Supplementary Data:

Sequence Selectivity of the Cleavage Sites Induced by Topoisomerase I Inhibitors: A Molecular Dynamics Study

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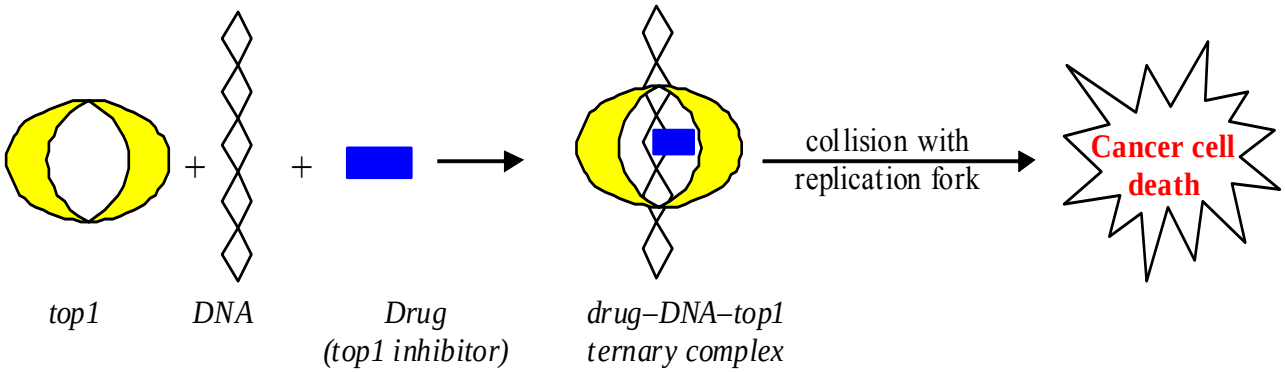
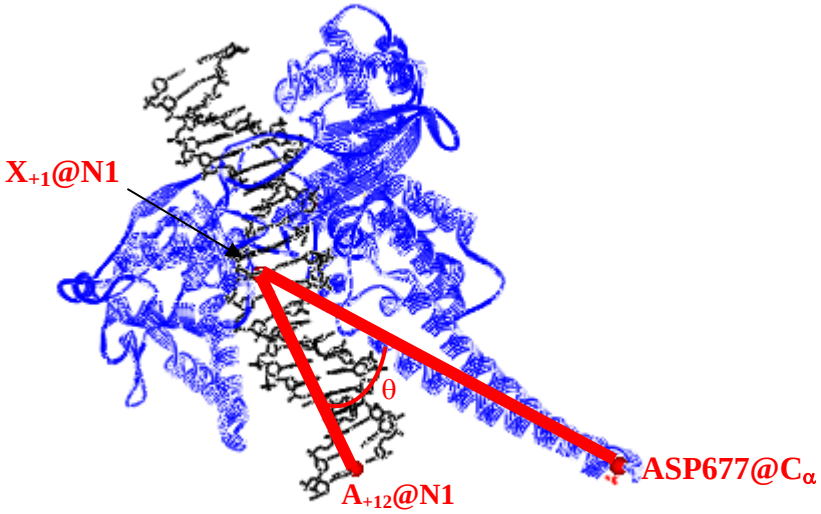
Scheme S1. Mechanisms of Action of Top1 inhibitors.



Scheme S2. Schematic view of the DNA-linker angle.



Scheme S3. Potential of mean force (PMF) was calculated along the reaction coordinate (χ). An insert is present to highlight the flanking base pairs and CPT at the cleavage site.

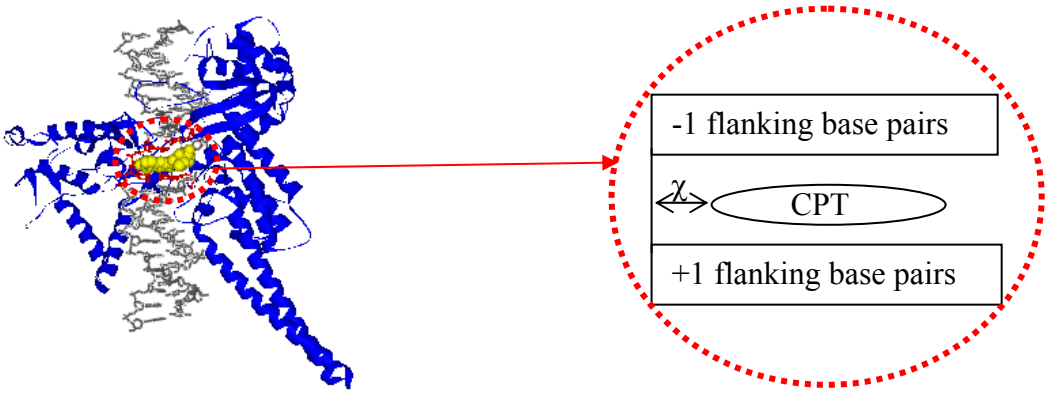
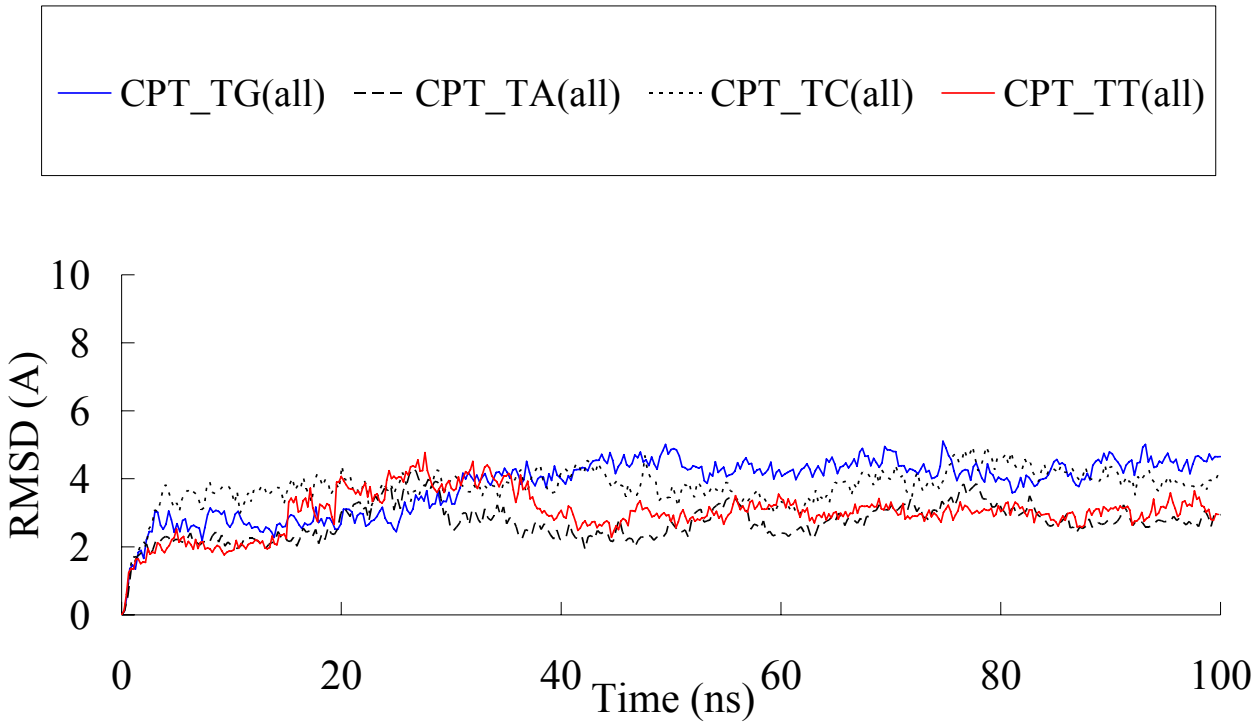


Figure S1. (A) RMSD of the ternary complexes. (B) RMSD of the ternary complexes calculated without the linker domain.

A



B

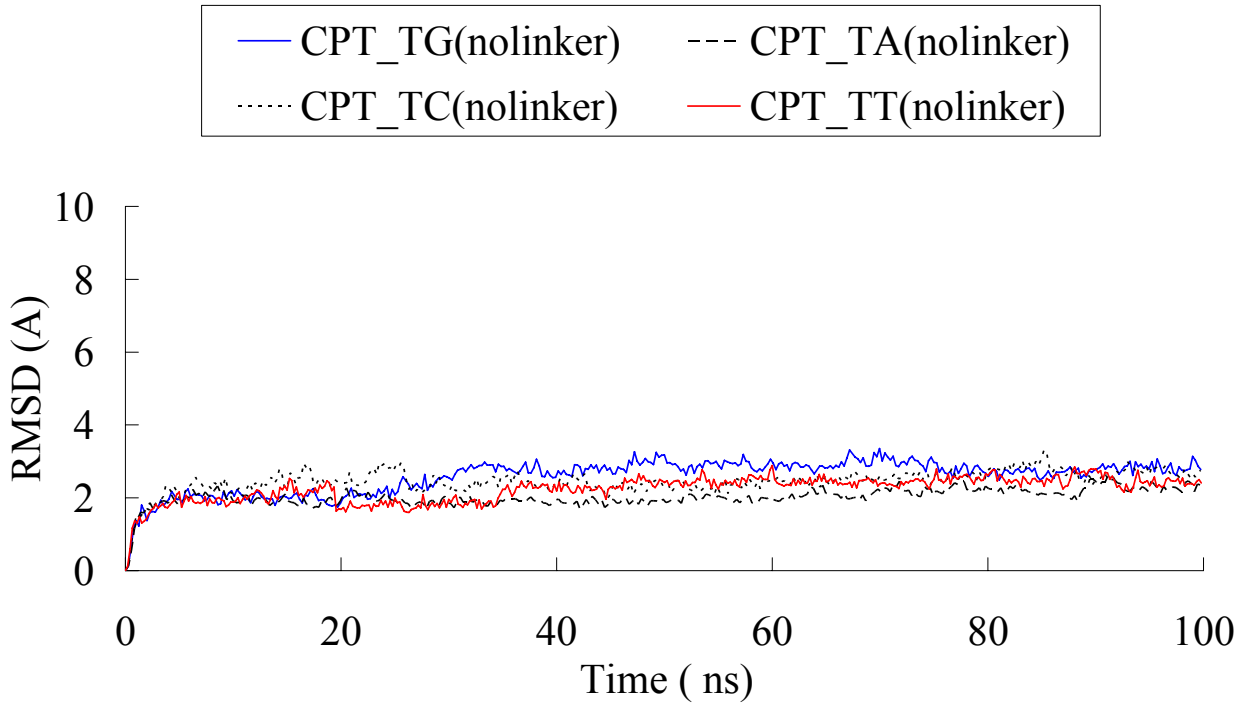


Figure S2. Schematic representation of the protein-DNA (phosphate atoms), CPT-protein, CPT-DNA (phosphate atoms) hydrogen bonds.

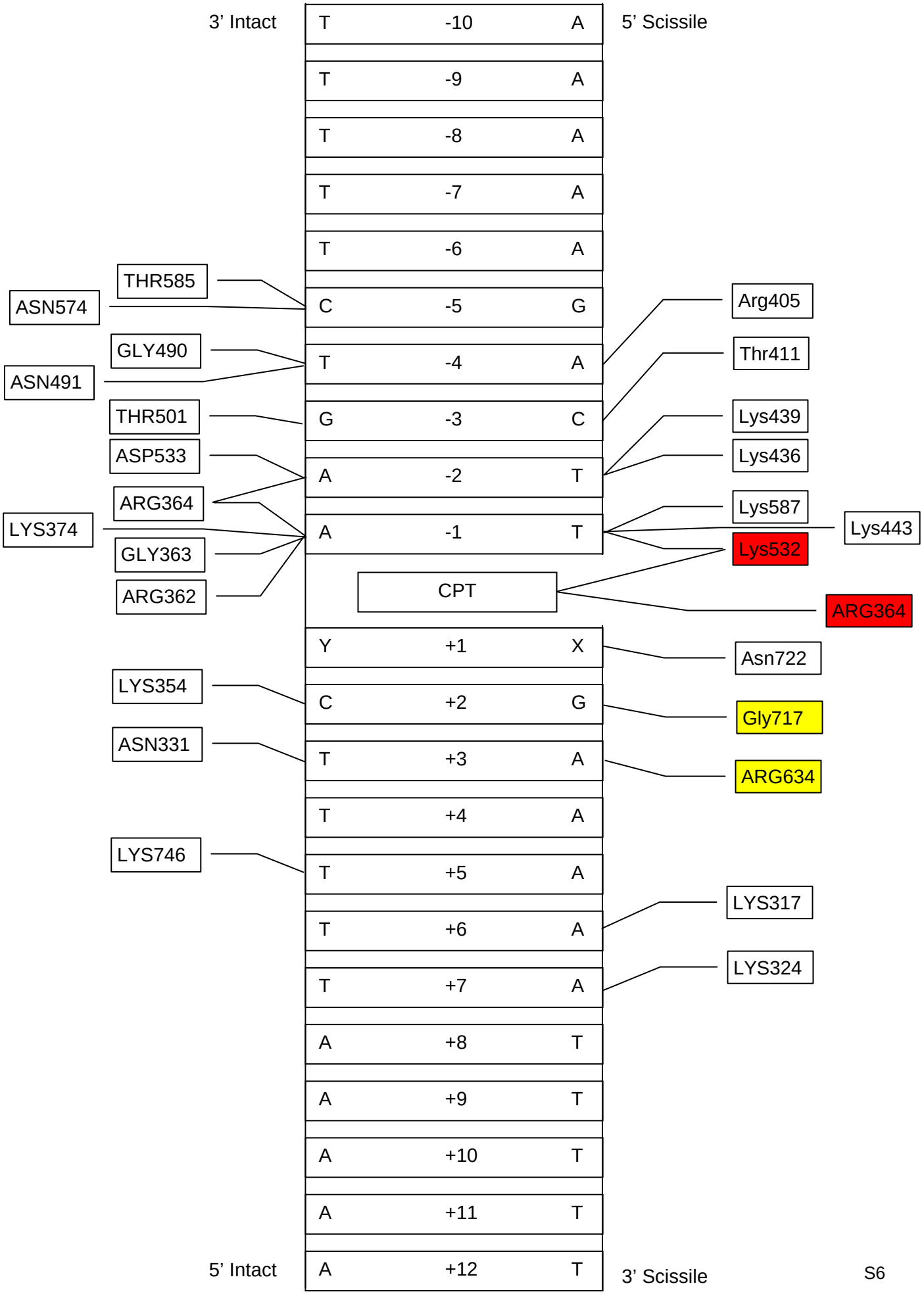


Figure S3. X-ray crystal structures of the drug-bound ternary complex (1K4T) and the Top1-DNA binary complex (1A31). The residues 627-719 are missing in the 1A31 structure.

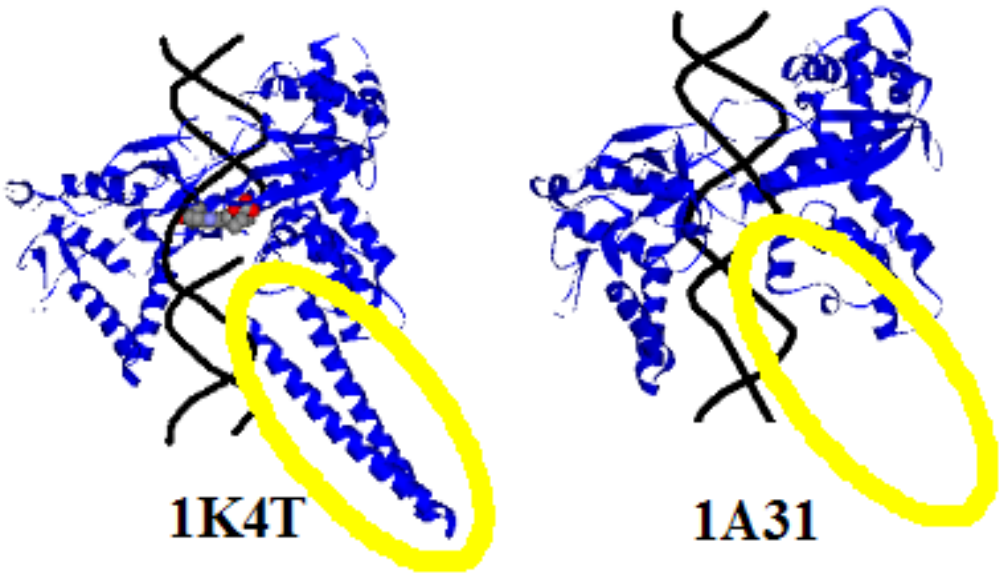
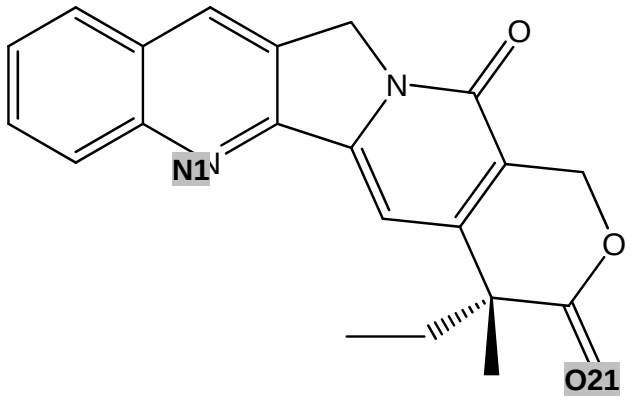
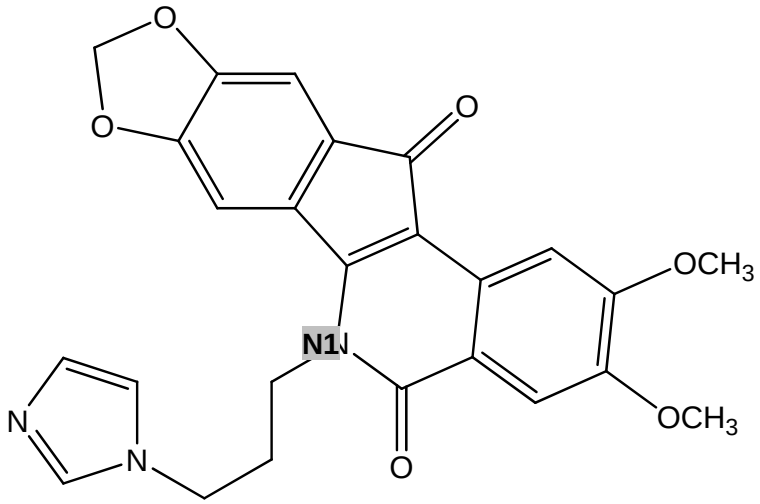


Chart S1. Structures of the CPT and LMP-776 (NSC725776, non-CPT indenoisoquinoline).



CPT



LMP-776

Full references

6. Arimondo, P.B., Laco, G.S., Thomas, C.J., Halby, L., Pez, D., Schmitt, P., Boutorine, A., Garestier, T., Pommier, Y., Hecht, S.M., Sun, J. S. and Bailly, C. (2005) Activation of camptothecin derivatives by conjugation to triple helix-forming oligonucleotides. Biochemistry, 44, 4171-4180.

63. Antony, S., Agama, K.K., Miao, Z.H., Takagi, K., Wright, M.H., Robles, A.I., Varticovski, L., Nagarajan, M., Morrell, A., Cushman, M. and Pommier, Y. (2007) Novel indenoisoquinolines NSC 725776 and NSC 724998 produce persistent topoisomerase I cleavage complexes and overcome multidrug resistance. Cancer Res., 67, 10397-10405.

68. Gongora, C., Vezzio-Vie, N., Tuduri, S., Denis, V., Causse, A., Auzanneau, C., Collod-Beroud, G., Coquelle, A., Pasero, P., Pourquier, P., Martineau, P., Del Rio, M. (2011) New Topoisomerase I mutations are associated with resistance to camptothecin. Mol Cancer, 10, 64.