ELUCIDATING MECHANISMS OF METALLOPEPTIDASES AND THEIR SYNTHETIC ANALOGUES *Xiaoxia Zhu, Mehmet Ozbil, Arghya Barman, Ram Prasad Bora and Rajeev Prabhakar, Department of Chemistry, University of Miami, Coral Gables, FL 33146*

The selective hydrolytic cleavage of proteins and peptides plays a critical role in cellular as well as in modern bioanalytical and bioengineering applications. The most critical step in these applications is the selective cleavage of the highly stable peptide bonds. The mononuclear metal center containing peptidases such as insulin degrading enzyme (IDE) and matrix metalloproteinase (MMP) are implicated in the degradation of a variety of amyloidogenic substrates. In a multistep computational strategy, we have applied molecular dynamics (MD) simulations, QM (B3LYP) and QM/MM (B3LYP/Amber) approaches to investigate the catalytic activities of enzymes and their synthetic analogues. In the first step, we have studied the interactions of the substrates with the active form of enzymes through MD simulations. In the next step, the structures derived from MD simulations were utilized to elucidate the catalytic mechanisms for the hydrolysis of substrates by enzymes and their synthetic analogues.