Structural Studies on ST1481, Gimatecan, a 7-substituted Camptothecin with Anti-tumor Activity

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Camptothecins are a class of of active antitumor agents that target the nuclear enzyme DNA topoisomerase I, inhibiting single strand religation. Several camptothecin derivatives are in clinical trials [1]. The substitution of position 7 by lipophilic side chains seems to be important as it increases cytotoxic potency, helps in the drug delivery and in stabilizing the DNA-topoisomerase I cleavable complex that forms in ST1481 presence and is is as part of its mechanism of action. Of 44 compounds synthesized [1] the most potent derivative contains a $CH{=}NOC(CH_3)_3$ substituent and its X-ray crystal structure has been determined. The unit cell parameters are space group: $\boldsymbol{P2_1}$, a = 12.131(8)Å, b = 6.712(5)Å, c = 13.817(8)Å, β = 96.05(3). This derivative (gimatecan) is orally administered, and thus, represents a significant advantage compared to other camptothecins. *Ab initio* studies have been performed using Density Functional Theory to analyze the lactone ring opening, a critical step in the interaction with topoisomerase I.

[1] Dallavalle S., Ferrari A., Biasotti B., Merlini L., Penco S., Gallo G., Marzi M., Tinti M. O., Martinelli R., Pisano C., Carminati P., Carenini N., Beretta G., Perego P., De Cesare M., Pratesi G., Zunino F., *J. Med. Chem.,* 2001, **44**, 3264.

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