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SUPPLEMENTARY MATERIAL

Structural Basis for the Structure–Activity Behaviour of Oxaliplatin and its Enantiomeric Analogues: A Molecular Dynamics Study of Platinum-DNA Intrastrand Cross-Link Adducts

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S1.1 Binding energy calculation

The free energy of each species was calculated and the binding energy is defined according to the equations shown in as follows:

$$\Delta G_{binding} = G_{complex} - G_{receptor} - G_{ligand} \quad (1)$$

$$\Delta G = \Delta E_{MM} + \Delta G_{solv} - T\Delta S$$

$$\Delta E_{MM} = \Delta E_{ele} + \Delta E_{vdw}$$

$$\Delta G_{solv} = \Delta G_{ele,sol} + \Delta G_{nonpol,sol} = \Delta G_{ele,sol} + \gamma\, \Delta SASA + b$$

In Equation (1) the free energy is split into a 'gas phase' term, containing internal composed of containing internal energy (ΔE_{MM}) and entropic (TΔS parts, and a solvation contribution (ΔG_{solv}). ΔE_{MM} denotes the molecular mechanics energy, which represents the internal energy (bond, angle and dihedral angle), van der Waals and electrostatic contributions. G_{solv} corresponds to the solvation free energy and it includes the polar contribution to solvation and nonpolar contribution, where γ, representing the surface tension, and b, being a constant, are empirical constants and in this work were set to 0.0072 kcal/(mol • Å^2) and 0, respectively. SASA is the solvent accessible surface area (Å^2) that was estimated using the MSMS algorithm with a probe radius of 1.4 Å. The conformational entropy change of the complex formation contributes to the entropy term $T\Delta S$. For reasons of computational economics and large standard deviations, we omitted the entropy term, thus it was deemed as relative binding energy. The binding energy was calculated from a single trajectory of the Pt-DNA complex with MM-PBSA, implemented in AMBER10. The average values and standard errors of the mean values were calculated from 200 snapshots in the last 10 ns of each MD trajectory.

S2.2 Bhattacharyya distance (BD) analysis

The BD(*i*,*j*) between class *i* and *j* is defined as

$BD(i,j) = 2[1 - e^{-a(i,j)}]$,

where a(i,j) is defined as $a(i,j) = \frac{1}{8}(m_i - m_j)^T \left(\frac{1}{2}(\sum_i + \sum_j)\right)^{-1}(m_i - m_j) + \frac{1}{2}\ln\left[\frac{\left|\frac{1}{2}(\sum_i + \sum_j)\right|}{\sqrt{|\sum_i||\sum_j|}}\right]$,

and m_i and $\sum_i$ denote the mean and covariance matirx of class i, respectively.

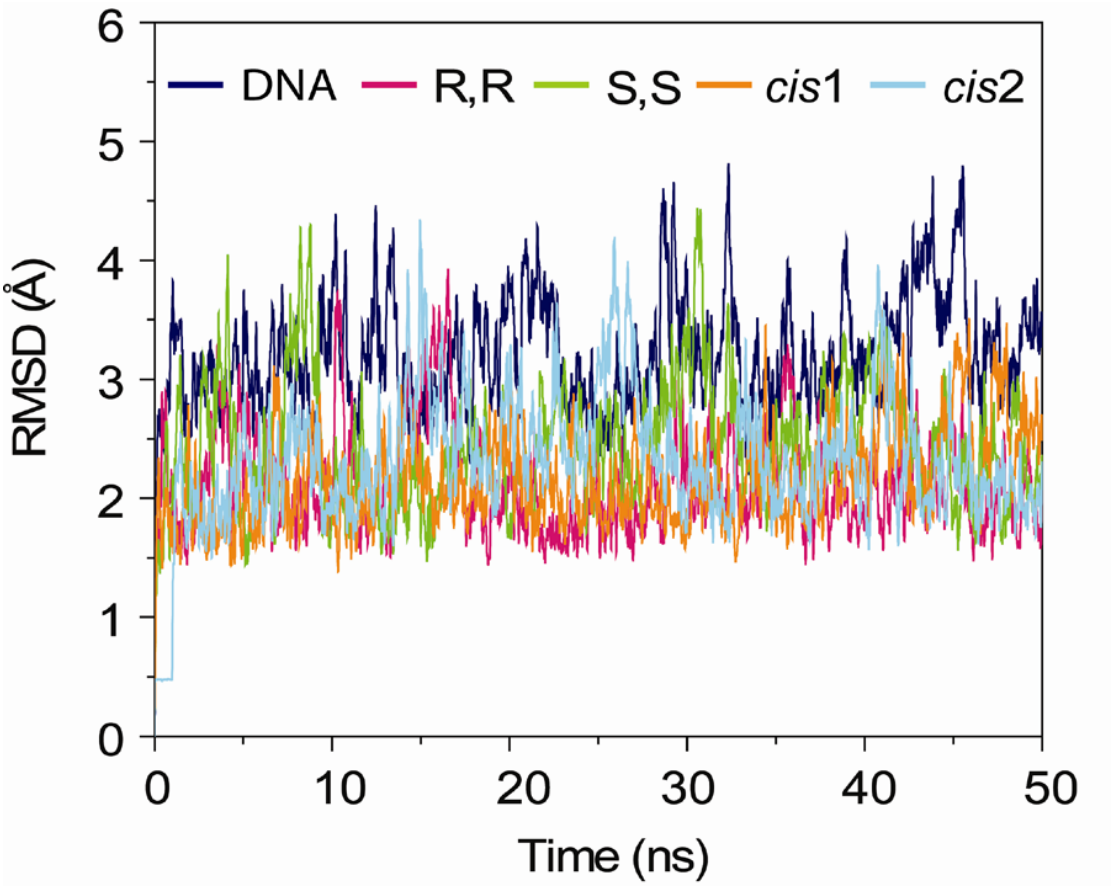

Figure S1. Root Mean Squared Deviations (RMSD) for molecular dynamics (MD) simulations over time. The undamaged DNA (navy) and drugs bound DNA (pink: *trans*-R,R-DACH-Pt-DNA; green: *trans*-S,S-DACH-Pt-DNA; orange: *cis*1- DACH-Pt-DNA; cyan: *cis*2-DACH-Pt-DNA) are represented as continuous lines. The values show that the positions of the drug-bound DNA remain fairly constant with minimal deviation.

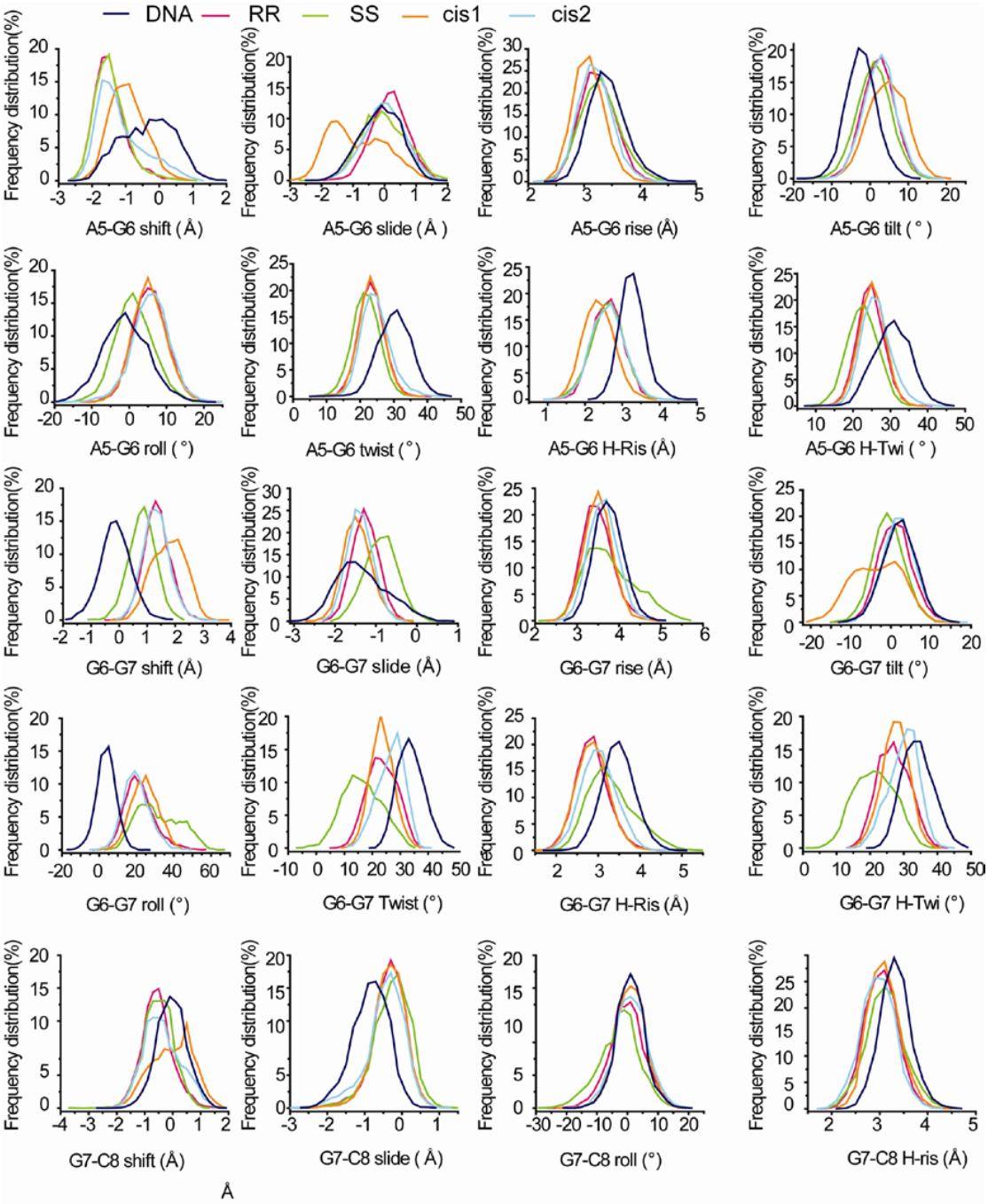

Figure S2. Selected frequency distributions of the representative DNA duplex base pair step helical parameters for the central four binding base pairs for the different crosslinks. Navy: undamaged DNA; pink: *trans*-*R*,*R*-DACH-Pt-DNA; green: *trans*-*S*,*S*-DACH-Pt-DNA; orange: *cis*1-DACH-Pt-DNA; cyan: *cis*2-DACH-Pt-DNA are represented as continuous lines.

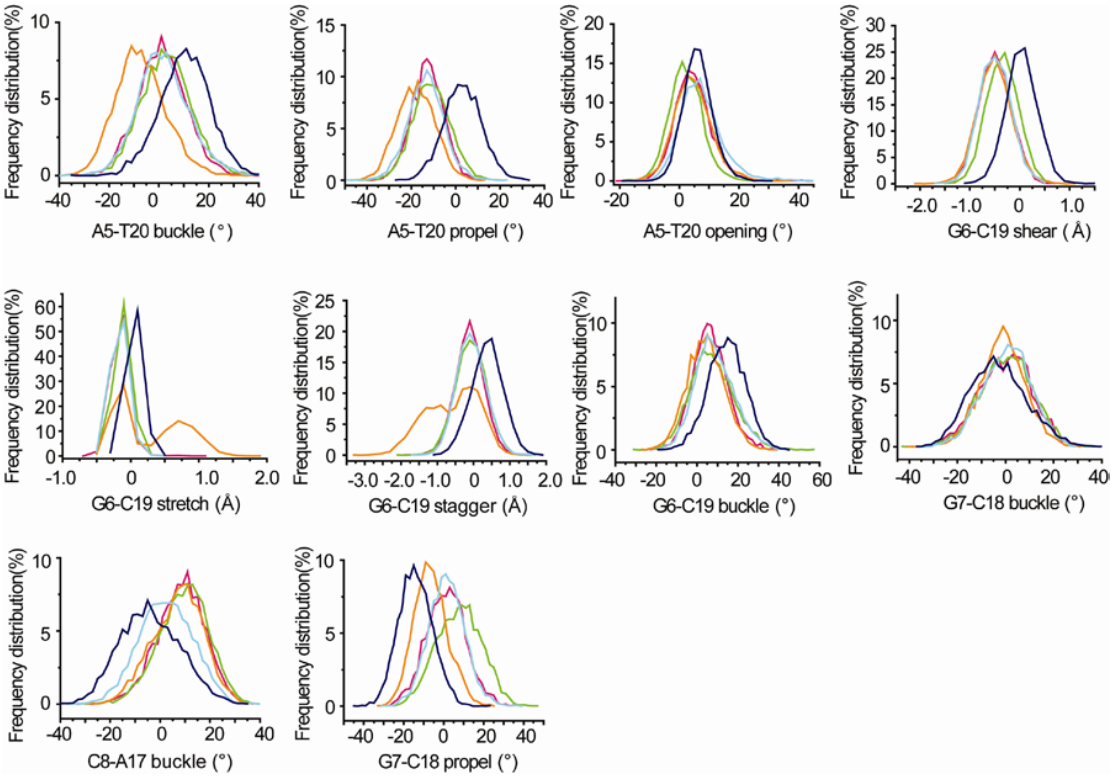

Figure S3. Selected frequency distributions of the representative DNA duplex base pair helical parameters for the central four binding base pairs for the different crosslinks. Navy: undamaged DNA; pink: *trans*-*R*,*R*-DACH-Pt-DNA; green: *trans*-*S*,*S*-DACH-Pt-DNA; orange: *cis*1-DACH-Pt-DNA; cyan: *cis*2-DACH-Pt-DNA are represented as continuous lines.

Table S1. Estimated relative binding energy of DNA duplexes from MM-PBSA

	R,R-trans		*S,S-trans*		*cis1*		*cis2*	
#	Mean	SE	Mean	SE	Mean	SE	Mean	SE
ΔE(ele)	-1109.5	2.3	-1149.8	1.6	-1155.2	1.7	-1118.7	1.9
ΔE(vdw)	-10.1	0.1	-10.4	0.1	-14.9	0.2	-9.9	0.1
ΔE(internal)	9.7	0.1	9.9	0.2	9.8	0.2	10.4	0.1
ΔE(gas)	-1109.9	2.4	-1150.2	1.7	-1160.3	1.8	-1118.3	1.9
ΔE(PBsur)	-1.7	0.0	-1.7	0.0	-2.2	0.0	-1.5	0.0
ΔE(PBcal)	990.3	2.3	1033.2	1.7	1045.9	1.7	1010.4	2.0
ΔE(PBsol)	988.6	2.3	1031.5	1.7	1043.8	1.7	1008.8	2.0
ΔE(PBele)	-119.3	0.6	-116.5	0.6	-109.3	0.5	-108.3	0.6
ΔG(PBtot)	-121.3	0.7	-118.6	0.6	-116.5	0.6	-109.4	0.6

Δ*E*(ele) = Electrostatic energy

Δ*E*(vdw) = van der Waals energy

Δ*E*(gas) = total gas phase energy ($\Delta E_{ele} + \Delta E_{vdw} + \Delta E_{internal}$)

Δ*E*(PBsur) = nonpolar solvation energy

Δ*E*(PBcal) = polar solvation energy

Δ*E*(PBsol) = total solvation energy ($\Delta E_{PBsur} + \Delta E_{PBcal}$)

Δ*E*(PBele) = total electrostatic energy ($\Delta E_{ele} + \Delta E_{PBcal}$)

Δ*G*(PBtot) = enthalpy of binding ($\Delta E_{gas} + \Delta E_{PBcal}$)

SE = standard error of mean