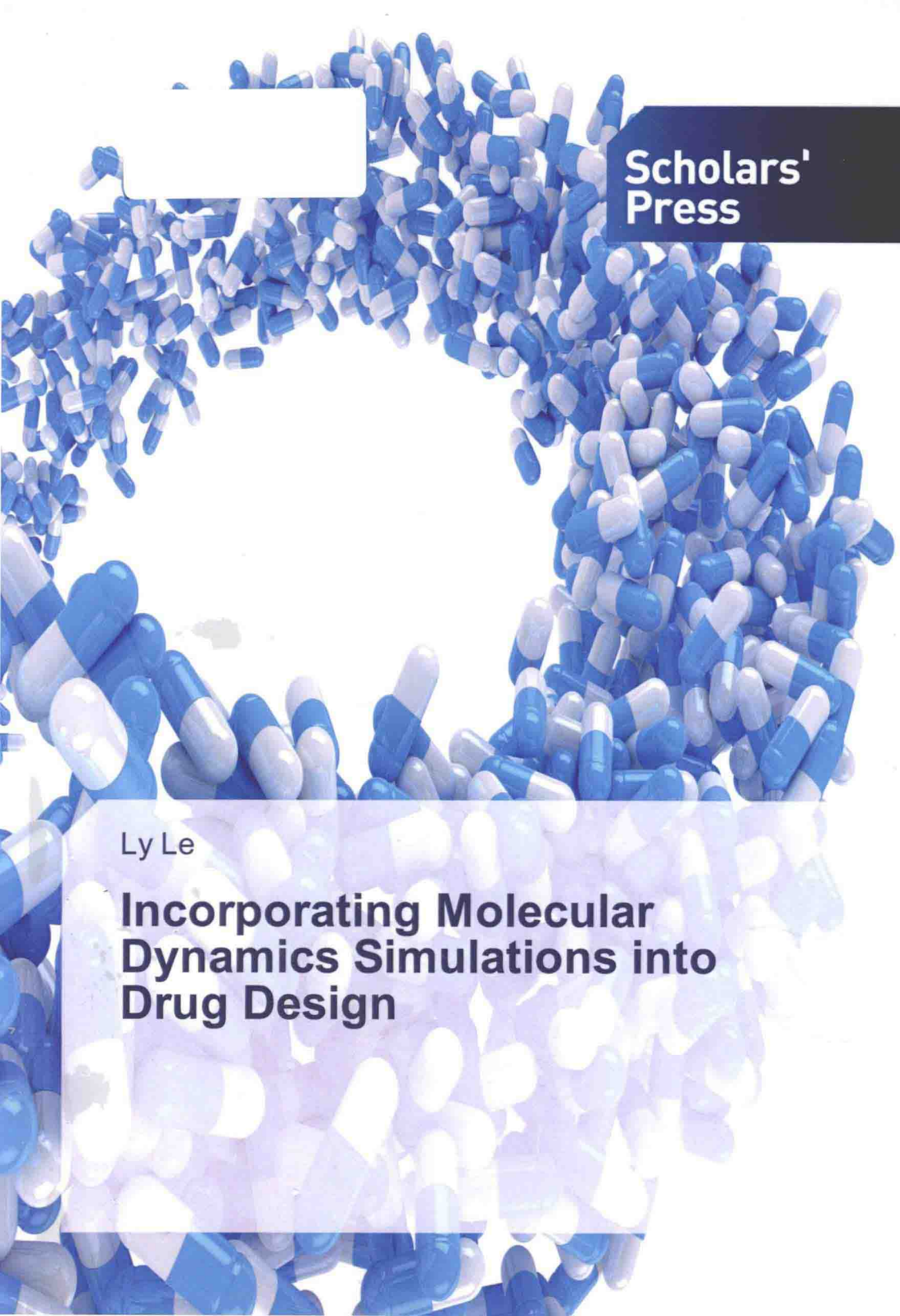

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Incorporating Molecular Dynamics Simulations into Drug Design

INCORPORATING MOLECULAR DYNAMICS SIMULATIONS INTO DRUG DESIGN TARGETING INFLUENZA N1 NEURAMINIDASES

by

Ly Le

A dissertation submitted to the faculty of

The University of Utah

in partial fulfillment of the requirements for the degree of

Doctor of Philosophy

Department of Chemistry

The University of Utah

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ABSTRACT

The FDA antiviral drug, Tamiflu (oseltamivir)[1] is the front-line antiviral drug for the fight against 2003 avian flu (H5N1)[2] as well as, more recently, for the 2009 swine flu (H1N1pdm).[3] The drug functions as a neuraminidase inhibitor that prevents the release of new virions. Unfortunately, there is emerging evidence that the neuraminidase mutations H274Y and N294S[4] render oseltamivir ineffective against the H5N1 virus. Of greater concern is the growing likelihood of the emergence of similar oseltamivir-resistant strains of H1N1pdm. It is therefore critical to understand the mechanisms for mutation-induced drug resistance in the H5N1 and H1N1pdm flu viruses in order to develop new and effective therapies. As molecular dynamics (MD) simulations have become an important tool for the study of biological systems, this dissertation aims to employ MD simulations for computer-aided rational drug design. Specifically, different MD simulation techniques were utilized in the investigation of oseltamivir-resistant mechanisms of H5N1/H1N1pdm and for the development of new antiviral drugs.

Chapter 1 is simply a general introduction to the whole thesis. Chapter 2 presents top-hits for H1N1pdm neuraminidase identified by virtual screening using ensemble-based docking technique, which incorporates protein flexibility into molecular docking. Next in Chapter 3, progress in the development of two related methodologies for calculation of solvation free energy, one called the Coupled Reference Interaction Site model-hyper-netted chain/molecular dynamics (RISM/MD) approach, and another called Molecular Mechanics Poisson–Boltzmann linear response approximation and surface area contributions (MMPB-LRA-SA), are presented. The methods are expected to be applicable to the lead refinement process since they provide more reliable results than the continuum model but are less computationally expensive than conventional MD methods. In Chapter 4, we discuss our observations based on drug-protein endpoint interactions on how the mutations H274Y and N294S induce oseltamivir resistance in neuraminidase N1 subtypes. However, since the two mutations are non-active-site,

endpoint interactions alone cannot fully account for the drug resistance. In Chapter 5, we present our finding of the drug binding pathway through electrostatic surface potential and steered MD simulation.[5] The results reveal a novel oseltamivir-resistant mechanism in which the mutations rupture the drug binding funnel, in conjuction with the findings reported in Chapter 4. Our study not only assists understanding of oseltamivir-resistance in neuraminidase N1 subtypes, but also bears several important consequences for the intelligent design of new inhibitors that can overcome the established resistance strain.

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