Supporting Information

Smoothed Potential MD Simulations for Dissociation Kinetics of Etoposide to Unravel Isoform Specificity in Targeting Human Topoisomerase II

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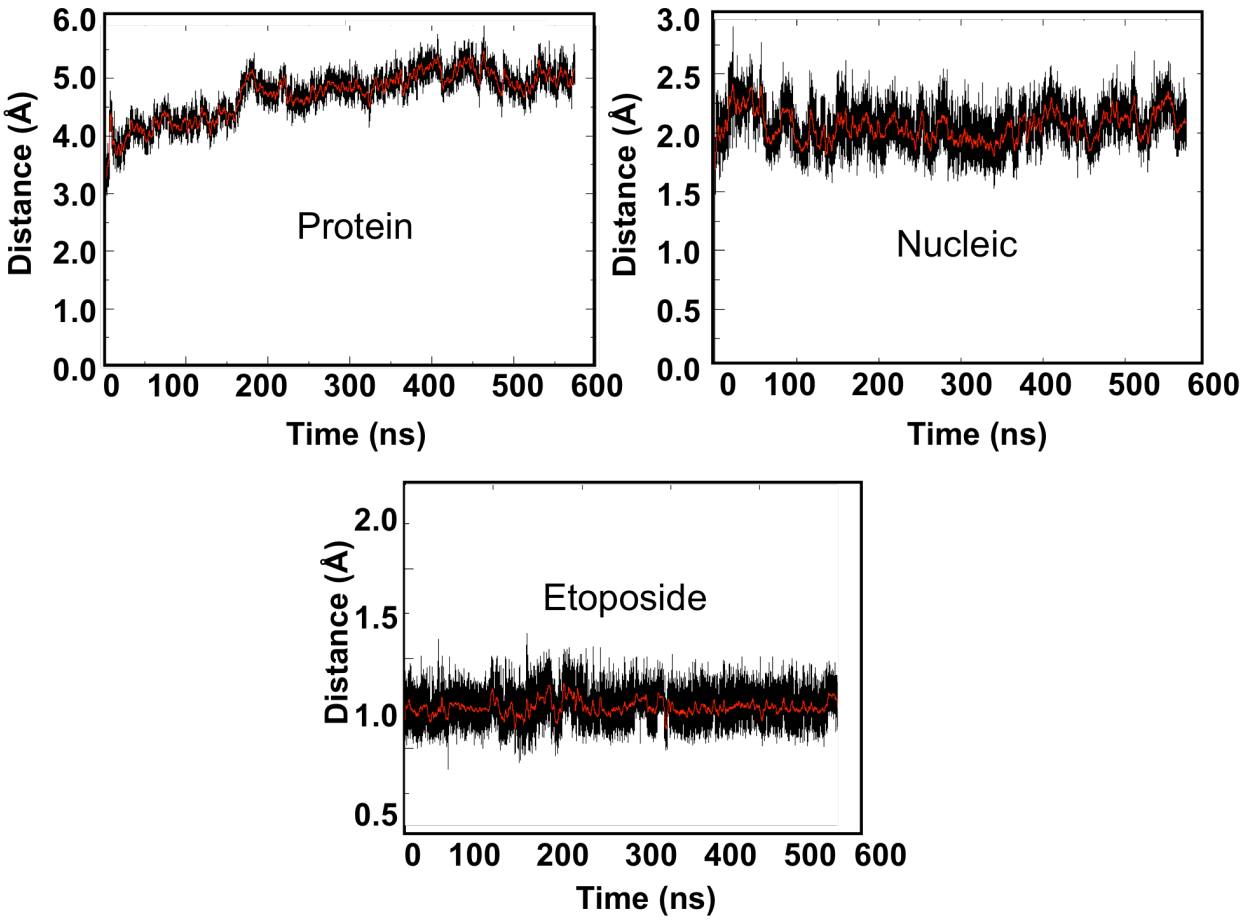

Figure S1. Time evolution of the Root Mean Square Deviation (RMSD) with respect to the initial MD configuration of the protein, nucleic acid chain, and etoposide heavy atoms for the TopoIIα/DNA/etoposide complex. The RMSD is expressed in Å.

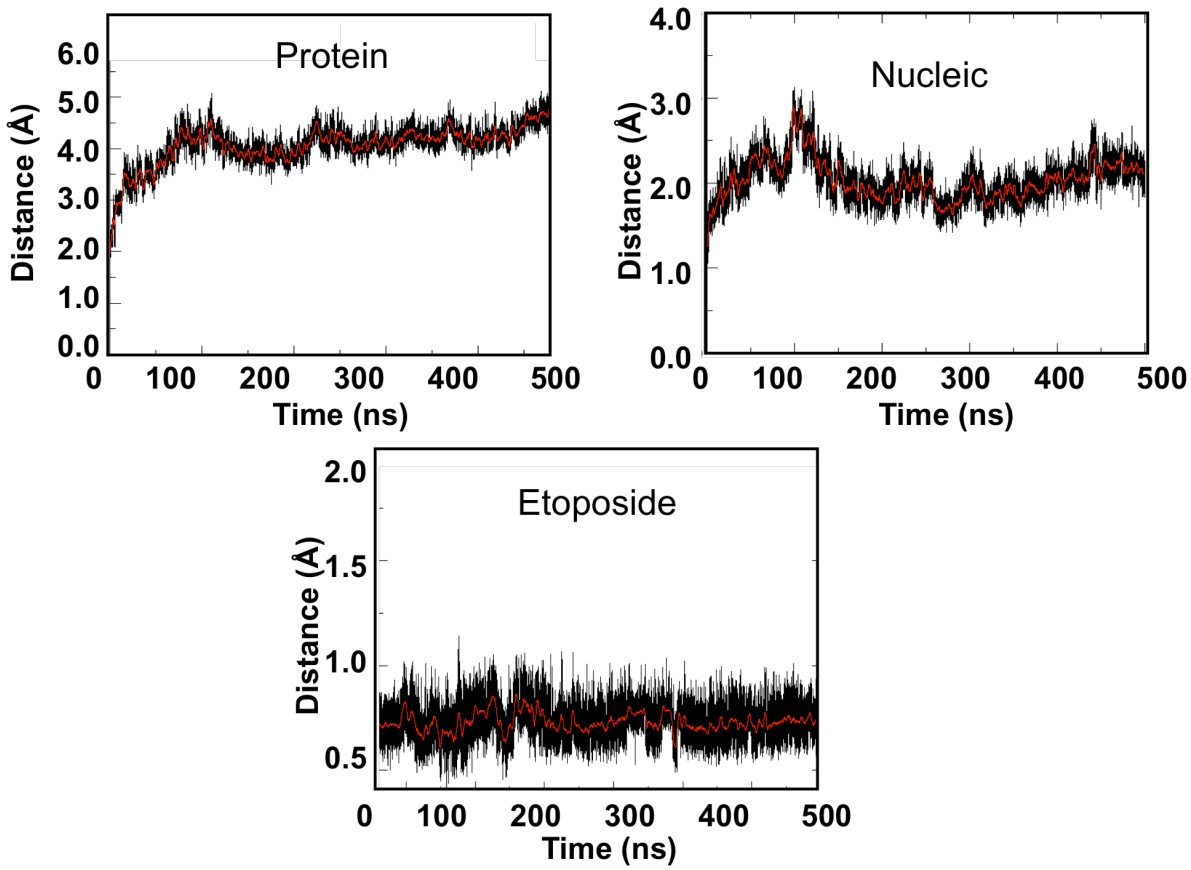

Figure S2. Time evolution of the Root Mean Square Deviation (RMSD) with respect to the initial MD configuration of the protein and nucleic acid chain, and etoposide heavy atoms for the TopoIIβ /DNA/etoposide complex. The RMSD is expressed in Å.

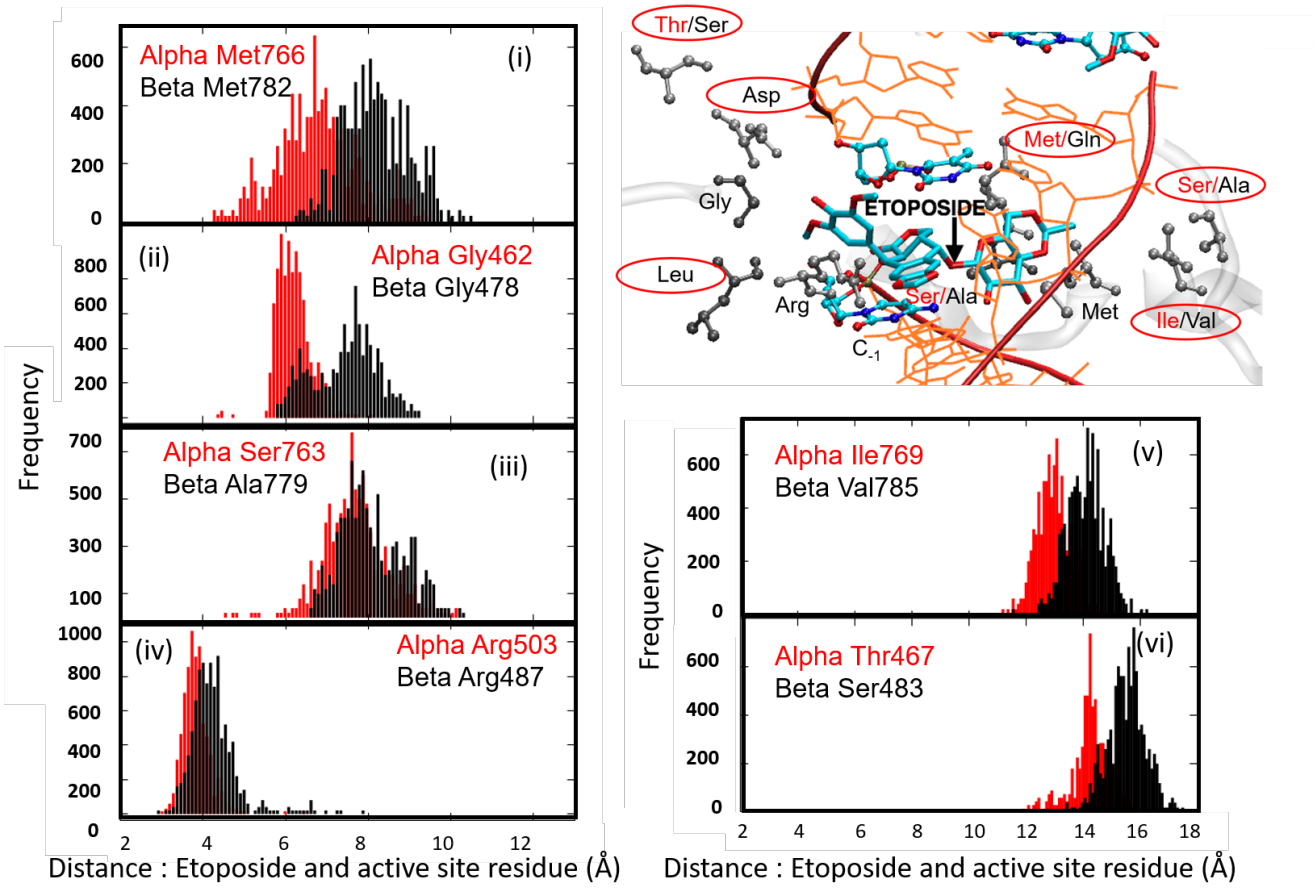

Figure S3. Binding site compactness in TopoII from MD simulations. Plots of the distance between the center of mass (COM) of the etoposide sugar moiety and the COM of i) Met766α and Met782β and ii) Ser763α and Ala779β; the COM of the etoposide E-ring and the COM of iii) Gly462α and Gly478β and iv) Arg487α and Arg503β (v) Ile769α and Val785 β (vi) Thr467α and Ser483β. These distances depict an enhanced compactness of the active site of the TopoIIα isoform.

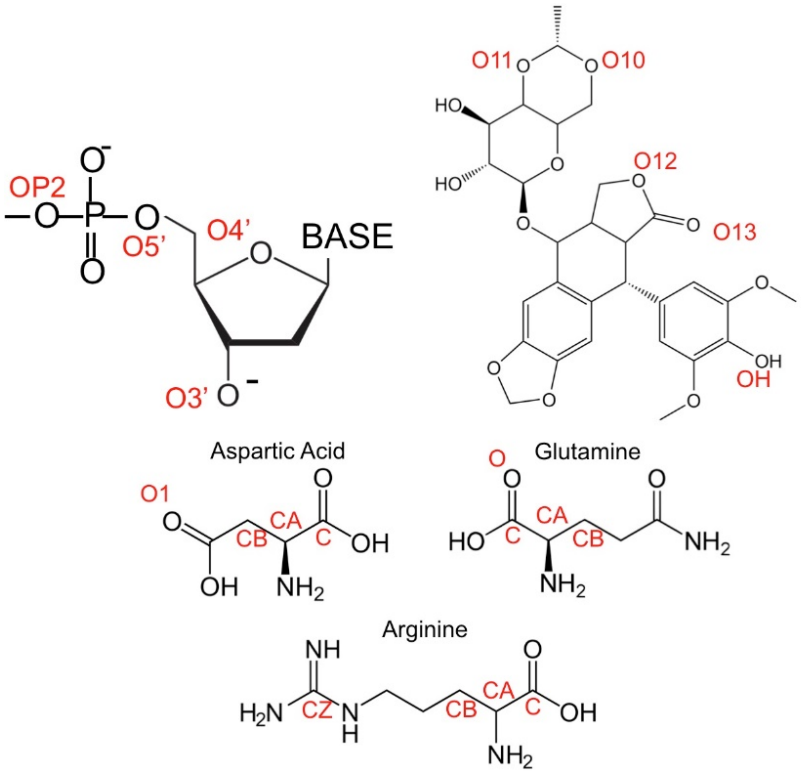

Figure S4. Structure of etoposide, amino acid residues (arginine, glutamine and aspartic acid), and nucleotide forming the binding site with atom naming for reference of Table S1.

Table S1. Structural differences between Site1 and Site2 of TopoIIβ. (Refer to Fig. S4 for the atom naming and numbering)

Angles (°)	Site 1	Site 2	Distance (Å)	Site 1	Site2
P(C_{-1})-O_{12}(Eto)- P(T_{+1})	81.7	85.1	P (C_{-1})-P(T_{+1})	8.2	8.6
O5'(T_{+1})-O10 (Eto)-CB(Glu778)	43.3	39.3	O12 (Eto)-O4' (T+1)	3.5	3.4
O10 (Eto)- P(T_{+1}) -CB(Glu778)	24.1	32.2	CB(Glu778)-O10(Eto)	4.3	4.5
CZ(Arg503)- P(T_{+1})-O10 (Eto)	64.7	62.3	P (C_{-1})-CB(Glu778)	6.0	5.9
O(Glu778)-O4'(T_{+1})-O10 (Eto)	109.1	107.0	P (T_{+1})- O10(Eto)	9.0	9.2
O1(Asp479)-OH (Eto)-O3'(T_{+1})	110.4	105.9			
C(Arg503)-OH (Eto)-O3'(T_{+1})	146.1	145.0			

Movie S1. Etoposide Unbinding from Scaled Molecular Dynamics (SMD) simulations of the TopoII/DNA/etoposide system. The representative trajectory – chosen among 128 SMD simulations – shows etoposide unbinding via a center path. The protein (gray) is shown in molecular surface, and the DNA (pink) is highlighted as ribbons and sticks. Two etoposide molecules (green) are shown in licorice representation. The etoposide on right hand side is restrained to the cleavage site (see method section).