【Grant-in-Aid for Scientific Research (S)】

# Understanding deuterated medicine and its design guideline via “in silico” techniques


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## Purpose and Background of the Research

### ●Outline of the Research

We will elucidate the mechanism of deuterated medicines by our “in silico” techniques, together with several experimental ones. We will apply our deuterium quantum chemistry and data science to calculate the interaction of deuterated drugs with proteins in the blood and the reaction process by drug-metabolizing enzymes. Deuterated model drugs are synthesized and their interactions with blood proteins and metabolic processes by metabolic enzymes are experimentally measured. All data on deuterated drugs through theoretical calculations and experimental measurements will be analyzed using machine learning and explainable AI techniques. We will construct a pharmacokinetic estimation system for deuterated medicines, propose new candidate molecules for deuterium-substituted drugs, and experimentally validate them.

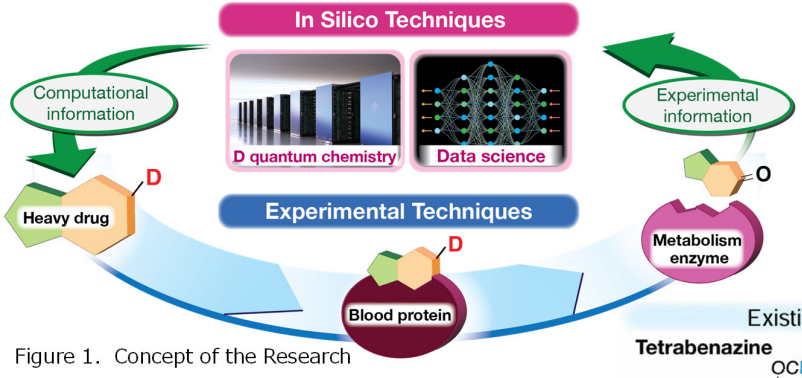


Figure 1. Concept of the Research

### ●Background of the Research

Recently, deuterated medicines (heavy drugs), which improve pharmacokinetics by replacing some light hydrogen atoms (H) in drugs with deuterium atoms (D), have attracted attention. In 2017, deuterated tetrabenazine (D-TBZ), a partially deuterated version of Huntington's disease drug tetrabenazine (TBZ), was approved as a new drug by the US FDA (Figure 2). These heavy drugs are based on the kinetic isotope effect (KIE), which is caused by differences in quantum mechanical effects such as vibrational states and tunneling effects. However, there is still a lack of knowledge on the affinity of heavy drugs with proteins involved in blood and on the enzymatic reaction rates in metabolic stability.

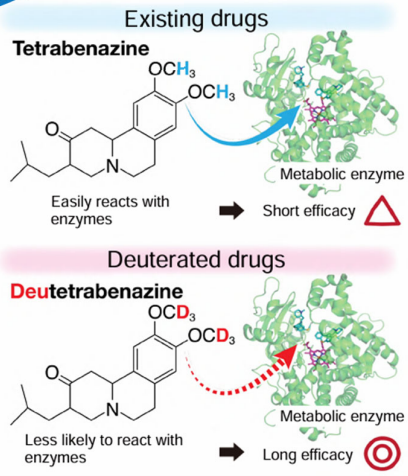


Figure 2. Deuterated drug approved by FDA in the United Staes

To understand such H/D isotope effect, one can expect to apply computational (in silico) techniques. Dr. Tachikawa has developed new quantum multi-component molecular theories (deuterium quantum chemistry) that can include nuclear quantum effect. He succeeded in explaining not only the H/D isotope effect in small molecules (Figure 3), but also the evaluation of KIE in the metabolic process of model drugs with proteins.

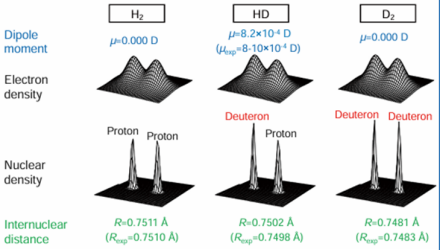


Figure 3. Differences between hydrogen and deuterium revealed by quantum multi-component molecular theory

### ●Purpose of the Research

We focus on deuterium-substituted pharmaceuticals and actively utilize “in silico” techniques (deuterium quantum chemistry and data science). In collaboration with experimental researchers of synthetic organic chemistry, biophysical chemistry, and analytical chemistry, we will set up deuterium-substituted model pharmaceuticals. We will also construct a pharmacokinetic estimation system for deuterium-substituted pharmaceuticals, propose new candidate molecules for deuterated pharmaceuticals, and validate them through experimental measurement.

## Expected Research Achievements

### ●Calculation and Synthesis of Deuterium Substituted Drugs

Deuterated model pharmaceuticals will be synthesized. Such substitution reaction mechanisms will be elucidated by our deuterium quantum chemical calculation.

### ●Interaction analysis with blood proteins

A multi-scale method will be implemented to calculate the binding nature of heavy pharmaceuticals to blood proteins. The complex structure and thermodynamic parameters will be determined by X-ray and isothermal titration calorimetry.

### ●Analysis of metabolic processes of deuterium-substituted medicines

To quantitatively evaluate “in silico” KIE, we will implement a reaction pathway analysis method based on our techniques. In vitro enzyme reaction kinetic analysis will be also performed (Figure 4).

### ●Understanding deuterated pharmaceuticals and Expectations for the Research

To elucidate the mechanism of the H/D isotope effect in pharmaceuticals, we will apply machine learning and explainable AI techniques using all the data from computation and experiment. We will propose new candidate molecules for deuterium-substituted drugs and experimentally validate them. Our research is expected to deepen and extend basic chemistry through the deuterium chemistry.

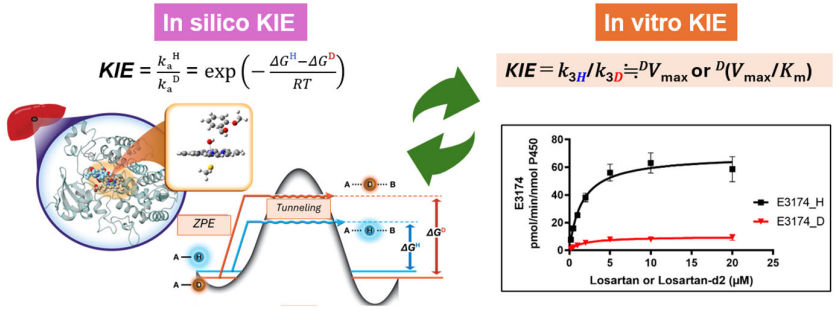


Figure 4. In silico KIE and in vitro KIE

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