Theoretical study on ternary complex stability and Michael addition reactivity of Thymidylate synthase/mTHF/XdUMP

Nopporn Kaiyawet,[1] Thanyada Rungrotmongkol,[2] Richard Lonsdalec,[3] Adrian J. Mulholland[3] and Supot Hannongbua,[1,*]

[1]Department of Chemistry, Faculty of Science, Chulalongkorn University, Thailand;
[2]Department of Biochemistry, Faculty of Science, Chulalongkorn University, Thailand;
[3]School of Chemistry, University of Bristol, United Kingdom

Tel: +66-2-218-7602, Fax: 0-2218-7603, E-mail: n.kaiyawet@gmail.com

Keywords: thymidylate synthase, cancer, Michael addition,

Thymidylate synthase (TS) catalyzes the reductive methylation of dUMP to dTMP during the DNA synthesis process. Herein, binding affinity, and activation energy of Michael addition and a covalent complex formation of TS/mTHF/XdUMP (where X is -H, -F, -Cl or -Br) were investigated using molecular dynamics (MD) and high level quantum mechanics-molecular mechanics (QM-MM) methods. Note that FdUMP is metabolite form of available anticancer agent, 5-FU, targeted at this enzyme. In MD results, the unique H-bonding between Y94 and the substituted fluorine of FdUMP was detected whereas the other systems share almost similar pattern in the overall H-bonding interactions. The B3LYP/6-31+G*-CHARMM potential energy surface according to the two reacting distances, d1: S-(C14)-C6(dUMP) and d2: C5(dUMP)-CH_2(mTHF) suggested that the Michael addition and covalent complex formation occurred in the concerted mechanism. In addition, the SCS-MP2/cc-pVTZ-CHARMM//B3LYP/6-31+G*-CHARMM barriers of this mechanism were 19.7, 23.6 and 25.1 kcal/mol for dUMP, FdUMP and CldUMP complexes.

[1] Carreras, C. W., Santi, D. V. *Annul. Rev. Biochem.*, 64, 721-762, 1995.
[2] Perry, K. M., Fauman, E. B., Finer-Moore, J. S., Montfort, W. R., Maley, G. F., Maley, F., Stroud, R. M. *Proteins: Struct., Funct., Genet.*, 8, 315-333, 1990.