

**Electronic Supplementary Information (ESI)**

**A Circular Dichroism Study Unvovers a Two-Step Interaction of  
Antitumor Azolato-Bridged Dinuclear Platinum(II) Complexes with  
Calf-Thymus DNA**

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## Experimental Section

### Materials

Cisplatin,  $cis\text{-Pt}(\text{NH}_3)_2(\text{NO}_3)_2$  (exists as  $cis\text{-[Pt}(\text{NH}_3)_2(\text{H}_2\text{O})_2]^{2+}$  or  $cis\text{-[Pt}(\text{NH}_3)_2(\text{H}_2\text{O})(\text{OH})]^+$ ) in aqueous solution at around pH 7.4), and  $[\{cis\text{-Pt}(\text{NH}_3)_2\}_2(\mu\text{-OH})_2]^{2+}$  (dihydroxo-bridged dimer, DHBD) were synthesized according to well established methods. A series of azolato-bridged dinuclear platinum(II) complexes:  $[\{cis\text{-Pt}(\text{NH}_3)_2\}_2(\mu\text{-OH})(\mu\text{-pyrazolato-}N1,N2)]^{2+}$  (**1**),  $[\{cis\text{-Pt}(\text{NH}_3)_2\}_2(\mu\text{-OH})(\mu\text{-1,2,3-triazolato-}N1,N2)]^{2+}$  (**2**),  $[\{cis\text{-Pt}(\text{NH}_3)_2\}_2(\mu\text{-OH})(\mu\text{-tetrazolato-}N1,N2)]^{2+}$  (**3**), and  $[\{cis\text{-Pt}(\text{NH}_3)_2\}_2(\mu\text{-OH})(\mu\text{-tetrazolato-}N2,N3)]^{2+}$  (**4**), were synthesized and characterized as reported elsewhere.<sup>1</sup> Calf thymus DNA type I (15–23 kbp) was purchased from Sigma (St. Louis, MO, USA) and used without further purification.

### Reaction with calf-thymus DNA

For the dose-dependent study, 30  $\mu\text{M}$  calf thymus (CT) DNA was reacted with each platinum complex at a ratio (the concentration of azolato-bridged complex/the concentration of CT DNA) of 0, 0.0333, 0.0667, 0.167, 0.333, 0.667, and 1.00 in 0.3 mM citric acid buffer (pH 7.4). (For cisplatin,  $cis\text{-[Pt}(\text{NH}_3)_2(\text{H}_2\text{O})_2]$  and DHBD, the ratios were 0, 0.0333, 0.167, 0.333, and 1.00.) The CD spectra were measured immediately after the addition of each azolato-bridged complex. For the time-dependent study, 30  $\mu\text{M}$  CT DNA was reacted with 10  $\mu\text{M}$  platinum complex in 0.3 mM citric acid buffer (pH 7.4) at 310 or 277 K for 72 h or more. The CD spectra were measured at appropriate time intervals. All measurements were conducted at 298 K using a JASCO J805 circular dichroism spectropolarimeter in the range of 220 to 340 nm at a scan rate of 50 nm/min. The cell length was 0.5 cm. The concentration of the CT DNA solution was determined spectrophotometrically at 259 nm, the absorption maximum, by using the value  $\epsilon_{\text{max}} = 6600$  ( $\text{P}^{-1} \text{cm}^{-1}$ ).

### References

- 1 S. Dhara, A rapid method for the synthesis of  $cis\text{-[Pt}(\text{NH}_3)_2\text{Cl}_2]$ . *Indian J Chem* 1970, 8. 193-194.
- 2 R. Faggiani, B. Lippert, C. Lock, B. Rosenberg, Hydroxo-bridged platinum (II) complexes. 1. Di- $\mu$ -hydroxo-bis [diammineplatinum (II)] nitrate,  $[(\text{NH}_3)_2\text{Pt}(\text{OH})_2\text{Pt}(\text{NH}_3)_2](\text{NO}_3)_2$ . Crystalline structure and vibrational spectra. *Journal of the American Chemical Society* 1977, 99. 777-781.
- 3 S. Komeda, M. Lutz, A. L. Spek, M. Chikuma, J. Reedijk, New antitumor-active azole-bridged dinuclear platinum(II) complexes: synthesis, characterization, crystal structures, and cytotoxic studies. *Inorg Chem* 2000, 39. 4230-6; S. Komeda, M. Lutz, A. L. Spek, Y. Yamanaka, T. Sato, M. Chikuma, J. Reedijk, A novel isomerization on interaction of antitumor-active azole-bridged dinuclear platinum(II) complexes with 9-ethylguanine. Platinum(II) atom migration from N2 to N3 on 1,2,3-triazole. *J Am Chem Soc* 2002, 124. 4738-46; S. Komeda, Y. L. Lin, M. Chikuma, A Tetrazolato - Bridged Dinuclear Platinum (II) Complex Exhibits Markedly High in vivo Antitumor Activity against Pancreatic Cancer. *ChemMedChem* 2011 6. 987-990.

### Reaction of 30 $\mu\text{M}$ calf-thymus DNA with 10 $\mu\text{M}$ DHBD and 1–4 at 277 K

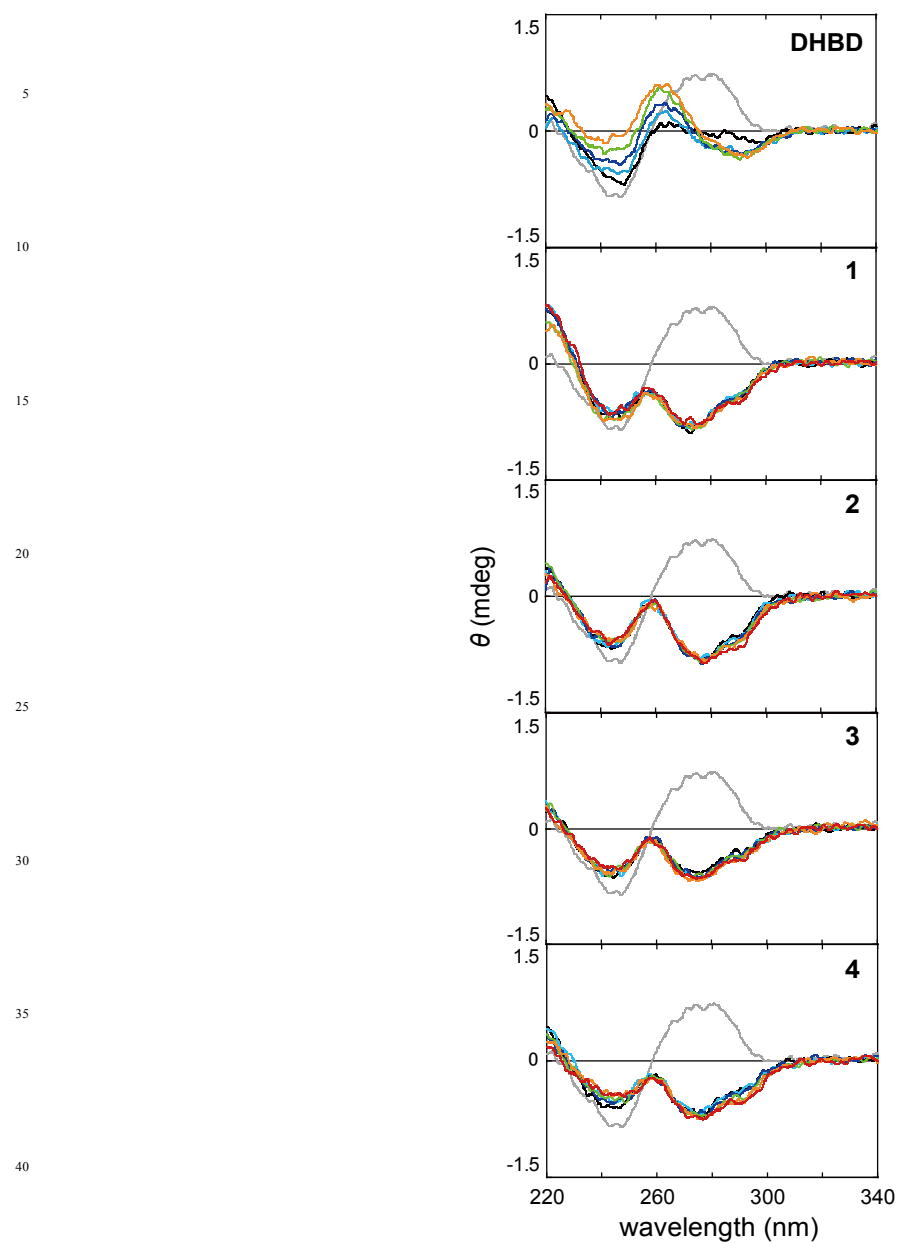


Fig. S1 CD spectra of 30  $\mu\text{M}$  calf-thymus DNA reacted with 10  $\mu\text{M}$  DHBD and 1–4 for 0 (black), 6 (light blue), 12 (blue), 24 (green), 48 (orange), and 72 h (red) at 277 K. The gray line shows the control (no azolato-bridged complex added).

### Reaction of 30 $\mu\text{M}$ calf-thymus DNA with 10 $\mu\text{M}$ $\text{cis-}[\text{Pt}(\text{NH}_3)_2(\text{H}_2\text{O})_2]^{2+}$ at 310 K

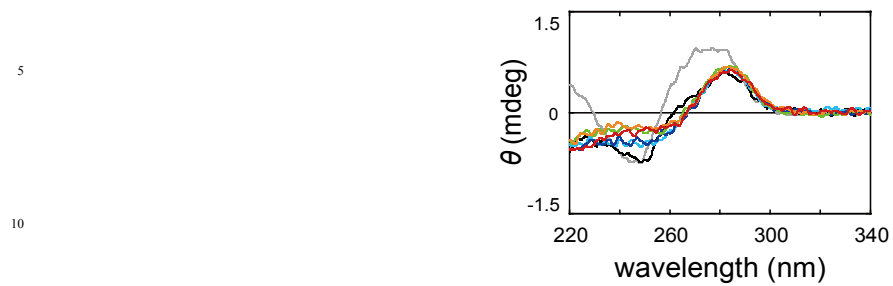


Fig. S2 CD spectra of 30  $\mu\text{M}$  calf thymus DNA reacted with 10  $\mu\text{M}$   $\text{cis-}[\text{Pt}(\text{NH}_3)_2(\text{H}_2\text{O})_2]^{2+}$  for 0 (black), 6 (light blue), 12 (blue), 24 (green), 48 (orange), and 72 h (red) at 310 K. The gray line shows the control (no azolato-bridged complex added).