SUPPLEMENTARY INFORMATION

Encapsulation of lipophilic kiteplatin Pt(IV) prodrugs in PLGA-PEG micelles.

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Content of Sup. Info.:

NMR characterization of **1** (Figure S1: 1H NMR; Figure S2: COSY; Figure S3: [^{1}H-^{195}Pt]-HSQC; Figure S4: [^{1}H-^{13}C] HSQC).

NMR characterization of **2** (Figure S5: ^{1}H NMR; Figure S6: TOCSY; Figure S7: [^{1}H-^{195}Pt]-HSQC; Figure S8: [^{1}H-^{13}C] HSQC).

IR characterization of PLGA-PEG (Figure S9: FT-IR spectrum).

Calculation of Pt atoms per NP.

NMR characterization of *cis,trans,cis*-[$PtCl_2${$O_2C(CH_2)_4CH_3$}$_2$(*cis*-1,4-DACH)] (1).

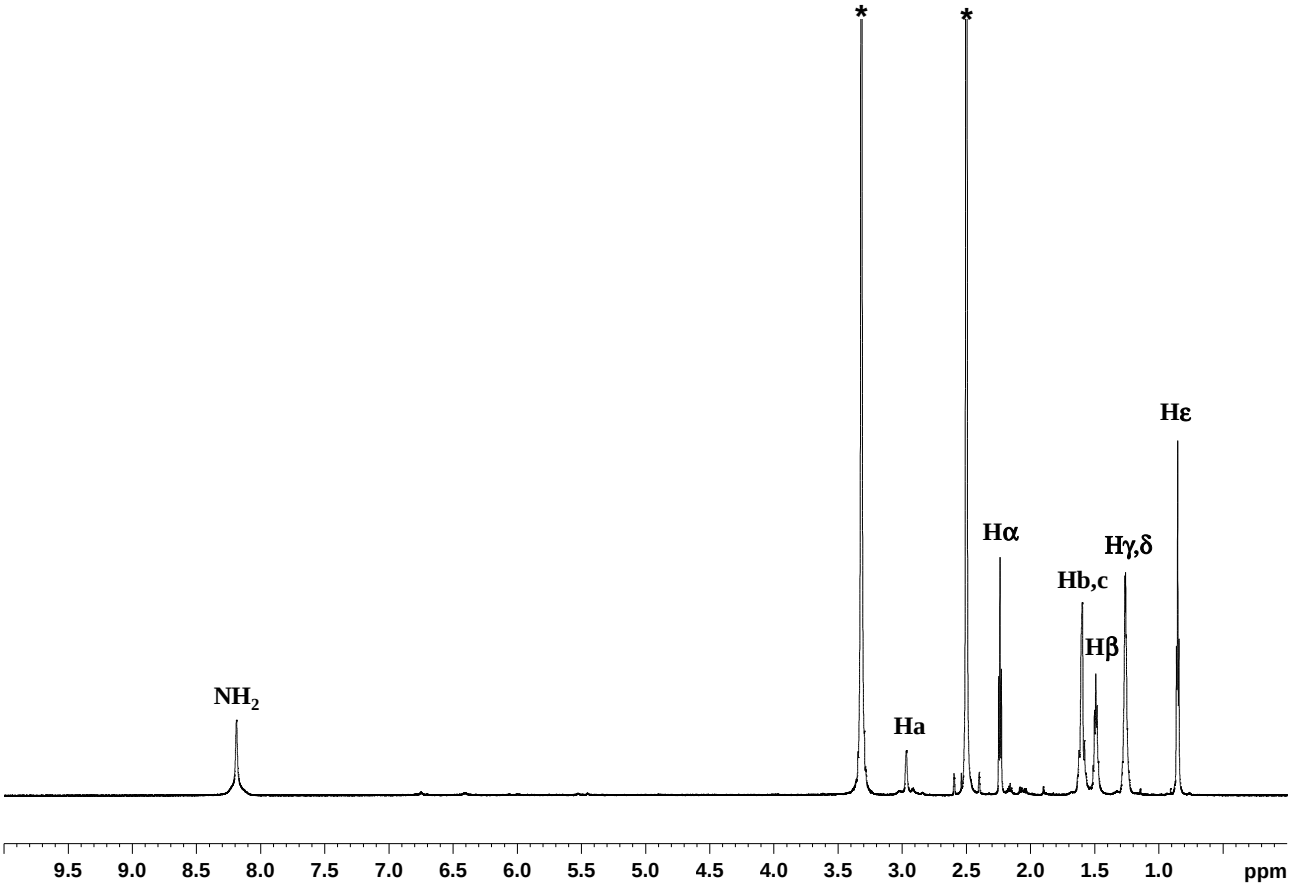

Figure S1. ^{1}H NMR (700 MHz, ^{1}H) spectrum of **1** in DMSO-d_6. The asterisks indicate residual solvent peaks.

The ^{1}H COSY 2D spectrum of compound **1** in DMSO-d_6 (Figure S2) shows a cross peak, falling at 2.96/1.58 ppm correlating the CH and CH_2 groups of coordinated DACH. A second cross peak falling at 2.22/1.47 ppm correlates the methylenic groups in α and β positions of the hexanoato ligand (see Chart 2 for numbering of protons). Finally, the cross peaks falling at 1.47/1.24 and 1.24/0.84 ppm correlate β CH_2 with γ CH_2 and γ CH_2 with the ε CH_3 of the alkyl chain, respectively.

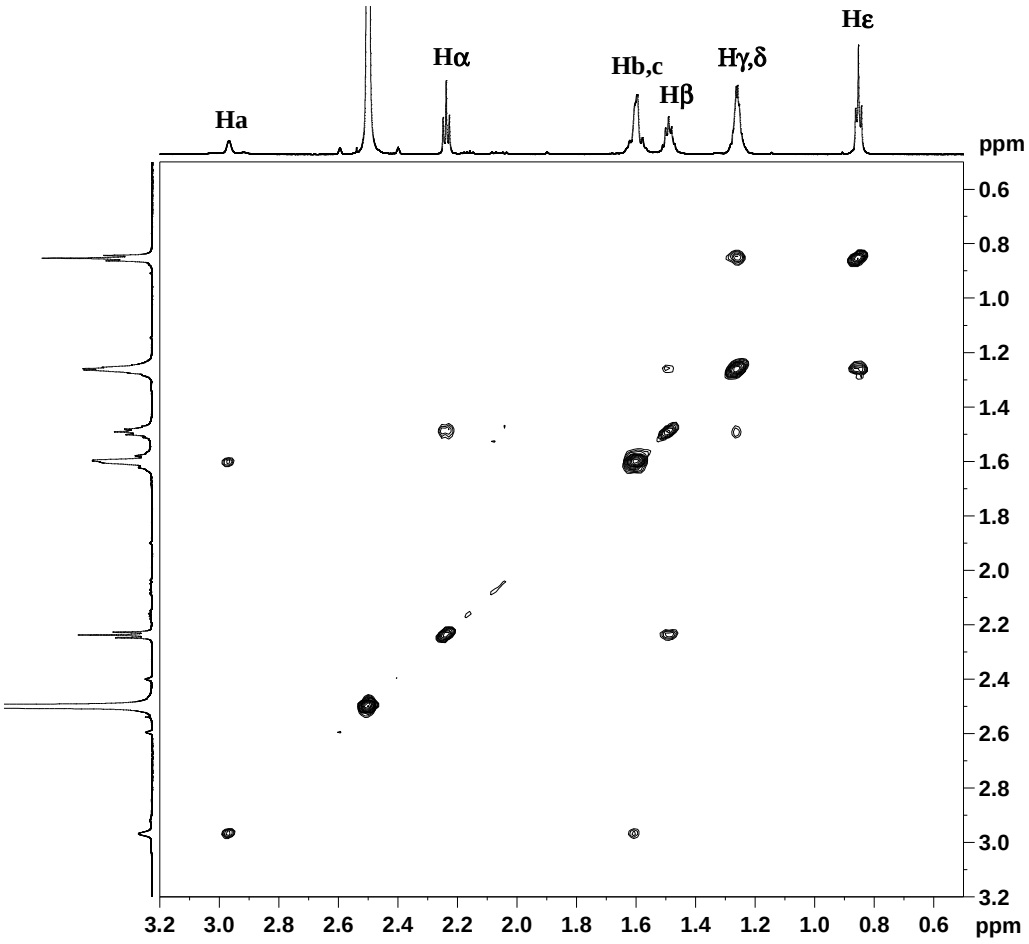

Figure S2. Portion of ^{1}H (top and left) and COSY 2D (central) NMR spectra (700 MHz, ^{1}H) of **1** in DMSO-d_6.

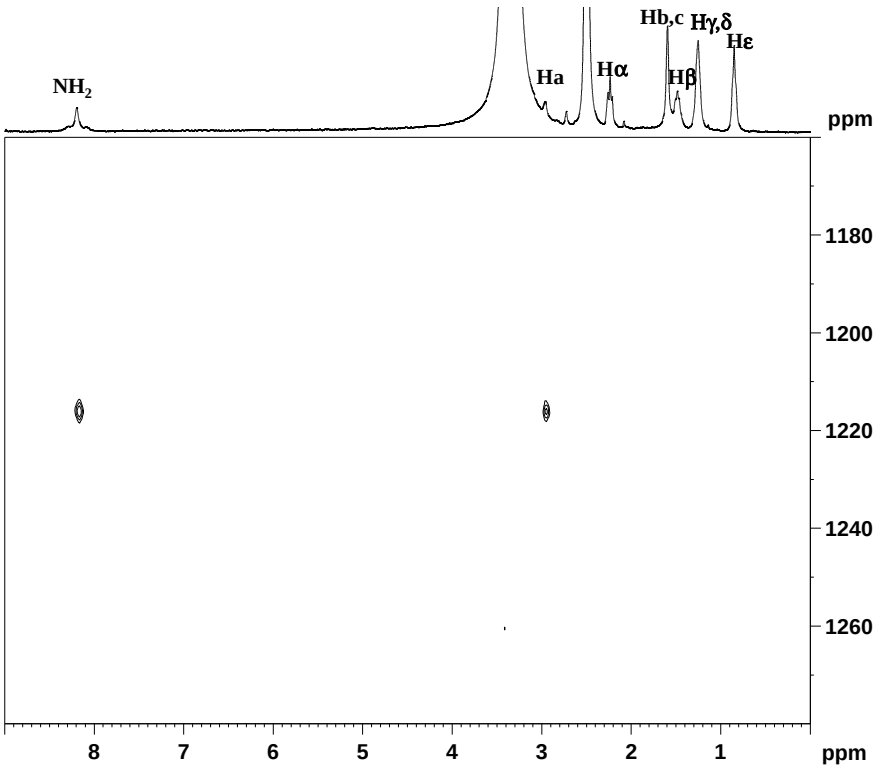

Figure S3. [^{1}H-^{195}Pt]-HSQC 2D NMR (300 MHz, ^{1}H) of **1** in DMSO-d_6.

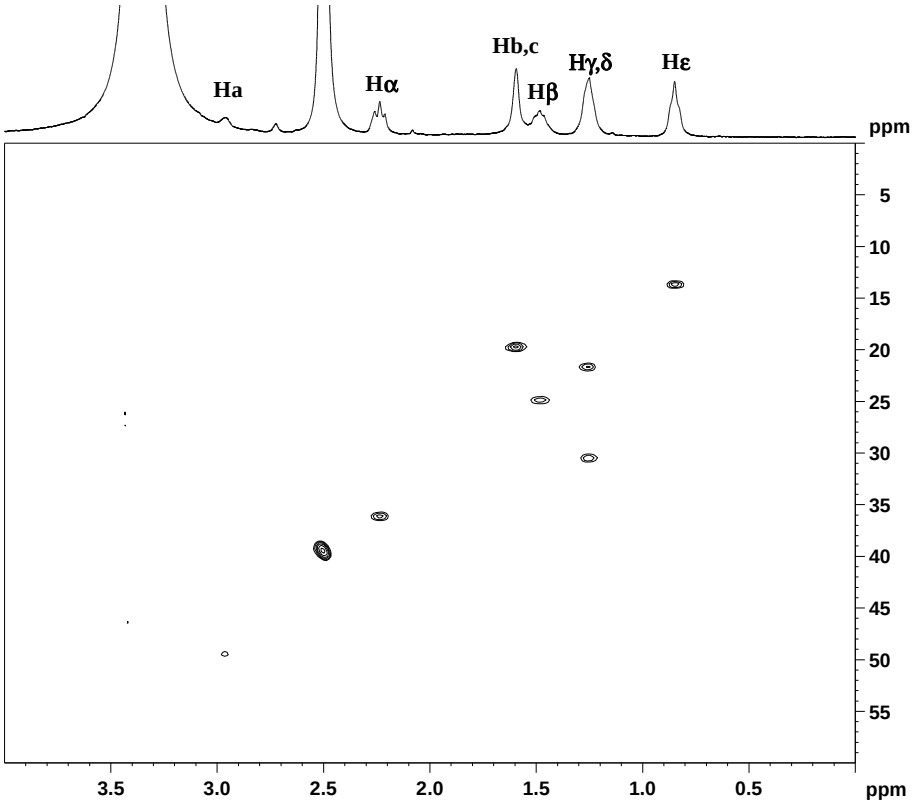

Figure S4. ^{1}H (top) and [^{1}H-^{13}C] HSQC 2D (bottom) NMR (300 MHz, ^{1}H) spectra of **1** in DMSO-d_6.

NMR characterization of *cis,trans,cis*-[$PtCl_2${$O_2C(CH_2)_8CH_3$}$_2$(*cis*-1,4-DACH)] (2).

The ^{1}H NMR of compound **2** in DMSO-d_6 showed seven different signals (Figure S5). The singlet with Pt satellites resonating at 8.19 ppm ($^2J_{H\text{-}Pt}$ = 64.3 Hz) was assigned to the aminic protons of coordinated *cis*-1,4-DACH. The singlet with Pt satellites falling at 2.96 ppm ($^3J_{Pt\text{-}H}$ = 81.0 Hz) was assigned to the methynic protons of coordinated DACH while the triplet located at 2.23 ppm and integrating for 4 protons was assigned to the CH_2 protons in α position to the carboxylate group of decanoato ligands (H_α, see Chart 2 for numbering of protons). The multiplet located at 1.59 ppm and integrating for eight protons was assigned to the methylenic groups of coordinated DACH. The quintet resonating at 1.48 ppm integrating for four protons was assigned to the CH_2 in β positions to the carboxylate group (H_β in Figure S5). The multiplet falling at 1.23 ppm and integrating for twenty-four protons was assigned to the methylenic groups in γ, δ, ε, ζ, η, and θ positions of coordinated decanoato ligand while the triplet resonating at 0.85 ppm and integrating for six protons was attributed to the terminal (ι) methyl groups (Figure S5).

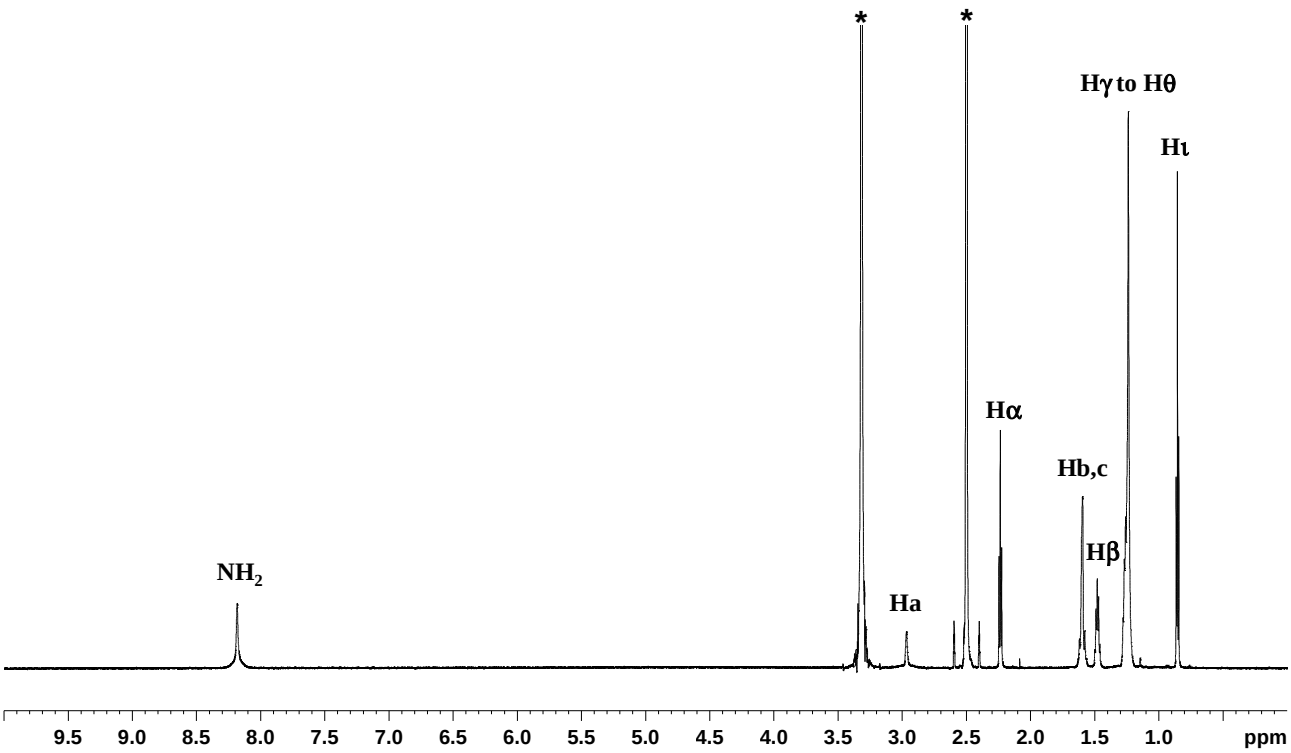

Figure S5. ^{1}H NMR (700 MHz, ^{1}H) spectrum of **2** in DMSO-d_6. The asterisks indicate residual solvent peaks.

The assignment was also supported by a TOCSY 2D NMR spectrum recorded in DMSO-d_6.

A portion of this spectrum is reported in Figure S6 and shows the cross peak falling at 2.96/1.59 ppm correlating the CH and CH_2 groups of coordinated DACH. Another cross peak falling at 2.23/1.48 ppm correlates the methylenic groups in α and β positions of the decanoato ligands. A third cross peak falling at 2.23/1.23 represents a long range coupling between the β CH_2 and one or more CH_2 overlapping at 1.23 ppm. Finally the cross peaks at 1.48/1.23 and 1.23/0.85 ppm indicate coupling between γ CH_2 and δ CH_2 and between θ CH_2 and terminal (ι) CH_3.

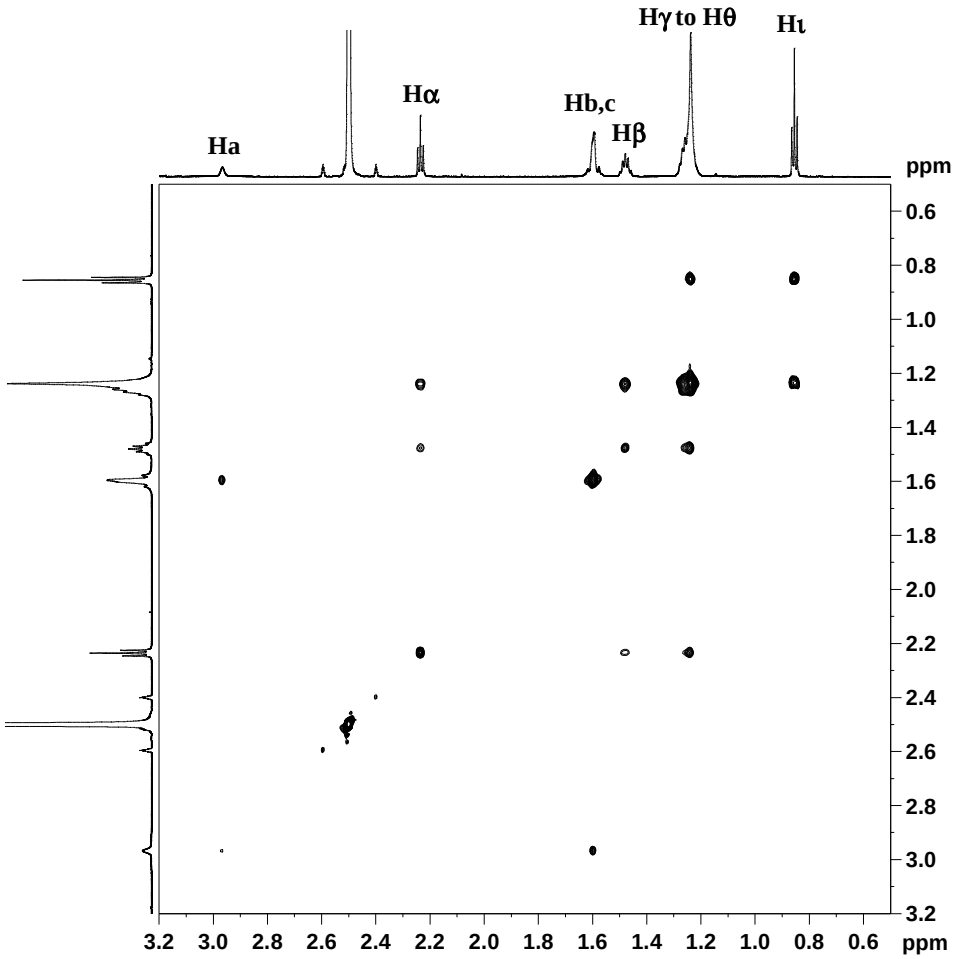

Figure S6. Portion of ^{1}H (top and left) and TOCSY 2D NMR spectra (700 MHz, ^{1}H) of **2** in DMSO-d_6.

The [^{1}H-^{195}Pt]-HSQC 2D NMR spectrum of compound **2** in DMSO-d_6 is reported in Figure S7. The spectrum shows two cross peaks falling at 8.19/1217.2 and 2.96/1217.2 ppm (^{1}H/^{195}Pt). The ^{195}Pt chemical shift is in good agreement with that reported in the literature for the same complex (1085 ppm in $CDCl_3$ referenced to Na_2PtCl_6 as external standard placed at 0.00 ppm in D_2O).[1]

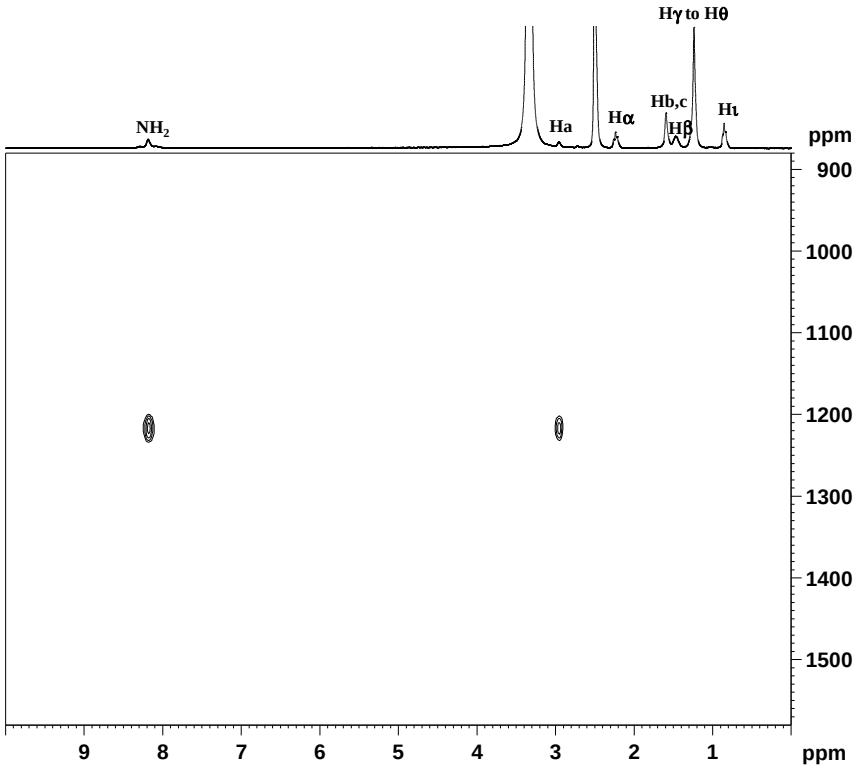

Figure S7. [^{1}H-^{195}Pt]-HSQC 2D NMR of **2** in DMSO-d_6.

The NMR characterization of the carbon atoms was obtained by a [^{1}H-^{13}C]-HSQC 2D NMR experiment performed in DMSO-d_6 (Figure S8). The cross peaks falling at 2.96/49.4 and 1.59/19.77 ppm (^{1}H/^{13}C), were attributed to the methynic and methylenic groups of DACH, respectively.

The ^{13}C chemical shifts of the alkyl chain of coordinated decanoate (13.70, 21.70, 25.22, 28.54, 30.97, and 36.27) are in good agreement with those reported in the literature for *cis,trans,cis*-$[PtCl_2\{O_2C(CH_2)_8CH_3\}_2(NH_3)_2]$ (13.97, 22.12, 25.46 28.65, 28.72, 28.95, 28.96, 31.33, and 35.70 ppm).[2]

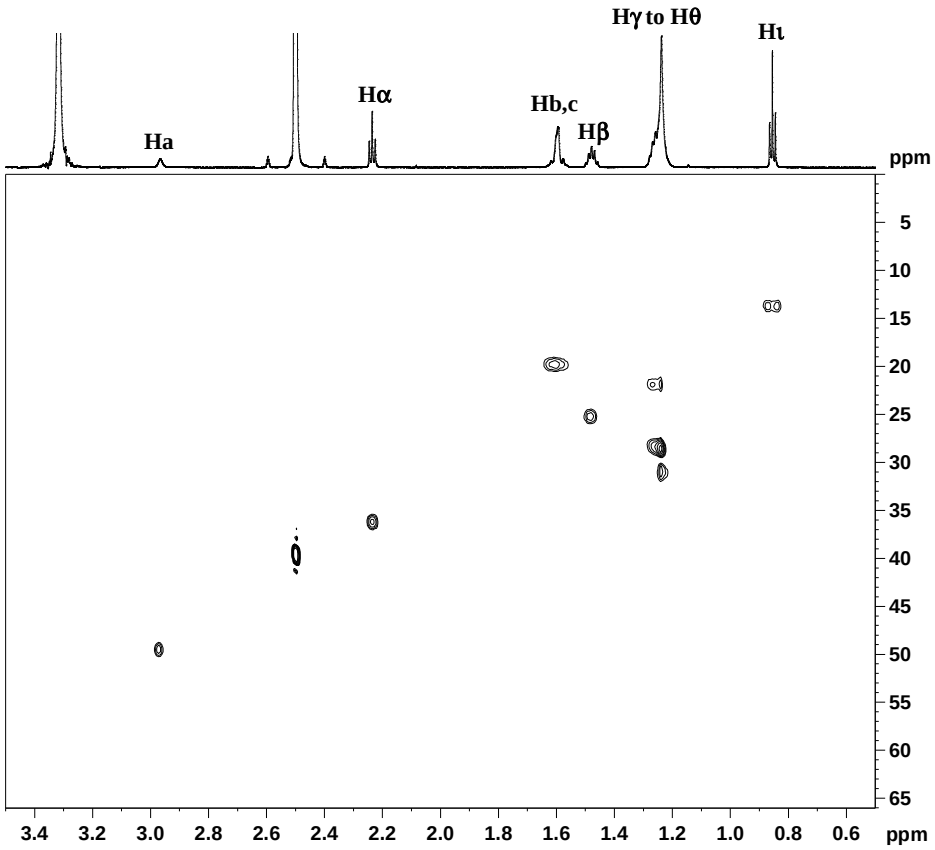

Figure S8. ^{1}H (top) and [^{1}H-^{13}C] HSQC 2D NMR (700 MHz, ^{1}H) spectra of **2** in DMSO-d_6

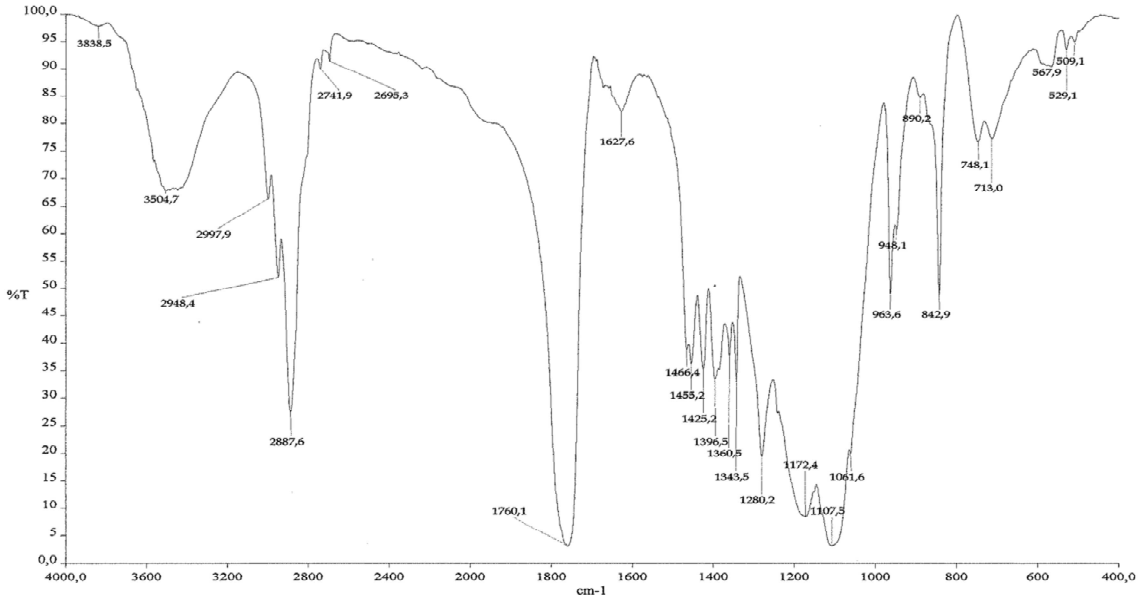

Figure S9. FT-IR spectrum of the PLGA-PEG polymer

Calculation of Pt atoms per nanoparticle.

The number of Pt atoms per nanoparticle has been calculated by entering the data reported in Table S1 in the following formula:

$$\frac{Ptatoms}{NP} = \frac{\left[Pt\_loading\left(\frac{g}{L}\right) * N\left(\frac{atoms}{mol}\right)\right]}{MW_{Pt} * [NP]\left(\frac{NPs}{mL}\right) * \ 10^3\ (\frac{mL}{L})}$$

where Pt_loading is the concentration (w/V) of Pt in the micellar solution (obtained by ICP-MS), *N* is the Avogadro's number, MW_{Pt} is the atomic weight of platinum, [NP] is the concentration of the nanoparticles has calculated by the protein utilities (DTS 5.0) software implemented in the Zetasizer Nano ZS instrument.

Table S1

Cpd_NP	[NP] (NPs/mL)	Pt_loading (g/L)	Ptatoms/NP
1	1,30E+10	0,008029975	1,91E+06
2	9,30E+09	0,007110888	2,36E+06
3	2,00E+10	0,008221723	1,27E+06
4	1,50E+10	0,007838701	1,61E+06

[1] Shamsuddin, S., Santillan, C. C., Stark, J. L., Whitmire, K. H., Siddik, Z. H., Khokhar, A. R. *J. Inorg. Biochem.* **1998**, *71*, 29-35.
[2] Johnstone T.C., Lippard S.J., *Inorg. Chem.*, **2013**, *52*, 9915–9920