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REGULAR ARTICLE

DFT Study of Binding Energies between Acetohydroxyacid Synthase and its Sulfonylurea Inhibitors: An Application of Quantum Pseudoreceptor Model

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Abstract: The quantum mechanical interaction energy between the Acetohydroxyacid synthase (AHAS) and its sulfonylurea inhibitors were calculated with an efficient density functional theory (DFT) and a pseudoreceptor model composed of the amino acids surrounding the ligands. The results show that the calculated quantum mechanical interaction energies correlate well with experimental free energies with the correlation coefficients of 0.92 for six sulfonylurea inhibitors and the standard deviation of 0.83kcal/mol. In comparison with the force field method, the binding free energies were estimated by AutoDock 4.2 program with the correlation coefficient of 0.76 and the standard deviation of 1.40kcal/mol. It indicates that the binding between the AHAS and herbicides can be well characterized by quantum pseudoreceptor model. Based on the quantum mechanical interaction energies, some AHAS inhibitors with high binding affinity were designed by introducing a hydroxyl group at the *para* position of aromatic ring and on the sulfonylurea bridge respectively.

AMS subject classifications: 92E10, 92C05

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1 Introduction

Acetohydroxyacid synthase (AHAS) is a key enzyme in the biosynthetic pathway of the branched-chain amino acids, such as valine, leucine and isoleucine in plants and microorganisms [1, 2]. It catalyzes the condensation of two molecules of pyruvate into 2-acetolactate or one molecule of pyruvate and one molecule of 2-ketobutyrate into 2-aceto-2-hydroxybutyrate as the precursors in valine, leucine and isoleucine biosynthesis [3-5]. Inhibition of AHAS may lead to the starvation of microorganisms and plants due to lack of branched-chain amino acids [6] . As a result, AHAS becomes an important target for inhibitors to be used as herbicides, and several class of effective herbicides were discovered [7,8]. AHAS herbicides fall into five families: sulfonylureas (SU), imidazolinones (IMI), triazolopyrimidines (TP), pyrimidinylbenzoates (PB), and sulfonylamino carbonyltriazolinones (SCT) [9,10]. The typical sulfonylurea herbicides are effective ultralow dosage agrochemicals that are non-toxic to animals. The general structure is a central bridge with an o-substituted aromatic ring attached to the sulfur atom and a heterocyclic ring disubstituted in both meta positions and attached to the distal nitrogen atom of the sulfonylurea bridge as shown in **Figure 1** [11]. The heterocyclic ring can be either a pyrimidine as in chlorimuron ethyl (CE) or a triazine as in metsulfuron methyl (MM) shown in **Table 1**. With the wide use of the sulfonylureas, resistant weeds began to emerge, to overcome the herbicidal resistance, it is imperative to develop new and high effective AHAS inhibitors [13,14]. Recently, Duggleby and coworkers reported the crystal structure of Arabidopsis thaliana AHAS (*At*AHAS) in complex with chlorimuron ethyl [15], thus it is possible to design some novel AHAS inhibitors with the aid of molecular modeling techniques.

In the computational aided drug design, the biggest challenge is accurate estimation of the binding affinity between protein and inhibitors [16]. Among a variety of methods for calculating the binding energy between inhibitor candidates and their biological targets, Molecular mechanics (MM) is generally applicable to study biological systems with thousands of atoms, but it is hard to describe the charge transfer and explicit polarization between the protein and the ligands [17-18]. Quantum mechanical (QM) method can fully take into account the electronic charge transfer and polarization, but most of QM approaches are limited to small systems with less than one hundred atoms [19,20]. Quantum mechanics