1P22

Using ultra accelerated QCMD method to study drug-protein interaction

○Kamlesh Kumar Sahu[1], Ai Suzuki[2], Hideyuki Tsuboi[1], Nozomu Hatakeyama[1], Akira Endou[1], Hiromitsu Takaba[1], Momoji Kubo[1] and Akira Miyamoto[2,1]

[1]Grad. Sch. Eng., Tohoku Univ. (6-6-11-1302 Aoba, Aramaki, Aoba-ku, Sendai 980-8579)
[2]NICHe, Tohoku Univ. (6-6-11-1302 Aoba, Aramaki, Aoba-ku, Sendai 980-8579)

【Introduction】

In order to design better analogue of Nevirapine drug, it is necessary to define those interactions, which anchor the drug in binding pocket of HIV-1 reverse transcriptase (HIV-1 RT). RT is an important antiviral target for the chemotherapy of AIDS because of its key role in virus replication. The inhibitors of HIV-1 RT can be divided into two main classes, nucleoside RT inhibitors (NRTIs) and non-nucleoside RT inhibitors (NNRTIs) [1–4]. We applied advanced QCMD method to investigate the interactions that help Nevirapine (NVP) inhibit this enzyme.

【Method】

Advanced quantum chemical molecular dynamic simulation method, which is 10 million times faster than conventional first principles method, was used in our calculation. We used a combination of MD simulation with quantum chemical calculation in the form of Colors-New Ryudo combination to investigate the RT-NVP system. Prior to this simulation, the complexes were subjected to a single point quantum chemical calculation by Colors program, which is based on our original tight-binding approximation. The Morse potentials between different pairs of atoms were used for MD simulation by New-Ryudo program. This combination of Colors and New-Ryudo was repeated for a number of times to get the accuracy of results.

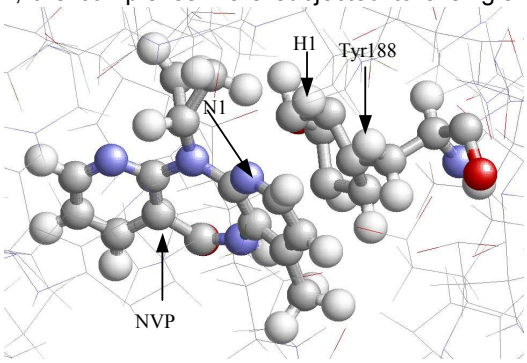

Fig.1 The structure of Nevirapine and tyr188 in the binding site of reverse Transcriptase after 10ps

【Result and discussion】

Fig.1 shows final structure of the binding pocket of Reverse Transcriptase containing Nevirapine after 10ps of simulation time. Hydrogen H-1 is attached to the tyrosine188 residue in the amino acid chain of reverse Transcriptase enzyme and nitrogen N-1 belongs to the pyridine ring of Nevirapine. Table 1 shows the Bond population bond distances and bond Energies between H1 from Tyr188 and N1 from Nevirapine in initial (0 picosecond) and final structure (after 10 picoseconds). The bond energy and bond distance indicate the interaction between drug molecule and the amino acids of enzyme at molecular level which is difficult to find out by conventional methods. The result shows us that we can design new analogue of NVP by substituting only those groups at N1, which may further increase the BP and bond energies reported in this interaction. Alternatively, the substitutions must be made on positions other than N1 nitrogen so that this point of attachment between drug and protein is preserved in newly design drug candidate. More interactions in the binding pocket of RT that result in inactivation of enzyme's binding site will be reported in the conference. More interactions of groups from NVP with surrounding amino acid residues like valine106, lys103 and tyr188 will be presented in the conference. Apart from our calculations on NVP-RT system, we have also tried to design methotrexate (MTX) analogue on the basis of our previous calculations on Dihydrofolate Reductase-MTX system, which will be presented in the conference.

Table1 Bond population (BP), energy and bond distance between N1 and H1

Time(ps)	Bond	Distance (Å)	Energy (kcal/mol)	BP
0	N1---H1	5.95	0	0
10	N1---H1	2.96	-4.6	0.02

【Reference】

[1] R.C. Rizzo, J. Tirado-Rives, W.L. Jorgensen, J. Med.Chem. 44 (2001) 145.
[2] H. Mitsuya, R. Yarchoan, S. Broder, Science 249 (1990) 1533.
[3] R.A. Katz, A.M. Skala, Annu. Rev. Biochem. 63 (1994) 133.
[4] J. Wang, P. Morin, W. Wang, P.A. Kollman, J. Am. Chem. Soc. 123 (2001) 5221.