**INFORMATION ON DOCTORAL THESIS**

**1.** Full name: **Nguyen Hoa Mi**

**2.** Sex: Female

**3.** Date of birth: 22/01/1982

**4.** Place of birth: Bac Ninh

**5.** Admission decision number: 5429/QD-SDH, issued on 30/10/2008 by President of Vietnam National University.

**6.** Changes in academic process: None

**7.** Official thesis number: ***Study on mechanism for reaction of PBP2a with β-lactams by computational methods***.

**8.** Major: Theoretical and Physical Chemistry

**9.** Code: 62 44 31 01

**10.** Supervisors: **Prof. Dr Dang Ung Van**

**Prof. Dr Truong Nguyen Thanh**

**11.** Summary of the new findings of the thesis

+ By comparing the crystal structure of apo enzyme PBP2a and its acyl complexes with methicillin and nitrocefin we exploit an active site adjacent cleft which has closed and open situation. The existence of a two conformation adjacent cleft of the active site should be paid attention in resistance mechanism. The cleft closed conformation detected in PBP2a apoenzyme structure prevents β-lactam far from active site. The cleft open conformation observed in PBP2a structure of acyl complexes allows β-lactam molecule pass over approaching the position suitable for nucleophilic attack.

+ The contrary known on the very stable covalent PBP2a-β-lactam complexes and the resistance of PBP2a has been explained by analyzing structure, dynamics of inhibitor and protein as well. The rearrangement of the helix α2 N-terminus and the strand β3 in active region is not only cause of the resistance. RMSF analyse shown that the flexibility of helix α2 N-terminus, the flexibility of the ligand molecule and Ser403 support significantly the acylation which is more convenience in

NC1-complex than in MC1 one. The dynamics of hot-spot residues and the active site adjacent cleft are of particular interest, as they should be suggested to provide additional opportunities for drug discovery that could potentially mitigate the effects of drug resistance.

+ The results of the thesis contribute to further elucidate the acylation reaction mechanism through the evaluation of the reaction energy barrier between NC1, MC1, the model of the NC1, MC1 with PBP2a enzyme.

+ The thesis also explained the reasons for differences in reactivity of the NC1 easier than MC1 in acylation reaction with PBP2a enzyme due to strain of angle of four member the ring when associated with the next round of six member ring of NC1 more than strain of angle of four member the ring when associated with five member ring of MC1. Also theses making a comment that can get higher efficiency of β-lactam antibiotics by the "subgroup that is longer than" through the analysis of weak interactions and the conjugate electron.

+ The thesis proposed using two modern methods of computational chemistry are QM/MM and MM/MD to study mechanisms of β-lactam resistance of staphylococcus *aureu*s bacteria, which opened a new research approach in Vietnam up date with science on the world. We believe that this is the future style of computer-aided drug design.

**12.** Practical applicability:

This mechanisms of drug resistance constitute a very complicated research subject attracting scientists in Vietnam and many other countries all around the world. Thesis have contributions solve resistance problem above. We try find reasons and explain why β-lactam was loss activity by bacteria. By using computational methods on high supercomputer to implement project of thesis because research reaction mechanism of enzyme is difficult to research by experimental carefully. This is also can contribute to the orientation for the design of new antibiotics have effective enough to deal the old antibiotic resistant bacteria.

**13.** Further research directions:

This project will continue research with other models to find model which have properties better than known α-lactam. Futher, we hope can to find drug that have ability against resistance for many diseases.

**14.** Thesis-related publications:

1, Dang Ung Van, Nguyen Hoa Mi (2009), “Hydration Free Energy Calculation of Amino Acid Analogs by Molecular Dynamics”, Journal *of Chemistry* Vol.47(6), pp. 709-715.

2, Nguyen Hoa Mi, Dang Ung Van (2010), “Study on The Mechanism for The Reaction of PBP2a with beta- lactam Inhibitors by ONIOM Method”, *Journal of Chemistry* Vol.48.(4B), pp. 544-548.

3, Nguyen Hoa Mi, Dang Ung Van, Le Kim Long, Truong Nguyen Thanh (2010), “Binding Free Energy Calculation of beta-lactam Inhibitors in The Covalent Complex With Methicillin Resistance S.Aureus”, *Journal of Chemistry* Vol.48(4B), pp. 532-537.

4, Dang Ung Van, Nguyen Hoa Mi (2011), “On the existence of SER403 active site adjacent cleft of methicillin resitance SauPBP2A (MRSA)”, *Journal of Chemistry* Vol. 49(4), pp. 421-425.

5, Dang Ung Van, Nguyen Hoa Mi (2011), “On the flexibility of ligand and active region residues in the acyl and michaelis complexes of nitrocefin and methicillin with methicillin resistance SauPBP2a (MRSA)”, *Journal of Chemistry* Vol.49(3), pp. 342-346.

6, Nguyen Hoa Mi, Hirao Hajime, Dang Ung Van, Keiji Morokuma (2011), “Study on the Mechanism for the Reaction of PBP2a with beta-lactam Inhibitors by Oniom Method”, *7th Congress of the international Society for Theoretical Chemical Physics September 2-8th,* pp. 380.

7, Nguyen Hoa Mi, Dang Ung Van (2011), “Calculation of the binding free energy of nitrocefin and methicillin with the structures of PBP2a”, *Journal of Chemistry* Vol.49(2ABC), pp. 467-471.

8, Nguyen Hoa Mi, Hirao Hajime, Dang Ung Van, Keiji Morokuma (2011), “Computational Studies of Bacterial Resistance to β-Lactam Antibiotics: Mechanism of Covalent Inhibition of the Penicillin-Binding Protein 2a (PBP2a)”, *J. Chem. Inf. Model*, 51, DOI: 10.1021/ci2004175, PP. 3226-3234.

9, Nguyen Hoa Mi, Hajime Hirao, Dang Ung Van, Thanh Nguyen Truong, Keiji Morokuma (2011), “Computational Studies of Bacterial Resistance to□□□Lactam Antibiotics: Mechanism of non-Covalent and Covalent Inhibitions of the Penicillin-Binding Protein 2a (PBP2a)”, *1st International Conference on Computational Science and Engineering in Ho-Chi-Minh City Vietnam on December 19-21th,* pp. 76.