for the bisadducts formed between dGMP and the Pt compounds. These peaks

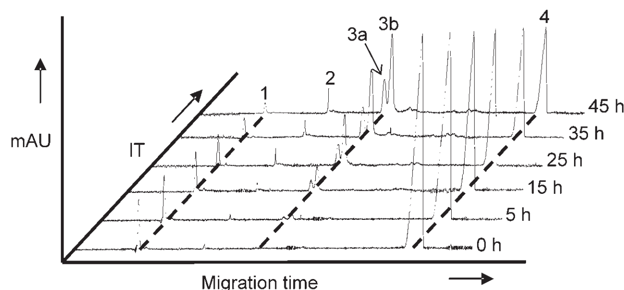


**Figure 6.** Monitoring (IT, incubation time) of the dGMP-binding reaction of compound **3** (oxalato). Separation Voltage: 15 kV. Detection wavelength: 254 nm. Other conditions: see experimental section. Peak identification: 1—complex; 2–-monoadduct; 3 a and 3 b—bisadducts (atropisomers); 4—dGMP.

probably correspond to the rotamers formed by guanosine and platinum complexes with bulky diamino ligands as already reported by Trani[34] and Williams.[35] It is speculated that the minor peak stems from the head-to-head (HH) and tail-to-tail (TT) atropisomers, the majority from the two possible head-to-tail (HT) isomers which are usually preferred because of interligand interactions. As a result of their similar shape and charge, HH and TT exhibit the same electrophoretic mobility (the same holds true for the two HT isomers) and can therefore not be separated.

The cytotoxicity of complexes **1**, **2**, **3**, and **4** was determined in comparison to oxaliplatin {*l*-OHP, (*SP*-4-2)-[(1*R*,2*R*)-cyclohexane-1,2-diamine)(oxalato)platinum(II)]} and its (1*S*,2*S*)-enantiomer (*d*-OHP), and to carboplatin by means of a colorimetric microculture assay (MTT assay). Concentration-effect curves are depicted in Figure 7, and $IC_{50}$ values are listed in Table 2. Antiproliferative effects are moderate to pronounced, with $IC_{50}$ values generally being in the micromolar range, and differences between the cytotoxic potencies of **1**–**4** are comparatively small. In three of the four cell lines (HeLa, SW480, U2OS), the chloro complex **1** and the malonato complex **4** are the most and the least active of the carbohydrate-Pt complexes, respectively, with $IC_{50}$ values differing only by factors of up to 3.2. In two of these cell lines (SW480, U2OS), cytotoxicity of the compounds decreases in the following rank order **1** > **2** > **3** > **4**, which corresponds to their reactivity to dGMP in the cell-free system (see above). The apparent deviations from this rank order in CH1 cells have to be taken with caution because of the small differences between the concentration-effect curves ($IC_{50}$ values differ only by factors of up to 1.9). In any case, cytotoxicity of the chloro complex is one to two orders of magnitude lower than that of oxaliplatin, but it is still comparable to that of carboplatin in two of the four cell lines (HeLa, SW480).

For all carbohydrate–Pt complexes, sensitivity of the cell lines decreases uniformly in the following rank order: CH1 (ovary) > HeLa (cervix) > SW480 (colon) > U2OS (osteosarcoma), which is consistent with the assumption that the complexes have the same mode of action, most likely by forming identical carbohydrate–Pt–DNA adducts, whereas the more or less readily exchangeable halogenide and carboxylate ligands only modify reaction kinetics.

The specific pharmacological properties of oxaliplatin as opposed to other platinum drugs such as cisplatin or carboplatin have to be ascribed to the presence of the cyclohexane ring. The resulting intrastrand cross-links between two adjacent guanines are somewhat bulkier and less polar, as this moiety protrudes directly into the narrowed major groove,[36] with a hydrogen bond between the pseudoequatorial nitrogen of the (1*R*,2*R*)-cyclohexane-1,2-diamine ligand and *O*6 of guanine being the only major difference in binding patterns.[37]

Substitution of the cyclohexane ring with small alkyl groups has been recognized as a strategy to increase cytotoxic potency,[13] but whether the steric demand or the hydrophobicity, or the combination of both is responsible for the specific antitumor effects remains elusive. Despite the structural similarity of the diaminoglucose ligand of complexes **1**–**4** and the diaminocyclohexane ligand of oxaliplatin, cytotoxic potencies differ tremendously. The oxalato analogue **3** is 12 to 290 times less cytotoxic than oxaliplatin (*l*-OHP) and 4 to 67 times less cytotoxic than the corresponding enantiomer *d*-OHP. Whether the hydroxy groups of the carbohydrate moiety are unfavorable for steric reasons, hindering the formation of oxaliplatin-analogous DNA adducts, or because of the more hydrophilic character of

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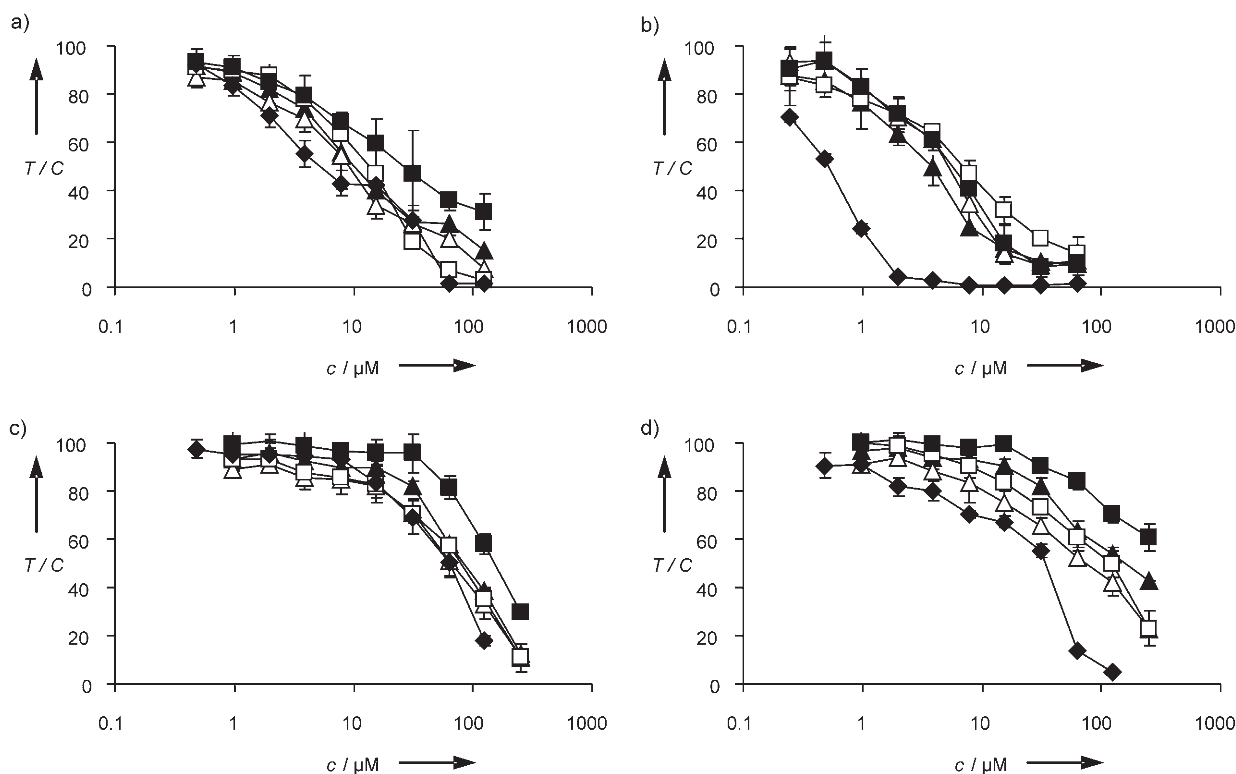


**Figure 7.** Cytotoxicity of complexes **1**–**4** and carboplatin. Comparison of concentration-effect curves of complex 1 (△), complex 2 (□), complex 3 (▲), complex 4 (■), and carboplatin (◆) in a) HeLa, b) CH1, c) SW480, and d) U2OS cells, obtained by the MTT assay (96 h exposure).

**Table 2.**
Cytotoxicity of diaminoglucose-based platinum complexes **1**, **2**, **3**, and **4**, as compared to carboplatin, oxaliplatin (*l*-OHP) and *d*-OHP in four human cancer cell lines.

| | $IC_{50}$ (μM)[a] | | | |
|---|---|---|---|---|
| Compd | CH1 | HeLa | SW480 | U2OS |
| **1** | 5.1 ± 0.3 | 7.3 ± 0.8 | 67 ± 13 | 82 ± 24 |
| **2** | 7.9 ± 2.3 | 14 ± 2 | 79 ± 4 | 119 ± 16 |
| **3** | 4.1 ± 0.1 | 10 ± 1 | 87 ± 3 | 175 ± 20 |
| **4** | 6.3 ± 0.4 | 23 ± 7 | 151 ± 23 | > 250 |
| Carboplatin | 0.52 ± 0.01 | 5.4 ± 1.5 | 61 ± 10 | 34 ± 1 |
| Osaliplatin, *l*-OHP | 0.34 ± 0.09 | 0.30 ± 0.08 | 0.30 ± 0.08 | 0.72 ± 0.24 |
| *d*-OHP | 1.0 ± 0.1 | 1.1 ± 0.4 | 1.3 ± 0.3 | 2.6 ± 0.7 |

[a] 50% inhibitory concentrations in CH1, HeLa, SW480, and U2OS cells in the MTT assay. Values are the mean ± standard deviation obtained from at least three independent experiments.

such adducts or whether the pyranose ring is disadvantageous, cannot be determined by our studies.

Nevertheless, the moderate cytotoxicity does not rule out the possibility of therapeutic efficacy in vivo. In fact, low toxicity allowing dose escalation to levels that are lethal in the case of cisplatin, a broad therapeutic window, and life-prolonging effects comparable to or even superior to those of cisplatin have been reported for compound **1** (among other aminocarbohydrate-platinum complexes) in the mouse model of intraperitoneal sarcoma-180,[26] encouraging further evaluation of this class of compounds in animal tumor models.

## Conclusions

Platinum complexes with a carbohydrate ligand, resembling the cyclohexane-1,2-diamine moiety in oxaliplatin were synthesized and characterized. The complexes were found to be capable of binding to DNA with the leaving groups having an important influence on the reactivity. In an in vitro MTT assay, the activity in four different human tumor cell lines was determined but a correlation between in vitro activity and DNA binding was only observed in SW480 and U2OS cells. The results indicate that the binding of DNA does not seem to be the only determinant of elucidating the complexes' activity. However, the cellular uptake might also have an important influence on the latter parameter. As the glycolytic energy production of cells can only be exploited properly in living organisms, in vivo tests will reveal the potential of the presented oxaliplatin analogues with 2,3-diamino-2,3-dideoxy-D-glucose instead of the (1*R*,2*R*)-cyclohexane-1,2-diamine ligand.

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## Experimental Section

The NMR spectra were recorded on a Bruker Avance DPX 400 instrument (Ultrashield Magnet) at 400.13 MHz ($^1H$) and 100.63 MHz ($^{13}C$) at 298 *K* in [$D_6$]DMSO or $D_2O$. Specific optical rotations were measured with a Perkin–Elmer 341 polarimeter using a 10 cm cell. Melting points were determined with a Büchi B-540 apparatus and are uncorrected. Electrospray ionization mass spectra were recorded on a Bruker Esquire 3000 spectrometer in positive ion mode. The elemental analyses were done by the Laboratory for Elemental Analysis of the Institute of Physical Chemistry, University of Vienna, with a Perkin–Elmer 2400 CHN Elemental Analyzer. Potassium tetrachloroplatinate was obtained from Johnson Matthey. All chemicals obtained from commercial suppliers were used as received and were of analytical grade. Water was used doubly distilled. The synthetic procedures were carried out in a light protected environment when platinum complexes were involved.

**Crystallographic Structure Determination.** X-ray diffraction measurements were performed on an APEX II CCD diffractometer at 296 *K*. The single crystal was positioned 40 mm from the detector, and 1887 frames were measured, each for 15 s over 0.5°. The data were processed using SAINT software. Crystal data, data collection parameters, and structure refinement details are given in Table 3.

**Table 3.**
Crystal data and details of data collection for complex **2**·$CH_3OH$.[a]

| Chemical formula | $C_7H_{18}PtI_2N_2O_5$ |
|---|---|
| *M* (g mol$^{-1}$) | 659.12 |
| Temperature (K) | 296 |
| Crystal size | 0.28×0.20×0.14 |
| Crystal colour, habit | white, block |
| Crystal system | monoclinic |
| Space group | $P2_1$ |
| *a* (Å) | 8.9846(2) |
| *b* (Å) | 8.1362(2) |
| *c* (Å) | 10.6595(3) |
| ß (°) | 103.219(1) |
| *V* (Å$^3$) | 758.57(3) |
| *Z* | 2 |
| $D_c$ (g cm$^{-3}$) | 2.886 |
| μ (cm$^{-1}$) | 133.29 |
| F(000) | 596 |
| θ range for data collection (°) | 2.68–38.18 |
| *h* range | −14/11 |
| *k* range | −12/13 |
| *l* range | −18/17 |
| No. refls. used in refinement | 6462 |
| No. Parameters | 159 |
| $R_{int}$ | 0.0219 |
| $R_1$ (obs.) | 0.0201 |
| $wR_2$ (all data) | 0.0433 |
| **S** | **0.885** |

[a] Refinement was by full-matrix least-squares ($F_o^2$) for all reflections, $R1=\Sigma||F_o|-|F_c||/\Sigma w|F_o|$, $wR2=[\Sigma(F_o^2-F_c^2)^2/\Sigma wF_o^4]^{1/2}$, $w=1/[(\sigma^2(F_o^2)+(0.0173P)^2+5.64P$, with $P=\{[F_o^2+2F_c^2)/3\}$. Goodness of fit, $S=\Sigma[(F_o^2-F_c^2)^2]/(n-p)^{1/2}$.

The structures were solved by direct methods and refined by full-matrix least-squares techniques. Nonhydrogen atoms were refined with anisotropic displacement parameters. H atoms were inserted at calculated positions and refined with a riding model. The following computer programs were used: structure solution, SHELXS-97[38] refinement, SHELXL-97[39] molecular diagrams, SCHAKAL-97,[40] computer, Pentium IV; scattering factors.[41] CCDC 624130 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44–1223/336–033; E-mail: deposit@ccdc.cam.ac.uk].

**Chemicals, electrolytes, and samples for dGMP binding studies.** Sodium hydroxide, sodium dihydrogenphosphate, dGMP (disodium 2′-deoxyguanosine 5′-monophosphate hydrate), and HEPES (*N*-[2-hydroxyethyl]piperazine-*N*′-[2-ethanesulfonic acid]) were of analytical grade and obtained from Fluka (Buchs, Switzerland). Disodium hydrogenphosphate was purchased from Riedel-de Haen (Seelze, Germany). High purity water used throughout this work was obtained from a Millipore Synergy 185 UV Ultrapure Water system (Molsheim, France). For incubation, a 20 mM HEPES buffer at physiological pH (7.4) and 37 °C, was chosen. As HEPES absorbs in the UV range, a different buffer had to be used as background electrolyte (BGE) for the electrophoretic separations—a 20 mM phosphate buffer (pH 7.4) was utilized for this purpose. The incubation solutions and BGE were passed through a 0.45 μm disposable membrane filter (Sartorius, Goettingen, Germany) before being injected hydrodynamically into the CZE system.The platinum complexes were dissolved in the dGMP-containing incubation buffer, constituting a drug-to-dGMP ratio of 1:2—an initial concentration of 0.5 mM was chosen for the complexes.

**Studies on dGMP binding by capillary zone electrophoresis.** CZE experiments were performed on a HP$^{3D}$ CE system (Agilent, Waldbronn, Germany) equipped with an on-column diode-array detector. For all measurements, uncoated fused silica capillaries of 50 cm total length (50 μm ID, 42 cm effective length) were used (Polymicro Technologies, Phoenix, AZ, USA). Capillary and sample tray were thermostated at 37 °C, injections were performed by applying a pressure of 10 mbar for 15 s, and a constant voltage of 15 kV was used for all separations (the resulting current was about 25 μA). Detection was carried out at 200 nm and 254 nm. Prior to the first use, the capillary was flushed with 0.1 M HCl, water, 1 M NaOH, and again with water, each for 10 min and was then equilibrated with the BGE for 10 min. Before each injection, the capillary was purged with 0.1 M NaOH and water for 2 min each and finally conditioned with the BGE for 3 min. The rate of binding to dGMP was measured by monitoring the decrease of the peak area response corresponding to the dGMP signal. The peak areas were normalized using the area of the incubation buffer signal as an internal standard. The kinetic series was repeated at least three times for each of the compounds. To find an equation that most closely describes the behavior and character of kinetic curves and fits the experimental data, regression analysis was undertaken (natural logarithm of the dGMP concentration, that is, its peak area against time)—the reactions follow pseudo first order kinetics. Pseudo rate constants ($k_{bind}$) were calculated from fitted curves, half-lives were determined graphically.

**Cell lines and culture conditions.** Human CH1 (ovarian carcinoma) and SW480 (colon carcinoma) cells were kindly provided by Lloyd R. Kelland (CRC Centre for Cancer Therapeutics, Institute of Cancer Research, Sutton, UK) and Brigitte Marian (Institute of Cancer Research, Medical University of Vienna, Austria), respectively. U2OS (osteosarcoma) and HeLa (cervix carcinoma) cells were provided by Thomas Czerny (Institute Of Genetics, University of Veterinary Medicine Vienna). Cells were grown in 75 cm$^2$ culture flasks (Iwaki/Asahi Technoglass, Gyouda, Japan) as adherent monolayer cultures in complete culture medium, that is, minimal essential medium (MEM) supplemented with 10% heat-inactivated fetal bovine serum, 1 mM sodium pyruvate, 2 mM L-glutamine, and 1% nones-


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sential amino acids (100×) (all purchased from Gibco/Invitrogen, Paisley, UK). Cultures were maintained at 37 °C in a humidified atmosphere containing 5% $CO_2$.

**Cytotoxicity in cancer cell lines.** Cytotoxicity was determined by means of a colorimetric microculture assay (MTT assay, MTT = 3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2*H*-tetrazolium bromide). CH1, SW480, U2OS, and HeLa cells were harvested from culture flasks by trypsinization and seeded into 96-well microculture plates (Iwaki/Asahi Technoglass, Gyouda, Japan) in cell densities of $2\times10^3$, $2.5\times10^3$, $3.5\times10^3$, and $1.5\times10^3$ cells/well, respectively, to ensure exponential growth throughout drug exposure. After a 24 h preincubation, cells were exposed to serial dilutions of the test compounds in 200 μL/well complete culture medium for 96 h. At the end of exposure, drug solutions were replaced by 150 μL/well RPMI 1640 culture medium (supplemented with 10% heat-inactivated fetal bovine serum and 2 mM L-glutamine) plus 20 μL/well MTT solution in phosphate-buffered saline (5 mg mL$^{-1}$). After incubation for 4 h, the medium/MTT mixtures were removed, and the formazan crystals formed by the mitochondrial dehydrogenase activity of vital cells were dissolved in 150 μL DMSO per well. Optical densities at 550 nm were measured with a microplate reader (Tecan Spectra Classic), using a reference wavelength of 690 nm to correct for unspecific absorption. The quantity of vital cells was expressed in terms of *T/C* values by comparison to untreated control microcultures, and 50% inhibitory concentrations ($IC_{50}$) were calculated from concentration-effect curves by interpolation. Evaluation is based on means from at least three independent experiments, each comprising at least six microcultures per concentration level.

**2-Acetamido-2-deoxy-D-glucose 1b.** A freshly prepared sodium methoxide solution from sodium (7 g, 0.304 mol) in anhydrous methanol (600 mL) was added to a suspension of 2-amino-2-deoxy-D-glucose hydrochloride (60 g, 0.279 mol) in dry methanol (200 mL). The reaction mixture was stirred for 30 min at room temperature. Acetic anhydride (40 mL, 0.423 mol) was added to the solution of 2-amino-2-deoxy-D-glucose **1a** and the reaction mixture was stirred for 12 h at room temperature. The product was allowed to precipitate for 24 h at −18 °C. Afterwards, **1b** was filtered off, washed with diethyl ether (3×10 mL), and dried in vacuum. Yield: 60.4 g (98%); mp: 202–204 °C (200–204 °C[42]); $^1$H NMR (400.13 MHz, [D$_6$]DMSO, 25 °C): α-Anomer: $\delta$ = 7.63 (d, $^3J$ (H-2,NH) = 8.0 Hz, 1H; NH), 6.41 (d, $^3J$ (H-1,OH-1) = 4.5 Hz, 1H; OH-1), 4.92 (t, $^3J$ (H-2,H-1), $^3J$ (OH,H-1) = 4.0 Hz, 1H; H-1), 4.89 (d, $^3J$ (H-4,OH-4) = 5.5 Hz, 1H; OH-4), 4.61 (d, $^3J$ (H-3,OH-3) = 5.5 Hz, 1H; OH-3), 4.41 (t, $^3J$ (H-6,OH-6), $^3J$ (H-6′,OH-6) = 5.8 Hz, 1H; OH-6), 3.60 (m, 3H; H-2, H-5, H-6′), 3.48 (m, 2H; H-3, H-6′), 3.11 (dt, $^3J$ (OH-4, H-4) = 5.5 Hz, $^3J$ (H-3,H-4), $^3J$ (H-5,H-4) = 9.0 Hz, 1H; H-4), 1.83 ppm (s, 3H; $CH_3$); β-Anomer: $\delta$ = 7.72 (d, $^2J$ (H-2,NH) = 8.0 Hz, 1H; NH), 6.50 (d, $^2J$ (H-1,OH-1) = 6.0 Hz, 1H; OH-1), 4.93 (m, 1H; OH-3), 4.83 (d, $^2J$ (H-4,OH-4) = 5.0 Hz, 1H; OH-4), 4.52 (t, $^2J$ (H-6,OH-6), $^2J$ (H-6′,OH-6) = 5.8 Hz, 1H; OH-6), 4.44 (m, 1H; H-1), 3.66 (m, 1H; H-6), 3.45 (m, 1H; H-6′), 3.29 (m, 2H; H-2, H-4), 3.04 (m, 2H; H-3, H-5), 1.81 ppm (s, 3H; $CH_3$); $^{13}$C NMR (100.63 MHz, [D$_6$]DMSO, 25 °C): α-Anomer: $\delta$ = 170.2 (CO), 91.4 (C-1), 72.9 (C-5), 72.0 (C-4), 71.3 (C-3), 62.0 (C-6), 55.1 (C-2), 23.6 ppm ($CH_3$); β-Anomer: $\delta$ = 170.5 (CO), 96.3 (C-1), 77.6 (C-5), 75.2 (C-4), 71.7 (C-3), 62.0 (C-6), 58.1 (C-2), 23.9 ppm ($CH_3$); MS (ESI$^+$): *m/z*: 244 [*M*+Na]$^+$, 465 [2*M*+Na]$^+$.

**Benzyl-2-acetamido-2-deoxy-α-D-glucopyranoside 1c.** 2-Acetamido-2-deoxy-D-glucose (30 g, 0.136 mol) was added to benzylalcohol (800 mL) containing 0.5 *w/v*% of hydrochloric acid and the reaction mixture was refluxed for 30 min. A third of the benzylalcohol was removed under reduced pressure (10–15 mbar) and **1c** was precipitated by addition of diethyl ether (300 mL). The crude product was recrystallized from ethanol, filtered off, washed with cold ethanol (2×10 mL), and dried in vacuum. Yield: 27.5 g (65%); mp: 182–184 °C (183–184 °C[43]); $^1$H NMR (400.13 MHz, [D$_6$]DMSO, 25 °C): $\delta$ = 7.84 (d, $^3J$ (H-2,NH) = 8.0 Hz, 1H; NH), 7.33 (m, 5H; $C_{Ar}$), 5.03 (d, $^3J$ (H-4,OH-4) = 6.0 Hz, 1H; OH-4), 4.74 (d, $^3J$ (H-3,OH-3) = 6.0 Hz, 1H; OH-3), 4.71 (d, $^3J$ (H-2,H-1) = 3.5 Hz, 1H; H-1), 4.67 (d, $^2J$ (H,H) = 12.5 Hz, 1H; $CH_2Ph$), 4.56 (t, $^3J$ (H-6,OH-6), $^3J$ (H-6′,OH-6) = 5.8 Hz, 1H; OH-6), 4.43 (d, 1H; $CH_2Ph$), 3.68 (m, 2H; H-2, H-6), 3.50 (m, 3H; H-3, H-5, H-6′), 3.17 (dt, $^3J$ (OH-4, H-4) = 5.5 Hz, $^3J$ (H-3, H-4), $^3J$ (H-5, H-4) = 9.0 Hz, 1H; H-4), 1.84 ppm (s, 3H; $CH_3$); $^{13}$C NMR (100.63 MHz, [D$_6$]DMSO, 25 °C): $\delta$ = 170.3 (CO), 138.8 ($C_{Ar}$), 129.1 ($C_{Ar}$), 128.4 ($C_{Ar}$), 128.3 ($C_{Ar}$), 96.8 (C-1), 74.0 (C-5), 71.8 (C-4), 71.5 (C-3), 61.7 (C-6), 54.6 (C-2), 23.4 ppm ($CH_3$); MS (ESI$^+$): *m/z*: 334 [*M*+Na]$^+$, 644 [2*M*+Na]$^+$.

**Benzyl-2-acetamido-4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranoside 1d.** Benzyl-2-acetamido-2-deoxy-α-D-glucopyranoside **1c** (31.6 g, 0.102 mol) was added to a suspension of zinc chloride (31.6 g, 0.232 mol) in benzaldehyde (110 mL) under argon atmosphere. The reaction mixture was immersed in an ultrasonic bath for 1 min, heated to 60 °C (to get a clear solution), and stirred at this temperature for 30 min. The product was obtained after pouring the reaction mixture into ice-water, filtering off, washing with water (3×50 mL) and ethanol (10 mL), and suspending in diethyl ether (100 mL). **1d** was purified by recrystallization from pyridine/water (1/3) and dried in vacuum. Yield: 28.5 g (70%); mp: 260–262 °C (260–261 °C [43]); $^1$H NMR (400.13 MHz, [D$_6$]DMSO, 25 °C): $\delta$ = 8.02 (d, $^3J$ (H-2,NH) = 8.0 Hz, 1H; NH), 7.39 (m, 10H; $H_{Ar}$), 5.63 (s, 1H; CHPh), 5.20 (d, $^3J$ (H-3,OH-3) = 6.0 Hz, 1H; OH-3), 4.80 (d, $^3J$ (H-2,H-1) = 3.5 Hz, 1H; H-1), 4.71 (d, $^2J$ (H,H) = 12.5 Hz, 1H; $CH_2Ph$), 4.50 (d, 1H; $CH_2Ph$), 4.15 (dd, $^2J$ (H-6′,H-6) = 8.0 Hz, $^3J$ (H-5,H-6) = 3.0 Hz, 1H; H-6), 3.86 (ddd, $^3J$ (H-3,H-2) = 10.3 Hz, 1H; H-2), 3.73 (m, 3H; H-3, H-5, H-6′), 3.52 (t, $^3J$ (H-3,H-4), $^3J$ (H-5,H-4) = 9.0 Hz, 1H; H-4), 1.86 ppm (s, 3H; $CH_3$); $^{13}$C NMR (100.63 MHz, [D$_6$]DMSO, 25 °C): $\delta$ = 170.3 (CO), 138.9 ($C_{Ar}$), 138.6 ($C_{Ar}$), 129.7 ($C_{Ar}$), 129.1 ($C_{Ar}$), 128.9 ($C_{Ar}$), 128.5 ($C_{Ar}$), 128.4 ($C_{Ar}$), 127.3 ($C_{Ar}$), 101.7 (CHPh), 97.8 (C-1), 83.0 (C-4), 70.0 ($CH_2Ph$), 69.0 (C-6), 68.0 (C-3), 63.7 (C-5), 55.0 (C-2), 23.4 ppm ($CH_3$); MS (ESI$^+$): *m/z*: 400 [*M*+H]$^+$, 422 [*M*+Na]$^+$, 821 [2*M*+Na]$^+$.

**Benzyl-2-acetamido-4,6-*O*-benzylidene-2-deoxy-3-*O*-mesyl-α-D-glucopyranoside 1e.** Methanesulfonyl chloride (3.4 mL, 0.044 mol) was added dropwise to a solution of **1d** (3.8 g, 0.017 mol) in pyridine (43 mL) at 4 °C and the reaction mixture was kept at this temperature for an additional 12 h. The pyridine solution was poured into ice water (200 mL) and the solid was filtered off and washed with water (3×50 mL). The pure product was obtained after recrystallization from methanol and was dried in vacuum. Yield: 7.3 g (90%); mp: 197–200 °C (198–199 °C[23]); $^1$H NMR (400.13 MHz, [D$_6$]DMSO, 25 °C): $\delta$ = 8.23 (d, $^3J$ (H-2,NH) = 9.5 Hz, 1H; NH), 7.38 (m, 10H; $H_{Ar}$), 5.73 (s, 1H; CHPh), 4.88 (d, $^3J$ (H-2,H-1) = 3.5 Hz, 1H; H-1), 4.75 (d, $^2J$ (H,H) = 12.5 Hz, 1H; $CH_2Ph$), 4.74 (t, $^3J$ (H-2,H-3), $^3J$ (H-4,H-3) = 9.8 Hz, 1H; H-3), 4.57 (d, 1H; $CH_2Ph$), 4.31 (dt, $^3J$ (H-3,H-2), $^3J$ (NH,H-2) = 10.0 Hz, 1H; H-2), 4.22 (dd, $^2J$ (H-6,H-6′) = 9.5 Hz, $^3J$ (H-5,H-6′) = 4.3 Hz, 1H; H-6′), 3.95 (t, $^2J$ (H-3,H-4), $^3J$ (H-5,H-4) = 9.3 Hz, 1H; H-4), 3.84 (t, $^2J$ (H-6′,H-6), $^3J$ (H-5,H-6) = 9.8 Hz, 1H; H-6), 3.77 (dt, 1H; H-5), 3.12 (s, 3H; $SCH_3$), 1.89 ppm (s, 3H; $CH_3$); $^{13}$C NMR (100.63 MHz, [D$_6$]DMSO, 25 °C): $\delta$ = 170.5 (CO), 138.1 ($C_{Ar}$), 138.1 ($C_{Ar}$), 129.7 ($C_{Ar}$), 129.2 ($C_{Ar}$), 129.0 ($C_{Ar}$), 129.0 ($C_{Ar}$), 127.0 ($C_{Ar}$), 101.0 (CHPh), 98.3 (C-1), 79.5 (C-4), 79.1 (C-3), 70.0 ($CH_2Ph$), 69.5 (C-6), 63.8 (C-5), 51.9 (C-2), 37.5 ($SCH_3$), 23.3 ppm ($CH_3$); MS (ESI$^+$): *m/z*: 500 [*M*+Na]$^+$, 978 [2*M*+Na]$^+$.

**Benzyl-2-acetamido-4,6-*O*-benzylidene-2-deoxy-α-D-allopyranoside 1f.** A solution of **1e** (7.2 g, 0.015 mol) and anhydrous sodium acetate (7.2 g, 0.088 mol) in 2-methoxyethanol (12.5 mL) containing 5 *v/v*% of water was refluxed for 48 h. The reaction mixture was allowed to cool to room temperature, poured into ice-water (400 mL), and kept at room temperature for 2 h. The product **1f**

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was filtered off, washed with water (3×50 mL), recrystallized from methanol, and dried in vacuum. Yield: 5.4 g (90%); mp: 207–210 °C (203–206 °C[23]); $^1$H NMR (400.13 MHz, [D$_6$]DMSO, 25 °C): $\delta$ = 7.73 (d, $^3J$ (H-2,NH) = 9.0 Hz, 1H; NH), 7.39 (m, 10H; H$_{Ar}$), 5.66 (s, 1H; CHPh), 4.93 (d, $^3J$ (H-3,OH-3) = 5.0 Hz, 1H; OH-3), 4.74 (d, $^3J$ (H-2,H-1) = 4.0 Hz, 1H; H-1), 4.69 (d, $^2J$ (H,H) = 12.5 Hz, 1H; CH$_2$Ph), 4.50 (d, 1H; CH$_2$Ph), 3.93 (m, 6H; H-2, H-3, H-4, H-5, H-6, H6′), 1.91 ppm (s, 3H; CH$_3$); $^{13}$C NMR (100.63 MHz, [D$_6$]DMSO, 25 °C): $\delta$ = 170.0 (CO), 138.9 (C$_{Ar}$), 138.7 (C$_{Ar}$), 129.7 (C$_{Ar}$), 129.0 (C$_{Ar}$), 128.8 (C$_{Ar}$), 128.6 (C$_{Ar}$), 128.3 (C$_{Ar}$), 127.3 (C$_{Ar}$), 101.5 (CHPh), 97.4 (C-1), 79.1 (C-4), 69.9 (CH$_2$Ph), 69.2 (C-6), 67.5 (C-3), 58.2 (C-5), 50.5 (C-2), 23.4 ppm (CH$_3$); MS (ESI$^+$): *m/z*: 404 [*M*+Na−H$_2$O]$^+$, 422 [*M*+Na]$^+$.

**Benzyl-2-acetamido-3-azido-4,6-*O*-benzylidene-2,3-dideoxy-α-D-glucopyranoside 1 g.** Methanesulfonyl chloride (1.6 mL, 0.021 mol) was added dropwise to a solution of **1 f** (2.3 g, 0.006 mol) in pyridine (19 mL) at 4 °C and kept at this temperature for 12 h. The reaction mixture was poured into ice-water and the crude product was extracted with chloroform (3×50 mL). The combined chloroform fractions were washed with diluted sulfuric acid (7×150 mL) and with a saturated solution of sodium bicarbonate (1×200 mL). The chloroform was removed at reduced pressure and the product was dried in vacuum. Sodium azide (1.6 g, 0.025 mol) was added to a solution of benzyl-2-acetamido-3-methanesulfonato-4,6-*O*-benzylidene-2,3-dideoxy-α-D-allopyranoside in dimethylsulfoxide (19 mL) and the reaction mixture was stirred at 150 °C for 1 h. Then it was poured into ice-water, the resulting solid was filtered off, washed with water (3×50 mL), and the product was isolated after recrystallization from ethanol and dried in vacuum. Yield: 1.5 g (60%); mp: 243–245 °C (244–245 °C[23]); $^1$H NMR (400.13 MHz, [D$_6$]DMSO, 25 °C): $\delta$ = 8.33 (d, $^3J$ (H-2,NH) = 8.0 Hz, 1H; NH), 7.39 (m, 10H; H$_{Ar}$), 5.73 (s, 1H; CHPh), 4.83 (d, $^3J$ (H-2,H-1) = 3.0 Hz, 1H; H-1), 4.74 (d, $^2J$ (H,H) = 12.5 Hz, 1H; CH$_2$Ph), 4.53 (d, 1H; CH$_2$Ph), 4.19 (m, 1H; H-6), 3.91 (m, 2H; H-2, H-4), 3.78 (m, 3H; H-3, H-5, H-6′), 1.87 ppm (s, 3H; CH$_3$); $^{13}$C NMR (100.63 MHz, [D$_6$]DMSO, 25 °C): $\delta$ = 170.4 (CO), 138.3 (C$_{Ar}$), 138.1 (C$_{Ar}$), 129.8 (C$_{Ar}$), 129.2 (C$_{Ar}$), 129.0 (C$_{Ar}$), 128.6 (C$_{Ar}$), 126.9 (C$_{Ar}$), 101.4 (CHPh), 97.2 (C-1), 80.4 (C-3), 69.7 (CH$_2$Ph), 68.7 (C-6), 63.8 (C-5), 60.7 (C-4), 52.5 (C-2), 23.3 ppm (CH$_3$); MS (ESI$^+$): *m/z*: 447 [*M*+Na]$^+$.

**Benzyl-2,3-diacetamido-2,3-dideoxy-α-D-glucopyranoside 1 h.** A solution of benzyl-2-acetamido-3-azido-4,6-*O*-benzylidene-2,3-dideoxy-α-D-glucopyranoside **1 g** (1.4 g, 0.003 mol) in acetic acid (70 mL, 80%) was stirred at 90 °C for 2 h. The acetic acid was removed under reduced pressure by codistillation with water (7×20 mL). A mixture of the resulting white solid in methanol (60 mL) and palladium on carbon (0.56 g, 5% Pd) was stirred under hydrogen atmosphere at room temperature for 4 h. The catalyst was removed by filtration through celite and washed with methanol (2×5 mL). Acetic anhydrate (1 mL, 0.009 mol) was added to the solution and the mixture was stirred for 3 h at room temperature. The solvent was removed under reduced pressure and a trace of acetic acid was removed by codistillation with water (7×10 mL). The pure product was obtained after recrystallization from ethanol and was dried in vacuum. Yield: 0.74 g (70%); mp: 267–268 °C (244–245 °C[23]); $^1$H NMR (400.13 MHz, [D$_6$]DMSO, 25 °C): $\delta$ = 7.73 (d, $^3J$ (H-3,NH-3) = 9.0 Hz, 1H; NH-3), 7.48 (d, $^3J$ (H-2,NH-2) = 8.5 Hz, 1H; NH-2), 7.36 (m, 10H; H$_{Ar}$), 4.99 (d, $^3J$ (H-4,OH-4) = 6.5 Hz, 1H; OH-4), 4.71 (d, $^3J$ (H-2,H-1) = 3.5 Hz, 1H; H-1), 4.71 (d, $^2J$ (H,H) = 12.5 Hz, 1H; CH$_2$Ph), 4.60 (t, $^3J$ (H-6,OH-6), $^3J$ (H-6′,OH-6) = 5.8 Hz, 1H; OH-6), 4.46 (d, 1H; CH$_2$Ph), 4.01 (dt, $^3J$ (H-2,H-3) = 11.4 Hz, $^3J$ (H-4,H-3), $^3J$ (NH-3,H-3) = 9.4 Hz, 1H; H-3), 3.81 (ddd, $^3J$ (NH-2,H-2) = 8.7 Hz, 1H; H-2), 3.70 (dd, $^2J$ (H-6′,H-6) = 10.3 Hz, $^3J$ (H-5,H-6) = 5.3 Hz, 1H; H-6), 3.52 (m, 2H; H-5, H-6′), 3.29 (dt, $^3J$ (H-5,H-4) = 6.4 Hz, $^3J$ (H-3,H-4) = 9.4 Hz, 1H; H-4), 1.80 ppm (s, 3H; CH$_3$); $^{13}$C NMR (100.63 MHz, [D$_6$]DMSO, 25 °C): $\delta$ = 171.2 (CO-3), 170.4 (CO-2), 138.7 (C$_{Ar}$), 129.1 (C$_{Ar}$), 128.7 (C$_{Ar}$), 128.4 (C$_{Ar}$), 96.3 (C-1), 74.8 (C-5), 69.1 (C-4), 68.7 (CH$_2$Ph), 61.5 (C-6), 53.1 (C-2), 52.3 (C-3), 23.8 (CH$_3$-3), 23.4 ppm (CH$_3$-2); MS (ESI$^+$): *m/z*: 375 [*M*+Na]$^+$, 726 [2*M*+Na]$^+$.

**2,3-Diamino-2,3-dideoxy-D-glucose hydrochloride 1 i.** Palladium on activated carbon (0.5 g, 10% Pd) was added to a solution of **1 h** (2.0 g, 0.006 mol) in hydrochloric acid (20 mL, 6 N) and the reaction mixture was kept under hydrogen atmosphere (5 bar) for 18 h. The catalyst was removed by filtration through Celite and the reaction mixture was heated at 90 °C for 1 h. The solvent was removed under reduced pressure by codistillation with water (7×10 mL). The resulting syrup was dissolved in ethanol (20 mL), treated with activated charcoal, and filtered. The colorless filtrate was evaporated to dryness and the rest of the water was removed by codistillation with absolute ethanol (5×10 mL) affording a pale yellow oil. The pure product was solidified by ultrasonification in ethanol (10 mL) and the white powder was dried in vacuum. Yield: 1.2 g (80%); mp: 200 °C decomp. (196 °C decomp.[23]); $^1$H NMR (400.13 MHz, [D$_6$]DMSO, 25 °C): α-Anomer: $\delta$ = 8.74 (m, 2H;NH-2, NH-3), 7.54 (m, 1H; OH-1), 5.31 (m, 1H; H-1), 3.60 (m, 4H; H-6, H-6′, H-5, H-4), 3.36 ppm (m, 2H; H-2, H-3); β-Anomer: $\delta$ = 4.87 (d, $^3J$ (H-2,H-1) = 7.5 Hz, 1H; H-1), 3.60 (m, 1H; H-4), 3.43 (m, 1H; H-3), 3.26 (m, 1H; H-5), 3.13 ppm (m, 1H; H-2); $^{13}$C NMR (100.63 MHz, [D$_6$]DMSO, 25 °C): α-Anomer: $\delta$ = 88.9 (C-1), 72.0, 66.4, 60.6 (C-6), 53.8, 51.9 ppm; β-Anomer: $\delta$ = 94.0 (C-1), 78.1 (C-5), 66.9 (C-4), 60.8(C-6), 55.6 (C-3), 54.5 ppm (C-2); MS (ESI$^+$): *m/z*: 161 [*M*+H−H$_2$O−2 HCl]$^+$, 178 [*M*+H−2 HCl]$^+$.

**(*SP*-4–3)-dichloro(2,3-diamino-2,3-dideoxy-D-glucose-κ$^2$*N,N′*)platinum(II) 1.** A solution of 2,3-diamino-2,3-dideoxy-D-glucopyranose hydrochloride **1 i** (500 mg, 2 mmol) and potassium hydroxide (168 mg, 3 mmol) in water (1 mL) was added to a solution of potassium tetrachloroplatinate (830 mg, 2 mmol) in water (1 mL). The mixture was stirred for 12 h at room temperature and was then kept at 4 °C for 2 d. The yellow precipitate was filtered off, washed with acetone (2×0.1 mL), recrystallized from water, and dried in vacuum. Yield: 270 mg (30%); mp: 253 °C (decomp.); Elemental analysis, found C, 16.08; H, 3.04; N, 6.07. Calcd for $C_6H_{14}Cl_2N_2O_4Pt$ (444 g mol$^{-1}$) C, 16.22; H, 3.18; N, 6.31; $[\alpha]_D^{20} = -70 \pm 2$ ($c$ = 0.25 in water for 24 h); $^1$H NMR (400.13 MHz, D$_2$O, 25 °C): α-Anomer: $\delta$ = 5.24 (d, $^3J$ (H-2,H-1) = 3.5 Hz, 1H; H-1), 3.77 (dd, $^2J$ (H-6′,H-6) = 12.5 Hz, $^3J$ (H-5,H-6) = 2.0 Hz, 1H; H-6), 3.68 (dd, $^3J$ (H-5,H-6′) = 4.8 Hz, 1H; H-6′), 3.61 (m, 1H; H-5), 3.48 (t, $^3J$ (H-3,H-4), $^3J$ (H-5,H-4) = 9.5 Hz, 1H; H-4), 2.90 (dd, $^3J$ (H-2,H-3) = 12.3 Hz, $^3J$ (H-4,H-3) = 9.3 Hz, 1H; H-3), 2.82 ppm (dd, 1H; H-2); β-Anomer: $\delta$ = 4.73 (d, $^3J$ (H-2,H-1) = 8.0 Hz, 1H; H-1), 3.82 (dd, $^2J$ (H-6′,H-6) = 12.5 Hz, $^3J$ (H-5,H-6) = 2.0 Hz, 1H; H-6), 3.64 (dd, $^3J$ (H-5,H-6′) = 5.3 Hz, 1H; H-6′), 3.47 (t, $^3J$ (H-3,H-4), $^3J$ (H-5,H-4) = 9.5 Hz, 1H; H-4), 3.30 (ddd, 1H; H-5), 2.77 (dd, $^3J$ (H-2,H-3) = 12.5 Hz, 1H; H-3), 2.53 ppm (dd, 1H; H-2); $^{13}$C NMR (100.63 MHz, D$_2$O, 25 °C): α-Anomer: $\delta$ = 90.4 (C-1), 72.2 (C-5), 70.0 (C-4), 62.5 (C-3), 62.4 (C-2), 60.2 ppm (C-6); β-Anomer: $\delta$ = 95.5 (C-1), 78.2 (C-5), 70.1 (C-4), 65.8 (C-3), 64.5 (C-2), 59.9 ppm (C-6); MS (ESI$^+$): *m/z*: 467 [*M*+Na]$^+$, 483 [*M*+K]$^+$.

**(*SP*-4-3)-diiodo(2,3-diamino-2,3-dideoxy-D-glucose-κ$^2$*N,N′*)platinum(II) 2.** A solution of potassium iodide (2.5 g, 15.1 mmol) in water (5 mL) was added to a solution of potassium tetrachloroplatinate (1.24 g, 2 mmol) in water (1 mL). The mixture was stirred for 30 min at room temperature before a solution of 2,3-diamino-2,3-dideoxy-D-glucopyranose hydrochloride **1 i** (1.17 g, 4.7 mmol) and potassium hydroxide (0.391 g, 7 mmol) in water (2 mL) was added. The reaction mixture was stirred for 12 h at room temperature and kept at 4 °C for 48 h. The resulting yellow precipitate was filtered off, washed with acetone (2×0.1 mL), recrystallized from water, and dried in vacuum. Yield: 1.23 g (73%); mp: 233 °C (decomp.); Elemental analysis, found C, 11.42; H, 2.32; N, 4.29. Calcd for $C_6H_{14}I_2N_2O_4Pt$ (627 g mol$^{-1}$) C, 11.49; H, 2.25; N,

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4.46; $[\alpha]_D^{20}=-83\pm2$ ($c=0.25$ in water for 24 h); $^1$H NMR (400.13 MHz, $D_2O$, 25 °C): α-Anomer: $\delta=5.27$ (d, $^3J$ (H-2,H-1)=3.5 Hz, 1H; H-1), 3.79 (dd, $^2J$ (H-6′,H-6)=12.0 Hz, $^3J$ (H-5,H-6)=2.0 Hz, 1H; H-6), 3.70 (dd, $^3J$ (H-5,H-6′)=5.0 Hz, 1H; H-6′), 3.62 (m, 1H; H-5), 3.51 (t, $^3J$ (H-3,H-4), $^3J$ (H-5,H-4)=9.8 Hz, 1H; H-4), 2.91 (dd, $^3J$ (H-2,H-3)=12.3 Hz, $^3J$ (H-4,H-3)=9.8 Hz, 1H; H-3), 2.79 ppm (dd, 1H; H-2); β-Anomer: $\delta=4.75$ (d, $^3J$ (H-2,H-1)=8.0 Hz, 1H; H-1), 3.84 (dd, $^2J$ (H-6′,H-6)=12.5 Hz, $^3J$ (H-5,H-6)=2.0 Hz, 1H; H-6), 3.66 (dd, $^3J$ (H-5,H-6′)=5.2 Hz, 1H; H-6′), 3.50 (t, $^3J$ (H-3,H-4), $^3J$ (H-5,H-4)=9.8 Hz, 1H; H-4), 3.31 (ddd, 1H; H-5), 2.73 (dd, $^3J$ (H-2,H-3)=12.0 Hz, 1H; H-3), 2.50 ppm (dd, 1H; H-2); $^{13}$C NMR (100.63 MHz, $D_2O$, 25 °C): α-Anomer: $\delta=90.5$ (C-1), 72.2 (C-5), 70.1 (C-4), 63.1 (C-3), 62.8 (C-2), 60.2 ppm (C-6); β-Anomer: $\delta=95.5$ (C-1), 78.3 (C-5), 70.1 (C-4), 66.4 (C-3), 65.1 (C-2), 59.9 ppm (C-6); MS (ESI$^+$): *m/z*: 650 $[M+Na]^+$.

**(*SP*-4-3)-(2,3-diamino-2,3-dideoxy-D-glucose-κ$^2$*N,N′*)(oxalato-κ$^2$*O,O′*)platinum(II) 3.** A solution of silver nitrate (163 mg, 0.96 mmol) in water (0.6 mL) was added to a suspension of (*SP*-4-3)-diiodo(2,3-diamino-2,3-dideoxy-D-glucose-κ$^2$*N,N′*)platinum(II) **2** (300 mg, 0.48 mmol) in water (3 mL). The reaction mixture was stirred for 1 h and the silver iodide was removed by centrifugation. The freshly prepared sodium oxalate solution [from oxalic acid (39 mg, 0.43 mmol) and sodium hydroxide (17 mg, 0.43 mmol) in water (1 mL)] was added to the centrifugate and the reaction mixture was stirred for 12 h at room temperature. The resulting (*SP*-4-3)-(2,3-diamino-2,3-dideoxy-D-glucose-κ$^2$*N,N′*)(oxalato-κ$^2$*O,O′*)platinum(II) **3** was precipitated by the addition of acetone (30 mL), filtered off, and dried in vacuum. Yield: 100 mg (45%); mp: 212 °C (decomp.); Elemental analysis, found C, 20.55; H, 3.29; N, 5.82. Calcd for $C_8H_{14}N_2O_8Pt$ (461 g mol$^{-1}$) C, 20.83; H, 3.06; N, 6.07; $[\alpha]_D^{20}=-60\pm2$ ($c=0.25$ in water for 24 h); $^1$H NMR (400.13 MHz, $D_2O$, 25 °C): α-Anomer: $\delta=5.26$ (d, $^3J$ (H-2,H-1)=3.0 Hz, 1H; H-1), 3.77 (dd, $^2J$ (H-6′,H-6)=12.0 Hz, $^3J$ (H-5,H-6)=1.5 Hz, 1H; H-6), 3.68 (dd, $^3J$ (H-5,H-6′)=5.0 Hz, 1H; H-6′), 3.62 (m, 1H; H-5), 3.47 (m, 1H; H-4), 2.81 (dd, $^3J$ (H-4,H-3)=9.8 Hz, $^3J$ (H-2,H-3)=12.3 Hz, 1H; H-3), 2.68 ppm (dd, 1H; H-2); β-Anomer: $\delta=4.70$ (m, 1H; H-1), 3.77 (dd, $^2J$ (H-6′,H-6)=12.0 Hz, $^3J$ (H-5,H-6)=1.5 Hz, 1H; H-6), 3.68 (dd, $^3J$ (H-5,H-6′)=5.0 Hz, 1H; H-6′), 3.47 (m, 1H; H-4), 3.30 (m, 1H; H-5), 2.59 (dd, $^3J$ (H4,H3)=9.5 Hz, $^3J$ (H2,H3)=12.0 Hz, 1H; H-3), 2.38 ppm (dd, 1H; H-2); $^{13}$C NMR (100.63 MHz, $D_2O$, 25 °C): α-Anomer: $\delta=168.7$ (CO), 90.3 (C-1), 72.2 (C-5), 69.8 (C-4), 61.7 (C-3), 61.6 (C-2), 59.8 ppm (C-6); β-Anomer: $\delta=168.7$ (CO), 95.5 (C-1), 78.3 (C-5), 69.8 (C-4), 65.1 (C-3), 63.7 (C-2), 60.1 ppm (C-6); MS (ESI$^+$): *m/z*: 484 $[M+Na]^+$, 500 $[M+K]^+$, 522 $[M+Na+K-H]^+$.

**(*SP*-4-3)-(2,3-diamino-2,3-dideoxy-D-glucose-κ$^2$*N,N′*)(malonato-κ$^2$*O,O′*)platin(II) 4.** An aqueous solution of silver nitrate (163 mg, 0.96 mmol) in water (1 mL) was added to a suspension of (*SP*-4-3)-diiodo(2,3-diamino-2,3-dideoxy-D-glucose-κ$^2$*N,N′*)platinum(II) (300 mg, 0.48 mmol) in water (3 mL). The reaction mixture was stirred for 1 h, silver iodide was removed by centrifugation, and a solution of sodium malonate (70.8 mg, 0.48 mmol) in water (1 mL) was added to the centrifugate. The reaction mixture was stirred for 12 h at room temperature, and the resulting complex (*SP*-4-3)-(2,3-diamino-2,3-dideoxy-D-glucose-κ$^2$*N,N′*)(malonato-κ$^2$*O,O′*)platinum(II) was precipitated by the addition of acetone (30 mL), filtered off, and dried in vacuum. Yield: 139 mg (61%); mp: 235 °C (decomp.); Elemental analysis, found C, 22.44; H, 3.22; N, 5.69, Calcd for $C_9H_{16}N_2O_8Pt$ (475 g mol$^{-1}$) C, 22.73; H, 3.39; N, 5.89; $[\alpha]_D^{20}=-51\pm2$ ($c=0.25$ in water for 24 h); $^1$H NMR (400.13 MHz, $D_2O$, 25 °C): α-Anomer: $\delta=5.22$ (d, $^3J$ (H2,H1)=3.0 Hz, 1H; H-1), 3.75 (dd, $^2J$ (H-6′,H-6)=12.0 Hz, $^3J$ (H-5,H-6)=2.0 Hz, 1H; H-6), 3.68 (dd, $^3J$ (H-5,H-6′)=4.7 Hz, 1H; H-6′), 3.59 (ddd, $^3J$ (H-4,H-5)=9.5 Hz, 1H; H-5), 3.45 (t, $^3J$ (H-3,H-4), $^3J$ (H-5,H-4)=9.8 Hz, 1H; H-4), 2.93 (dd, $^3J$ (H-4,H-3)=10.0 Hz, $^3J$ (H-2,H-3)=12.0 Hz, 1H; H-3) 2.73 ppm (dd, 1H; H-2); β-Anomer: $\delta=4.75$–4.67 (m, 1H, H-1), 3.81 (dd, $^2J$ (H-6′,H-6)=12.5 Hz, $^3J$ (H-5,H-6)=2.0 Hz, 1H; H-6), 3.64 (dd, $^3J$ (H-5,H-6′)=5.5 Hz, 1H; H-6′), 3.45 (t, $^3J$ (H-3,H-4), $^3J$ (H-5,H-4)=9.8 Hz, 1H; H-4), 3.29 (ddd, 1H; H-5), 2.64 (dd, $^3J$ (H-4,H-3)=10.0 Hz, $^3J$ (H-2,H-3)=12.0 Hz, 1H; H-3), 2.43 ppm (dd, 1H; H-2); $^{13}$C NMR (100.63 MHz, $D_2O$, 25 °C): α-Anomer: $\delta=178.6$ (CO), 90.2 (C-1), 72.2 (C-5), 69.8 (C-4), 61.9 (C-3), 61.7 (C-2), 59.9 ppm (C-6); β-Anomer: $\delta=178.6$ (CO), 95.4 (C-1), 78.2 (C-5), 69.7 (C-4), 65.2 (C-3), 63.9 (C-2), 60.1 ppm (C-6); MS (ESI$^+$): *m/z*: 498 $[M+Na]^+$.

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