## **Electronic Supporting Information (ESI)**

# An albumin-based tumor-targeted oxaliplatin prodrug with distinctly improved anticancer activity *in vivo*

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#### Materials and methods

Potassium tetrachloridoplatinate (K<sub>2</sub>PtCl<sub>4</sub>) was purchased from Johnson Matthey (Switzerland). Water for synthesis was taken from a reverse osmosis system and distilled twice before use. For HPLC measurements Milli-Q water (18.2 MΩ·cm, Merck Milli-Q Advantage, Darmstadt, Germany) was used. Other chemicals and solvents were purchased from commercial suppliers (Sigma Aldrich, Merck, Acros, Fluka and Fisher Scientific). Cisplatin<sup>1</sup> (1) and oxaliplatin<sup>2</sup> (2) were prepared according to literature procedures. Thereafter, the complexes were oxidized with hydrogen peroxide (50%) using either methanol<sup>3</sup> or acetic acid<sup>4</sup> as a solvent to yield the unsymmetrically oxidized platinum(IV) precursors 3-6. The maleimide- and succinimide-functionalized ligands were prepared as recently published.<sup>5</sup> Electrospray ionization (ESI) mass spectra were recorded on a Bruker amaZon SL ion trap mass spectrometer in positive and/or negative mode by direct infusion. High resolution mass spectra were measured on a Bruker maXis™ UHR ESI time of flight mass spectrometer. All mass spectra were recorded at the Mass Spectrometry Centre of the University of Vienna. One- and two-dimensional <sup>1</sup>H-, <sup>13</sup>C-, <sup>15</sup>N- and <sup>195</sup>Pt- NMR spectra were recorded on a Bruker Avance III 500 MHz spectrometer at 500.10 (<sup>1</sup>H), 127.75 (<sup>13</sup>C), 50.68 (<sup>15</sup>N), and 107.51 (<sup>195</sup>Pt) MHz at 298 K. For <sup>1</sup>H- and <sup>13</sup>C-NMR spectra the solvent residual peak was taken as internal reference, whereas <sup>195</sup>Pt-shifts were referenced relative to external K<sub>2</sub>PtCl<sub>4</sub> and <sup>15</sup>N-shifts relative to external NH<sub>4</sub>Cl. Elemental analysis measurements were performed on a Perkin Elmer 2400 CHN Elemental Analyzer at the Microanalytical Laboratory of the University of Vienna.

## Synthesis

## General procedure for the synthesis of compounds 7–14:

The unsymmetrically, oxidized platinum(IV) compound (**3**–**6**) and the corresponding isocyanate were transferred into a Schlenk flask and set under argon atmosphere. After the addition of dry DMF, the suspension was stirred overnight. A remaining precipitate was filtered, before the DMF was removed under reduced pressure. The residue were taken up as a suspension in methanol and fully precipitated by addition of diethylether. After a few hours in the fridge the crude product was filtered off, washed with diethylether and dried under reduced pressure. The solid was taken up in water and filtered before it was purified by preparative RP-HPLC. Collected product fractions were concentrated, to remove methanol, thereafter lyophilized and dried under reduced pressure.

## Purification of compounds 7–14 by preparative RP-HPLC:

All compounds were purified by preparative RP-HPLC using a Waters XBridge C18 column on an Agilent 1200 Series system. Milli-Q water, containing 0.1% formic acid, and methanol were used as eluents.

## Characterization

## Compound 7

# (*OC*-6-44)-Diamminedichloridomethoxido[2-(2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)ethylcarbamato]platinum(IV)

The from compound was synthesized (*OC*-6-44)diamminedichloridohydroxidomethoxidoplatinum(IV) (140 mg, 0.40 mmol) and 1-(2isocyanatoethyl)-1*H*-pyrrole-2,5-dione (2 eq., 134 mg, 0.80 mmol) in 3 mL DMF (abs.). Purification via preparative RP-HPLC, isocratic with 8% methanol, yielded a pale yellow solid; Yield: 70.5 mg (18%); <sup>1</sup>H-NMR (DMSO- $d_6$ ):  $\delta$  = 6.98 (s, 2H, CH), 6.38 (s, 1H, NH), 6.17–5.73 (m, 6H, NH<sub>3</sub>), 3.46–3.36 (m, 2H, NCH<sub>2</sub>), 3.06–2.96 (m, 2H, NHCH<sub>2</sub>), 2.63 (bs, 3H, CH<sub>3</sub>) ppm; <sup>13</sup>C-NMR (DMSO- $d_6$ ):  $\delta$  = 171.1 (COCH), 164.8 (CONH), 134.5 (CH), 60.5 (CH<sub>3</sub>), 39.2 (NHCH<sub>2</sub>), 37.5 (NCH<sub>2</sub>) ppm; <sup>15</sup>N{<sup>1</sup>H}-NMR (DMSO-d<sub>6</sub>):  $\delta$  = 59.5 (NH), -31.7 (NH<sub>3</sub>) ppm; <sup>195</sup>Pt-NMR (DMSO- $d_6$ ):  $\delta = 2642$  (major), 2629 (minor) ppm; Two separated platinum signals were observed due to conformational isomers of the carbamate group.<sup>6</sup> HRMS (ESI-TOF): calcd. for  $[C_8H_{16}Cl_2N_4O_5Pt-Na^+]^+$ : 536.0043, found: 536.0028; elemental analysis calcd. for C<sub>8</sub>H<sub>16</sub>Cl<sub>2</sub>N<sub>4</sub>O<sub>5</sub>Pt·0.5H<sub>2</sub>O: C: 18.36, H: 3.27, N: 10.71, found: C: 18.38, H: 2.92, N: 10.32

## Compound 8

## (*OC*-6-44)-Acetatodiamminedichlorido[2-(2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)ethylcarbamato]platinum(IV)

The compound was synthesized from (*OC*-6-44)acetatodiamminedichloridohydroxidoplatinum(IV) (450 mg, 1.20 mmol) and (2 eq., 398 mg, 2.39 mmol) in 5 mL DMF (abs.). Purification via preparative RP-HPLC, isocratic with 3% methanol, yielded a pale yellow solid; Yield: 267.0 mg (42%); <sup>1</sup>H-NMR (DMSO-*d<sub>6</sub>*):  $\delta$  = 6.98 (s, 2H, CH), 6.80–6.37 (m, 6H, NH<sub>3</sub>), 6.67 (bs, 1H, NH), 3.45–3.37 (m, 2H, NCH<sub>2</sub>), 3.07–2.99 (m, 2H, NHCH<sub>2</sub>), 1.90 (s, 3H, CH<sub>3</sub>) ppm; <sup>13</sup>C-NMR (DMSO-*d<sub>6</sub>*):  $\delta$  = 178.2 (COCH<sub>3</sub>), 171.1 (COCH), 163.8 (CONH), 134.5 (CH), 38.9 (NHCH<sub>2</sub>), 37.4 (NCH<sub>2</sub>), 22.8 (CH<sub>3</sub>) ppm; <sup>15</sup>N{<sup>1</sup>H}-NMR (DMSO*d<sub>6</sub>*):  $\delta$  = 59.2 (*N*H), -39.4 (*N*H<sub>3</sub>) ppm; <sup>195</sup>Pt-NMR (DMSO-*d<sub>6</sub>*):  $\delta$  = 2880 (major), 2860 (minor) ppm; HRMS (ESI-TOF): calcd. for [C<sub>9</sub>H<sub>16</sub>Cl<sub>2</sub>N<sub>4</sub>O<sub>6</sub>Pt-Na<sup>+</sup>]<sup>+</sup>: 564.9944, found: 564.9977; elemental analysis calcd. for  $C_9H_{16}Cl_2N_4O_6Pt \cdot 1.5H_2O$ : C: 18.99, H: 3.36, N: 9.84, found: C: 18.73, H: 3.18, N: 9.70

## **Compound 9**

## (OC-6-44)-Diamminedichloridomethoxido[2-(2,5-dioxopyrrolidin-1-

## yl)ethyl)carbamato]platinum(IV)

The compound was synthesized from (*OC*-6-44)diamminedichloridohydroxidomethoxidoplatinum(IV) (200 mg, 0.57 mmol) and 1-(2isocyanatoethyl)pyrrolidine-2,5-dione (1.5 eq., 145 mg, 0.86 mmol) in 3 mL DMF (abs.). Purification via preparative RP-HPLC, isocratic with 5% methanol, yielded a pale yellow solid; Yield: 124.2 mg (42%); <sup>1</sup>H-NMR (DMSO- $d_6$ ):  $\delta$  = 6.32 (s, 1H, NH), 6.20–5.70 (m, 6H, NH<sub>3</sub>), 3.47-3.29 (m, 2H, NCH<sub>2</sub>), 3.10-2.92 (m, 2H, NHCH<sub>2</sub>), 2.63 (bs, 3H, CH<sub>3</sub>), 2.58 (bs, 4H, COCH<sub>2</sub>) ppm; <sup>13</sup>C-NMR (DMSO- $d_6$ ):  $\delta$  = 177.9 (COCH<sub>2</sub>), 164.9 (CONH), 60.5 (CH<sub>3</sub>), 38.3 (bs, NHCH<sub>2</sub>, NCH<sub>2</sub>), 28.1 (COCH2) ppm; <sup>195</sup>Pt-NMR (DMSO- $d_6$ ):  $\delta$  = 2642 (major), 2629 (minor) ppm; HRMS (ESI-TOF): calcd. for [C<sub>8</sub>H<sub>18</sub>Cl<sub>2</sub>N<sub>4</sub>O<sub>5</sub>Pt-Na<sup>+</sup>]<sup>+</sup>: 538.0200, found: 538.0195; elemental analysis calcd. for C<sub>8</sub>H<sub>18</sub>Cl<sub>2</sub>N<sub>4</sub>O<sub>5</sub>Pt: C: 18.61, H: 3.51, N: 10.85, found: C: 18.73, H: 3.66, N: 10.22

## **Compound 10**

## (OC-6-44)-Acetatodiamminedichlorido[2-(2,5-dioxopyrrolidin-1-

## yl)ethyl)carbamato]platinum(IV)

The compound from (OC-6-44)synthesized was acetatodiamminedichloridohydroxidoplatinum(IV) (600 mg, 1.60 mmol) and (1.5 eq., 402 mg, 2.39 mmol) in 5 mL DMF (abs.). Purification via preparative RP-HPLC, with a gradient from 5–10.5% methanol over 10 min, yielded a pale yellow solid; Yield: 232.2 mg (27%); <sup>1</sup>H-NMR (DMSO- $d_6$ ):  $\delta = 6.89-6.33$  (m, 7H, NH<sub>3</sub>, NH), 3.41-3.34 (m, 2H, NCH<sub>2</sub>), 3.03 (q, J = 6.2 Hz, 2H, NHCH<sub>2</sub>), 2.59 (bs, 4H, COCH<sub>2</sub>), 1.90 (s, 3H, CH<sub>3</sub>) ppm; <sup>13</sup>C-NMR (DMSO-d<sub>6</sub>): δ = 178.2 (COCH<sub>3</sub>), 177.8 (COCH<sub>2</sub>), 163.9 (CONH), 38.2 (NHCH<sub>2</sub>, NCH<sub>2</sub>), 28.1 (COCH<sub>2</sub>), 22.8 (CH<sub>3</sub>) ppm; <sup>195</sup>Pt-NMR (DMSO- $d_6$ ):  $\delta$  = 2880 (major), 2859 (minor) ppm; HRMS (ESI-TOF): calcd. for [C<sub>9</sub>H<sub>18</sub>Cl<sub>2</sub>N<sub>4</sub>O<sub>6</sub>Pt-Na<sup>+</sup>]<sup>+</sup>: 567.0100, found: 567.0138; elemental analysis calcd. for C<sub>9</sub>H<sub>18</sub>Cl<sub>2</sub>N<sub>4</sub>O<sub>6</sub>Pt·H<sub>2</sub>O: C: 19.23, H: 3.59, N: 9.96, found: C: 19.17, H: 3.35, N: 9.88

### Compound 11

## (*OC*-6-34)-[(1*R*,2*R*)-Cyclohexane-1,2-diamine]methoxidooxalato[2-(2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)ethylcarbamato]platinum(IV)

(OC-6-44)-[(1R,2R)-cyclohexane-1,2-The compound was synthesized from diamine]hydroxidomethoxidooxalatoplatinum(IV) (170 mg, 0.38 mmol) and 1-(2isocyanatoethyl)-1H-pyrrole-2,5-dione (2 eq., 127 mg, 0.76 mmol) in 7 mL DMF (abs.). Purification via preparative RP-HPLC, with a gradient from 15-35% methanol in 10 min, yielded a white solid; Yield: 88.7 mg (38%); <sup>1</sup>H-NMR (DMSO- $d_6$ ):  $\delta$  = 9.85–9.55 (m, 1H, N $H_2$ ), 8.33-8.09 (m, 1H, NH<sub>2</sub>), 7.79-7.59 (m, 1H, NH<sub>2</sub>), 7.07-6.83 (m, 1H, NH<sub>2</sub>), 6.98 (s, 2H, COCH), 6.44 (s, 1H, NH), 3.55-3.45 (m, 1H, NCH<sub>2</sub>), 3.39-3.29 (m, 1H, NCH<sub>2</sub>), 3.15-3.05 (m, 1H, NHCH<sub>2</sub>), 3.00–2.90 (m, 1H, NHCH<sub>2</sub>), 2.63–2.43 (m, 2H, CH<sub>dach</sub>), 2.41 (s, 3H, CH<sub>3</sub>), 2.19–2.07 (m, 1H, CH<sub>2,dach</sub>), 2.07–1.96 (m, 1H, CH<sub>2,dach</sub>), 1.60–1.42 (m, 3H, CH<sub>2,dach</sub>), 1.39–1.27 (m, 1H,  $CH_{2,dach}$ ), 1.25–1.07 (m, 2H,  $CH_{2,dach}$ ) ppm; <sup>13</sup>C-NMR (DMSO- $d_6$ ):  $\delta$  = 171.0 (COCH), 165.2 (CONH), 163.7 (CO<sub>ox</sub>), 163.6 (CO<sub>ox</sub>), 134.4 (COCH), 61.3 (CH<sub>dach</sub>), 59.5 (CH<sub>dach</sub>), 57.4 (CH<sub>3</sub>), 39.0 (NHCH<sub>2</sub>), 37.4 (NCH<sub>2</sub>), 30.6 (CH<sub>2,dach</sub>), 23.7 (CH<sub>2,dach</sub>), 23.6 (CH<sub>2,dach</sub>) ppm; <sup>15</sup>N{<sup>1</sup>H}-NMR (DMSO-d<sub>6</sub>):  $\delta$  = 60.9 (NH), -6.4 (NH<sub>2</sub>), -1.5 (NH<sub>2</sub>) ppm; <sup>195</sup>Pt-NMR (DMSO-d<sub>6</sub>):  $\delta$  = 3001 (major), 2995 (minor) ppm; HRMS (ESI-TOF): calcd. for [C<sub>16</sub>H<sub>24</sub>N<sub>4</sub>O<sub>9</sub>Pt-Na<sup>+</sup>]<sup>+</sup>: 634.1089, found: 634.1089; elemental analysis calcd. for C<sub>16</sub>H<sub>24</sub>N<sub>4</sub>O<sub>9</sub>Pt·H<sub>2</sub>O: C: 30.53, H: 4.16, N: 8.90, found: C: 30.29, H: 4.08, N: 8.75

## Compound 12

## (*OC*-6-34)-Acetato[(1*R*,2*R*)-cyclohexane-1,2-diamine]oxalato[2-(2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)ethylcarbamato]platinum(IV)

The compound was synthesized from (*OC*-6-44)-acetato[(1*R*,2*R*)-cyclohexane-1,2diamine]hydroxidooxalatoplatinum(IV) (200 mg, 0.42 mmol) and 1-(2-isocyanatoethyl)-1*H*pyrrole-2,5-dione (2 eq., 140 mg, 0.85 mmol) in 2 mL DMF (abs.). Purification via preparative RP-HPLC, isocratic with 15% methanol, yielded a white solid; Yield: 111.2 mg (41%); <sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>):  $\delta$  = 9.63 (bs, 1H, N*H*<sub>2</sub>), 8.74–8.00 (m, 3H, N*H*<sub>2</sub>), 6.99 (s, 2H, COC*H*), 6.79 (t, *J* = 5.9 Hz, 1H, N*H*), 3.58–3.45 (m, 1H, NC*H*<sub>2</sub>), 3.42–3.29 (m, 1H, NC*H*<sub>2</sub>), 3.19–3.08 (m, 1H, NHC*H*<sub>2</sub>), 3.01–2.89 (m, 1H, NHC*H*<sub>2</sub>), 2.70–2.60 (m, 1H, C*H*<sub>dach</sub>), 2.60–2.50 (m, 1H, C*H*<sub>dach</sub>), 2.15 (bs, 2H,  $CH_{2,dach}$ ), 1.95 (s, 3H,  $CH_3$ ), 1.59–1.10 (m, 6H,  $CH_{2,dach}$ ) ppm; <sup>13</sup>C-NMR (DMSO- $d_6$ ):  $\delta = 178.4$  (COCH<sub>3</sub>), 171.0 (COCH), 164.2 (CONH), 163.3 (CO<sub>ox</sub>), 134.5 (COCH), 61.1 ( $CH_{dach}$ ), 60.7 ( $CH_{dach}$ ), 39.0 (NHCH<sub>2</sub>), 37.2 (NCH<sub>2</sub>), 31.0 ( $CH_{2,dach}$ ), 30.9 ( $CH_{2,dach}$ ), 23.5 ( $CH_{2,dach}$ ), 23.4 ( $CH_{2,dach}$ ), 22.9 ( $CH_3$ ) ppm; <sup>195</sup>Pt-NMR (DMSO- $d_6$ ):  $\delta = 3236$  (major), 3227 (minor) ppm; HRMS (ESI-TOF): calcd. for [ $C_{17}H_{24}N_4O_{10}Pt-Na^+$ ]<sup>+</sup>: 662.1038, found: 662.1033; elemental analysis calcd. for  $C_{17}H_{24}N_4O_{10}Pt\cdot H_2O$ : C: 31.05, H: 3.99, N: 8.52, found: C: 30.96, H: 3.91, N: 8.44

## Compound 13

## (*OC*-6-34)-[(1*R*,2*R*)-Cyclohexane-1,2-diamine]methoxidooxalato[2-(2,5-dioxopyrrolidin-1yl)ethyl)carbamato]platinum(IV)

The compound synthesized from (OC-6-44)-[(1R,2R)-cyclohexane-1,2was diamine]hydroxidomethoxidooxalatoplatinum(IV) (200 mg, 0.45 mmol) and 1-(2isocyanatoethyl)pyrrolidine-2,5-dione (2 eq., 151 mg, 0.90 mmol) in 3 mL DMF (abs.). Purification via preparative RP-HPLC, isocratic with 14% methanol, yielded a white solid; Yield: 118.1 mg (43%); <sup>1</sup>H-NMR (DMSO- $d_6$ ):  $\delta$  = 9.84–9.42 (m, 1H, N $H_2$ ), 8.20 (bs, 1H, N $H_2$ ), 7.70 (bs, 1H, NH<sub>2</sub>), 6.98 (bs, 1H, NH<sub>2</sub>), 6.43 (t, J = 5.9 Hz, 1H, NH), 3.51–3.41 (m, 1H, NCH<sub>2</sub>), 3.35-3.25 (m, 1H, NCH<sub>2</sub>), 3.13-2.94 (m, 2H, NHCH<sub>2</sub>), 2.62-2.55 (m, 1H, CH<sub>dach</sub>), 2.58 (s, 4H, COCH<sub>2</sub>), 2.54–2.46 (m, 1H, CH<sub>dach</sub>), 2.41 (s, 3H, CH<sub>3</sub>), 2.17–2.08 (m, 1H, CH<sub>2.dach</sub>), 2.07–1.96 (m, 1H, CH<sub>2,dach</sub>), 1.58–1.42 (m, 3H, CH<sub>2,dach</sub>), 1.41–1.27 (m, 1H, CH<sub>2,dach</sub>), 1.22–1.08 (m, 2H,  $CH_{2,dach}$ ) ppm; <sup>13</sup>C-NMR (DMSO- $d_6$ ):  $\delta = 177.7$  (COCH<sub>2</sub>), 165.3 (CONH), 163.7 (CO<sub>ox</sub>), 163.6 (CO<sub>ox</sub>), 61.3 (CH<sub>dach</sub>), 59.5 (CH<sub>dach</sub>), 57.4 (CH<sub>3</sub>), 38.2 (NHCH<sub>2</sub>), 38.1 (NCH<sub>2</sub>), 30.6 (CH<sub>2,dach</sub>), 28.0  $(CH_{2,dach})$ , 23.7  $(CH_{2,dach})$ , 23.6  $(CH_{2,dach})$  ppm; <sup>195</sup>Pt-NMR (DMSO- $d_6$ ):  $\delta$  = 3000 (major), 2992 (minor) ppm; HRMS (ESI-TOF): calcd. for  $[C_{16}H_{26}N_4O_9Pt-Na^+]^+$ : 636.1245, found: 636.1249; elemental analysis calcd. for C<sub>16</sub>H<sub>26</sub>N<sub>4</sub>O<sub>9</sub>Pt·H<sub>2</sub>O: C: 30:43, H: 4:47, N: 8:87, found: C: 30:26, H: 4:59, N: 8:72

### Compound 14

## (*OC*-6-34)-Acetato[(1*R*,2*R*)-cyclohexane-1,2-diamine]oxalato[2-(2,5-dioxopyrrolidin-1yl)ethyl)carbamato]platinum(IV)

The compound was synthesized from (*OC*-6-44)-acetato[(1*R*,2*R*)-cyclohexane-1,2diamine]hydroxidooxalatoplatinum(IV) (200 mg, 0.42 mmol) and 1-(2isocyanatoethyl)pyrrolidine-2,5-dione (1.5 eq., 107 mg, 0.63 mmol) in 4 mL DMF (abs.). Purification via preparative RP-HPLC, isocratic with 17% methanol, yielded a white solid; Yield: 92.2 mg (18%); <sup>1</sup>H-NMR (DMSO-*d<sub>6</sub>*):  $\delta$  = 9.76–9.25 (m, 1H, N*H*<sub>2</sub>), 8.74–8.02 (m, 3H, N*H*<sub>2</sub>), 6.76 (t, *J* = 6.0 Hz, 1H, N*H*), 3.53–3.42 (m, 1H, NC*H*<sub>2</sub>), 3.37–3.25 (m, 1H, NC*H*<sub>2</sub>), 3.14– 2.95 (m, 2H, NHC*H*<sub>2</sub>), 2.71–2.62 (m, 1H, C*H*<sub>dach</sub>), 2.62–2.53 (m, 1H, C*H*<sub>dach</sub>), 2.58 (s, 4H, COC*H*<sub>2</sub>), 2.14 (bs, 2H, C*H*<sub>2,dach</sub>), 1.95 (s, 1H, C*H*<sub>3</sub>), 1.57–1.33 (m, 4H, C*H*<sub>2,dach</sub>), 1.29–1.10 (m, 2H, C*H*<sub>2,dach</sub>) ppm; <sup>13</sup>C-NMR (DMSO-*d<sub>6</sub>*):  $\delta$  = 178.4 (COCH<sub>3</sub>), 177.7 (COCH), 164.2 (CONH), 163.3 (CO<sub>ox</sub>), 61.1 (CH<sub>dach</sub>), 60.8 (CH<sub>dach</sub>), 38.1 (NHCH<sub>2</sub>), 37.9 (NCH<sub>2</sub>), 31.0 (CH<sub>2,dach</sub>), 30.9 (CH<sub>2,dach</sub>), 28.0 (COC*H*<sub>2</sub>), 23.5 (CH<sub>2,dach</sub>), 23.4 (CH<sub>2,dach</sub>), 22.9 (CH<sub>3</sub>) ppm; <sup>195</sup>Pt-NMR (DMSO-*d<sub>6</sub>*):  $\delta$  = 3236 (major), 3225 (minor) ppm; HRMS (ESI-TOF): calcd. for [C<sub>17</sub>H<sub>26</sub>N<sub>4</sub>O<sub>10</sub>Pt-Na<sup>+</sup>]<sup>+</sup>: 664.1194, found: 664.1189; elemental analysis calcd. for C<sub>17</sub>H<sub>26</sub>N<sub>4</sub>O<sub>10</sub>Pt·1.5H<sub>2</sub>O: C: 30.54, H: 4.37, N: 8.38, found: C: 30.37, H: 3.98, N: 8.24

## Single crystal X-ray crystallography

The X-ray intensity data were measured on a Bruker D8-Venture equipped with a multilayer monochromator, a Cu-K<sub>a</sub> INCOATEC micro focus sealed tube and Kryoflex II cooling device. The results were uploaded to the CCDC (codes see Table S1). The structures were solved by direct methods and refined by full-matrix least-squares techniques. Non-hydrogen atoms were refined with anisotropic displacement parameters. Hydrogen atoms were inserted in calculated positions and refined with a riding model respectively as rotating systems. The following software was used: Frame integration, *Bruker SAINT software package*<sup>7</sup> using a narrow-frame algorithm, Absorption correction, *SADABS*,<sup>8</sup> structure solution, *SHELXL*-2013,<sup>9</sup> SHELXLE,<sup>10</sup> molecular diagrams and *OLEX2*.<sup>11</sup>

Experimental data can be found in Table S1. Crystal data, data collection parameters, and structure refinement details are given in Table S2–S3 and Table S5–S6. Molecular Structures in "Ortep View" are depicted in Figure S1 and Figure S2.

Sample	Temp [K]	Detector distance [mm]	Time/Frame [s]	#Frames	Frame width [°]	CCDC
7	100 (2)	40	40	3724	0.4	1499561
10	100 (2)	35	35	2646	0.4	1499562

**Table S1:** Experimental parameters and CCDC-codes.

Compound 7: (*OC*-6-44)-Diamminedichloridomethoxido[2-(2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)ethylcarbamato]platinum(IV)



Figure S1: Asymmetric unit of 7 drawn at 50% displacement ellipsoids.

Chemical formula	C8H16Cl2N4O5Pt	Crystal system	monoclinic	
Formula weight [g/mol]	514.24	Space group		P21/c
Temperature [K]	100.0	Z		8
Measurement method	$\Phi and \omega scans$	Volume [ų]	2835.2(3)	
Radiation (wavelength [Å])	ΜοΚα (λ = 0.71073)	Unit cell dimensions [Å] and [°]	12.2584(7)	90
Crystal size / [mm <sup>3</sup> ]	0.053 × 0.038 × 0.009		10.9135(6)	104.6597(18)
Crystal habit	clear, colorless plate		21.9058(13)	90
Density (calculated) / [g/cm³]	2409	Absorption coefficient / [mm <sup>-1</sup> ]	10299	
Abs. correction Tmin	0.6112	Abs. correction Tmax	0.7460	
Abs. correction type	multiscan	F(000) [e ]	1952.0	

Table S2: Sample and crystal data of 7.

Index ranges	-14 ≤ h ≤ 14, -13 ≤ k ≤ 13, -26 ≤ l ≤ 26	Theta range for data collection [°]	4.198 to 50.698	
Reflections number	89933	Data / restraints / parameters	5193/0/375	
Refinement method	Least squares	Final D indicas	all data	R1 = 0.0280, wR2 = 0.0443
Function minimized	$\Sigma w (F_0^2 - F_c^2)^2$	Final K Indices	l>2σ(l)	R1 = 0.0218, wR2 = 0.0429
Goodness-of-fit on F <sup>2</sup>	1148	Weighting	w=1/[σ <sup>2</sup> (F <sub>o</sub> <sup>2</sup> )+(- 0.0134P) <sup>2</sup> +9.9013P]	
Largest diff. peak and hole [e Å <sup>-3</sup> ]	1.16/-0.67	scheme	where $P = (F_0^2 + 2F_c^2)/3$	

**Table S3:** Data collection and structure refinement of compound 7.

Table S4: Selected bond lengths (Å) and angles (°) of 7.

Tuble of it Sciected Bolia	icing this (i i) and angle			
Pt(1A)-Cl(1A)	2.3132(11)	Pt(1B)-Cl(1B)	2.3012(10)	
Pt(1A)-Cl(2A)	2.3248(11)	Pt(1B)-Cl(2B)	2.2951(11)	
Pt(1A)-N(3A)	2.044(3)	Pt(1B)-N(3B)	2.043(3)	
Pt(1A)-N(4A)	2.030(4)	Pt(1B)-N(4B)	2.058(4)	
Pt(1A)-O(1A)	2.040(3)	Pt(1B)-O(1B)	2.049(3)	
Pt(1A)-O(5A)	1.980(3)	Pt(1B)-O(5B)	1.978(3)	
Cl(1A)-Pt(1A)-Cl(2A)	91.44(4)	Cl(2B)-Pt(1B)-Cl(1B)	91.76(4)	
N(4A)-Pt(1A)-N(3A)	85.92(14)	N(3B)-Pt(1B)-N(4B)	91.29(15)	
O(5A)-Pt(1A)-O(1A)	178.67(13)	O(5B)-Pt(1B)-O(1B)	178.07(12)	

Compound 10: (*OC*-6-44)-Acetatodiamminedichlorido[2-(2,5-dioxopyrrolidin-1-yl)ethyl)carbamato]platinum(IV)



**Figure S2:** Asymmetric unit of **10**, drawn at 50% displacement ellipsoids. Two Platon Alerts Level B (971) are caused by residual densities close to Pt. Also the weighting scheme points out problems in the convergence of physical properties and structure refinement.

|--|

Chemical formula	C9H20N4O7Cl2Pt	Crystal system	monoclinic	
Formula weight [g/mol]	562.28	Space group	C2/c	
Temperature [K]	100.0	Z		8
Measurement method	$\Phi and \omega scans$	Volume [Å <sup>3</sup> ]	3365.1(8)	
Radiation (wavelength [Å])	ΜοΚα (λ = 0.71073)	Unit cell dimensions [Å] and [°]	27.345(5)	90
Crystal size / [mm <sup>3</sup> ]	0.258 × 0.212 × 0.108		10.1753(11)	101.328(5)
Crystal habit	clear, colorless block		12.3345(13)	90
Density (calculated) / [g/cm³]	2220	Absorption coefficient / [mm <sup>-1</sup> ]	8696	
Abs. correction Tmin	0.3897	Abs. correction Tmax	0.7452	
Abs. correction type	multiscan	F(000) [e <sup>-</sup> ]	2160.0	

Table S6: Data collection and structure refinement of 10.

Index ranges	-32 ≤ h ≤ 32, -12 ≤	Theta range for	4.282 to 50.694	
	k ≤ 12, -14 ≤ l ≤ 14	data collection		
		[°]		
<b>Reflections number</b>	44872	Data /	3089/0/214	
		restraints /		
		parameters		
Refinement method	Least squares	Final R indices	all data	R1 = 0.0263, wR2 =
				0.0670
Function minimized	$\Sigma w(F_o^2 - F_c^2)^2$		l>2σ(l)	R1 = 0.0241, wR2 =
				0.0638
Goodness-of-fit on	1089	Weighting	$w=1/[\sigma^2(F_o^2)+$	+(0.0368P) <sup>2</sup> +20.9744P]
F <sup>2</sup>		scheme		
Largest diff. peak	2.37/-1.28	1	where	$P = (F_o^2 + 2F_c^2)/3$
and hole [e Å <sup>-3</sup> ]				

Pt(1)-Cl(1)	2.3382(8)
Pt(1)-Cl(2)	2.3216(9)
Pt(1)-N(3)	2.037(3)
Pt(1)-N(4)	2.044(3)
Pt(1)-O(1)	2.015(3)
Pt(1)-O(5)	2.012(3)
CI(2)-Pt(1)-CI(1)	91.06(3)
N(3)-Pt(1)-N(4)	92.20(12)
O(5)-Pt(1)-O(1)	175.46(10)

## Table S7: Selected bond lengths (Å) and angles (°) of 10.

### **RP-HPLC stability and binding studies**

To determine the stability, especially of the maleimide-function, 0.5 mM solutions of the complexes were prepared in triple distilled water and measured repeatedly over several hours. For determination of the binding rate towards human serum albumin (HSA), freshly prepared 1 mM aqueous solutions of a compound and HSA were mixed 1:1 and also measured repeatedly over several hours. All studies were carried out using a reversed-phase Waters XBridge C18 column on a Dionex Summit System. Milli-Q water, containing 0.1% formic acid, and methanol were used as eluents and a standard gradient from 5–95% methanol in 20 minutes was chosen. The autosampler, where the samples were incubated, was temperature controlled at 20°C and the column at 25°C. The loss of the complexes was monitored via UV-VIS detector at 225 nm and evaluated by the decrease of the compound peak area.

### **SEC-ICP-MS studies**

A reagent I grade water (>10 M $\Omega$  cm<sup>-1</sup> resistance according to ISO 3696 water specifications) purification system (Ultra Clear basic Reinstwassersystem, SG Wasseraufbereitung und Regenerierstation GmbH, Barsbüttel, Germany) was used. Ammonium acetate (≥99%), glutathione disulfide (≥98%), human serum albumin (96-99%), myoglobine from equine skeletal muscle (95-100%) and homocysteine (≥98%) were purchased from Sigma Aldrich, St. Louis, MO, USA. The platinum standard (1002±6 µg/mL) was purchased from Inorganic Ventures, Christiansburg, Virginia, USA. Methionine (≥99%) and glutathione (≥99%) were purchased from Merck (Darmstadt, Germany). Fetal Calf Serum (FCS) was kindly provided by Prof. Walter Berger from the Institute of Cancer Research, University of Vienna, Austria.

## SEC-ICP-MS stability and FCS binding studies

For sample preparation compounds **7–14** were incubated separately in FCS. For this purpose they were dissolved in water and finally diluted 1:10 in FCS to obtain a final concentration of 100  $\mu$ M. The samples were then stored in the autosampler at 37°C for 21 h and analyzed every 2:20 h.

For ICP-MS measurements an ICP-QMS ELAN DRC II PerkinElmer (Ontario, Canada) equipped with a dynamic reaction cell was used. Oxygen (purity 4.5, Linde Gas GmbH, Vienna, Austria) was used as reaction gas. The ICP-MS operation parameters are given in Table S8.

Table S8: ICP-MS operation parameters.	
Nebulizer:	PFA-ST
Spray chamber:	Cyclonic
Nebulizer gas flow:	0.9 L/min
Aux. gas flow:	1.3 L/min
Plasma gas flow:	16 L/min
Reaction gas (oxygen) flow:	0.8 L/min
ICP RF power:	1300 W
m/z measured :	194.97, 47.97

As HPLC a Rheos System (Rheos 2000, Flux Instruments AG, Basel, Switzerland) in combination with a metal-free autosampler (AS 50 autosampler) and an ICS-3000DP dual pump system– all from Dionex (Sunnyvale, CA, USA) was coupled to the ICP-QMS ELAN DRC II from PerkinElmer. Chromeleon Chromatography Management System (Version 6.40) was used for data analysis.

Table	S9:	Chromatog	raphic	conditions.
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<b>U</b> 1	
HPLC column:	BioBasic SEC-60 A, 4.6x250 mm, 5µm.
Eluent:	50 mM CH <sub>3</sub> COONH <sub>4</sub> , pH = 6.0.
Flow rate:	250 μL/min
Split flow (entering the ICP-MS):	125 μL/min
Injection volume:	2 μL
Column temperature:	Room temperature
Autosampler temperature:	37°C

The analysis was carried out in isocratic mode and the flow was split 1:1 after the column since the concentration (100  $\mu$ M) for the incubation carried out in the autosampler was too high and not suitable for the ICP-MS detector. The chromatographic conditions are shown in Table S9.

A flow injection analysis (FI) was carried out to determine the real concentration of the platinum drugs in FCS and the column recovery. The column recovery was determined at time 0 h of incubation. The results are given in Table S10.

Drug	Conc. (μM)	SD	Column Recovery (%)	SD
7	112	5	78	4
8	122	1	86	1
9	98	4	76	5
10	115	3	83	1
11	105	2	76	6
12	111	2	81	1
13	126	0	80	1
14	134	3	82	1

Table S10: Column recovery.

A protein/amino acid mix was prepared to assess the separation performance of the applied SEC-HPLC setup. The mixture contained HSA, myoglobin, GSSG, and methionine. It has to be mentioned that HSA is forming dimers over time. However, the separation of the monomer and the dimer of HSA cannot be resolved with this chromatographic column.

## Table S11: Resulting size ladder.

Compound	Time [min]	kDa
Albumin (HSA)	7.6	66
Myoglobin	7.9	17
GSSG	9.2	0.6
Methionine	13.0	0.1

## SEC-ICP-MS measurements of in vivo serum samples

The ICP-QMS iCAP Thermo Scientific (Bremen, Germany) was used. Oxygen (purity 4.5, Linde Gas GmbH, Vienna, Austria) was used as reaction gas. The ICP-MS operation parameters are given in Table S12.

Table 512. Tel MS operation parameters.			
Nebulizer:	PFA-ST		
Spray chamber:	Cyclonic		
Nebulizer gas flow:	1.01 L/min		
Aux. gas flow:	0.80 L/min		
Plasma gas flow:	14 L/min		
Reaction gas (oxygen) flow:	0.370 mL/min		
ICP RF power:	1550 W		
m/z measured:	194.97, 47.97		

 Table S12: ICP-MS operation parameters.

As HPLC system a Thermo Scientific Transcend HPLC system (San Jose, CA, USA) was coupled to the ICP-QMS iCAP Thermo Scientific. Qtegra Intelligent Scientific Data Solution (version 2.4.1800.33) was employed for the data treatment. HPLC chromatographic conditions are given in Table S13.

Table S13: Chromatographic conditions.

HPLC column:	BioBasic SEC-60 A, 4.6x250 mm, 5μm.
Eluent:	50 mM CH₃COONH₄, pH = 6.0.
Flow Rate:	250 μL/min
Injection Volume:	10 μL
Column Temperature:	Room temperature
Autosampler Temperature:	37°C

A flow injection analysis (FI) was carried out to determine the real concentration of the platinum drugs in FCS and the column recovery. The results are given in Table S14.

		Dtaana			Column		
Drug	Mouse	ρτ conc. (μg/L)	St. dev.	RSD (%)	recovery (%)	St. dev.	RSD (%)
	#1	5590	54	1	95	1	1
12	#2	6068	75	1	85	1	1
12	#3	6305	43	1	95	1	1
	#4	6304	28	0	42	0	0
	#1	5869	41	1	70	1	1
	#2	6213	65	1	75	1	1
11	#3	6546	52	1	84	1	1
	#4	7675	88	1	98	1	1
	#1	3230	36	1	75	1	1
0	#2	2506	27	1	78	1	1
8	#3	2671	17	1	77	1	1
	#4	2798	25	1	72	1	1
Cisplatin	#1	48	1.5	3	88	11	12
	#2	46	0.4	1	99	4	4
	#3	43	0.2	0	80	2	2
	#4	44	1.0	2	94	10	10

Table S14: Column recovery.

## **DLS** measurements

The samples were prepared by incubating 100  $\mu$ M HSA with either 5 eq. of the oxaliplatinbased maleimide compound **12** or 5 eq. of the cisplatin-based maleimide compound **8** in 50 mM phosphate buffer (pH=7.4) for 6 h on a stirring table. As a reference, a HSA sample in 50 mM phosphate buffer (pH=7.4) without addition of a platinum compound was also put on a stirring table for 6 h. Prior to the measurements, the samples were diluted 1/9 (v/v) with 50 mM phosphate buffer (pH=7.4). The DLS spectra were recorded on a Malvern ZetaSizer Nano ZS (Malvern Instruments Ltd., Malvern, UK) equipped with a 4 mW He–Ne, 632.8 nm laser beam at 25 °C and at a scattering angle of 173 °.

### In vivo studies

## **Cell culture**

The murine (Balb/c) colon cancer cell model CT-26 (purchased from American Type Culture Collection, Manassas, VA, USA) was used. Cells were grown in DMEM/F12 (1:1) supplemented with 10% FCS. All cell culture media and reagents were purchased from Sigma-Aldrich Austria.

### Animals

Six- to eight-week-old Balb/c mice (~20-25 g) were purchased from Harlan Laboratories (San Pietro al Natisone, Italy). The animals were kept in a pathogen-free environment and every procedure was done in a laminar airflow cabinet. The experiments were done according to the regulations of the Ethics Committee for the Care and Use of Laboratory Animals at the Medical University Vienna (proposal number BMWF-66.009/0084-II/3b/2013), the U.S. Public Health Service Policy on Human Care and Use of Laboratory Animals as well as the United Kingdom Coordinating Committee on Cancer Prevention Research's Guidelines for the Welfare of Animals in Experimental Neoplasia.

## **CT-26** experiments

CT-26 cells (5x10<sup>5</sup> in serum-free medium) were injected subcutaneously into the right flank of Balb/c mice (gender is indicated in the respective figure). Animals were treated with the indicated oxaliplatin-releasing drugs at concentrations equimolar to 9 mg/kg oxaliplatin (i.v.; **12** was dissolved in 0.9% NaCl solution, **11** in 10% propylene glycol/0.9% NaCl, and oxaliplatin in 5% glucose solution according to the clinical protocol) twice a week (Mondays and Thursdays). In case of cisplatin-releasing prodrugs, a dose equimolar to 3 mg/kg cisplatin was applied twice a week. For all experiments four animals per treatment group were used. Animals were controlled for distress development every day and tumor size was assessed regularly by caliper measurement. Tumor volume was calculated using the formula: (length × width<sup>2</sup>). The experiments with oxaliplatin, **11** and **12** in male mice were performed twice with two different endpoints: 1) overall survival and 2) collection of organ and tumor material 24 h after the last day of treatment. In the second experiments, tumors were formalin-fixed and paraffin-embedded. The experiment with oxaliplatin and **12** in female mice was performed only with the endpoint overall survival. For cisplatin and **8**, the experiment with endpoint of organ and tumor collection 24 h after the last day of treatment was performed. For histological evaluation, tumor tissues were sliced and haematoxylin/eosin stained by routine procedures.

## **Organ distribution experiments**

CT-26 cells (5x10<sup>5</sup> in serum-free medium) were injected subcutaneously into the right flank of Balb/c mice. When tumors reached a size of about 500 mm<sup>3</sup>, animals were treated once with the platinum compounds as described above. After 24 h, animals were anaesthetized and sacrificed by heart puncture. Serum was isolated from the collected blood samples by centrifugation at 3000 rpm for 10 min for two times and stored together with the collected tissue samples at -20 °C.

### Statistics

Results were analyzed and illustrated and statistical analyses performed (as indicated) with GraphPad Prism (GraphPad Software version 5,San Diego, CA).

## Determination of the platinum concentration in mice tissues by ICP-MS

Digestion of tissue and blood samples (approx. 20 mg or 50  $\mu$ L gravimetrically) were performed with 2 ml of nitric acid (~30%) using a microwave system (Discover SP-D,CEM Microwave Technology, Germany). The following microwave parameters were used: 200 °C, 5 min ramp time, 6 min hold time and 300 W maximal power. Digested samples were diluted with Milli-Q water resulting in nitric acid concentrations <4% and platinum concentrations <15  $\mu$ g/kg.

Milli-Q water (18.2 M $\Omega$  cm, Milli-Q Advantage, Darmstadt, Germany) was used for all dilutions for ICP-MS measurements. Nitric acid ( $\geq$ 69%, TraceSELECT®, Fluka, Buchs, Switzerland) was used without further purification. Rhenium and platinum standards for ICP-MS measurements were derived from CPI International (Amsterdam, the Netherlands). All other reagents and solvents were obtained from commercial sources and were used without further purification.

The ICP-MS Agilent 7500ce (Agilent Technologies, Waldbronn, Germany) was equipped with a CETAC ASX-520 autosampler (Nebraska, USA) and a MicroMist nebulizer at a sample uptake rate of approx. 0.25 ml/min. The Agilent MassHunter software package (Workstation Software, version B.01.01, Build 123.11, Patch 4, 2012) was used for data processing. The experimental parameters for ICP-MS are summarized in Table S15. The instrument was tuned on daily basis to achieve maximum sensitivity.

Table \$15: ICP-MS parameters Agilent /500ce	Table S15: ICP-MS parameters Agilent 7500ce.				
RF power:	1560 W				
Cone material:	Nickel				
Carrier gas:	0.8–1.2 L/min				
Make up gas:	0.1–0.2 L/min				
Plasma gas:	15 L/min				
Monitored isotopes:	<sup>185</sup> Re, <sup>194</sup> Pt, <sup>195</sup> Pt				
Dwell time:	0.3 s				
Number of replicates:	10				
Number of sweeps:	100				

Table S15: ICP-MS	parameters	Agilent	7500ce.
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### **Reduction experiments**

1 mM solutions of the succinimide derivatives 9–10 and 13–14 in 100 mM phosphate buffer (pH=7.4) were freshly prepared, mixed with 10 mM solutions of ascorbic acid in 100 mM phosphate buffer (pH=7.4) and measured by RP-HPLC every hour for up to 24 h. The measurements were performed on a Dionex Summit System with a Waters XBridge C18 column. Milli-Q water, containing 0.1% formic acid, and methanol were used as eluents and a standard gradient from 5–95% methanol in 20 minutes was chosen. The autosampler, where the samples were incubated, was temperature controlled at 20°C and the column at 25°C. The reduction of the compound was monitored via UV-VIS detector at 225 nm and evaluated by the decrease of the initial compound peak area. Additionally, 1 mM solutions of the succinimide derivatives 9–10 and 13–14 in 50 mM phosphate buffer (in D<sub>2</sub>O, pD=7.4) were freshly prepared, mixed with 10 mM solutions of ascorbic acid in 50 mM phosphate buffer (in  $D_2O$ , pD=7.4) and measured by <sup>1</sup>H-NMR spectroscopy at different time points within the first 12–15 h (in case of the cisplatin-based derivatives 9–10) and within the first 42–48 h (in case of the oxaliplatin-based compounds 13–14), respectively.

## Platinum release from HSA-adduct

For the platinum release experiment, a 200 µM solution of compound **8** in 100 mM phosphate buffer (pH=7.4) was mixed 1:1 with a 1 mM solution of HSA (5 eq.) in 100 mM phosphate buffer (pH=7.4). The solution was shaken on a stirring table at room temperature for 24 h. After filtration through a 10 cm Sephadex G25 column, the high-molecular weight fraction was incubated with 10 eq. of ascorbic acid at room temperature for another 24 h. The resulting solution was measured by FI-ICP-MS for the total platinum content. Thereafter, the solution was filtered by centrifugation through a 10 kDa Amicon cut-off filter to remove the high-molecular-weight fraction and the resulting solution was analyzed by RP-HPLC chromatography coupled to an ICP-MS instrument. The result was compared to a reference run of a cisplatin standard. All measurements were performed on an HPLC Agilent 1620 infinity Bio-inert and an Agilent Triple Quadrupole ICP-MS Agilent 8800 (Agilent Technologies, Tokyo, Japan) with Agilent MassHunter software package (Work- station Software, Version C.01.03, 2016) for the data treatment. The instrument parameters and the method are summarized in **Table S16–S18**.

Table S16: HPLC Agilent 1620 infinity Bio-inert.				
HPLC column	synergi 4 μm Fusion-RP 80A, 2x150 mm.			
Eluent	A = 0.1% HCOOH, B = MeOH 0.1% HCOOH			
Flow rate	200 μL/min			
Injection volume	5 μL			
Autosampler temperature	2 °C			

Table 317. Oraclent method.			
	Time [min]	A [%]	B [%]
	0	100	0
	2.5	100	0
	6.5	70	30
	11.5	70	30
	11.6	100	0
	15.5	100	0

## Table S17: Gradient method

Nebulizer MicroMist Spray chamber Scott double-pass Nebulizer gas flow 1.05 L/min Plasma gas 15 L/min 1550 W ICP RF power

195

 Table S18: Triple Quadrupole ICP-MS Agilent 8800.

m/z measured

## **Tables and figures**

compound	number of eq. of HSA used	λ <sub>1/2</sub> [h]	_
7	1	5.1	
8	1	6.3	
11	1	8.5	
12	1	7.0	
12	2	4.5	

Table S19: Albumin-binding half-live	s of compounds <b>7–8</b> and	d 11–12 evaluated by RP-HPLC
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**Figure S3:** Size determination of HSA (red), HSA incubated with 5 eq. of compound **8** (blue) and HSA incubated with 5 eq. of compound **12** by DLS measurements.



**Figure S4:** *In vivo* **anticancer activity of 8 in comparison to cisplatin:** CT-26 cells were injected subcutaneously into the right flank of male BALB/c mice. Mice were treated twice a week (Monday and Thursday) i.v. with concentrations equimolar to 3 mg/kg cisplatin (each

experimental group contained four animals). Tumor volumes were calculated as described in the experimental part. Data are means ± SEM.



Figure S5: Apoptosis and mitosis levels in tumors after the treatment with compound 8, 11 and 12 in comparison to cis- and oxaliplatin: CT-26 cells were injected subcutaneously into the right flank of male BALB/c mice. Mice were treated twice a week (Monday and Thursday) i.v. with concentrations equimolar to 9 mg/kg oxaliplatin (in case of 11 und 12) and 3 mg/kg cisplatin (in case of 8). At day 12 after first treatment, animals were sacrificed and tumor tissues collected, formalin-fixed, paraffin-embedded and H/E-stained. The fractions of apoptotic and mitotic cells were evaluated by counting (4 pictures per sample, at least 300 cells per picture were counted). Each experimental group contained four animals (the respective tumor growth is shown in Figure 4A). an=3 because of one complete remission. The statistical significance was calculated by One-Way Anova and is indicated with asterisks (\* P < 0.05; \*\* P < 0.01; \*\*\* P < 0.001).



**Figure S6:** Reduction of the compounds **9–10** and **13–14** with 10 eq. ascorbic acid in phosphate buffer at pH=7.4 monitored by <sup>1</sup>H-NMR spectroscopy.



**Figure S7:** Normalized platinum traces of compound **8** (blue) in comparison to the reference chromatogram of cisplatin (red) measured by RP-HPLC coupled to ICP-MS.

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