TOYOHASHI UNIVERSITY of TECHNOLOGY
Hibarigaoka, Tempaku, Toyohashi, Aichi, 441-8580 Japan
PHONE: +81-532-44-6577 FAX: +81-532-44-6557
E-mail: press@office.tut.ac.jp

PRESS RELEASE

Source: Toyohashi University of Technology, Japan, Committee for Public Relations

Title: Chirality of vitamin-D derivatives affects the protonation states of its receptor protein
Subtitle: *Ab initio* molecular orbital calculations have elucidated that a change in the protonation states of the vitamin-D receptor is induced by altered chirality of vitamin-D derivatives

Full text:
Vitamin-D is recognized to play many important roles in the onset of immunological diseases, as well as the regulation of calcium level in the blood. These physiological actions caused by active vitamin-D are triggered by the specific interaction of active vitamin-D with the vitamin-D receptor (VDR); many types of vitamin-D derivatives have been developed as potent ligands against VDR. The binding affinity between human VDR and vitamin-D derivatives has been reported to depend significantly on the chirality of the derivative.

However, the reason for the dependence has not been clarified, which makes it a bottleneck in the development of novel and potent medicines against immunological diseases, whose onset is related to the activation of VDR.

Now, researchers at the Department of Computer Science and Engineering at Toyohashi University of Technology and at Teijin Pharma Ltd. and Teikyo University have demonstrated the possibility of the chirality of vitamin-D derivative to affect the protonation states of histidine residues in the VDR protein based on the results evaluated by state-of-the art molecular simulations and K-computer.

Researchers have observed the specific interactions between VDR and some vitamin-D derivatives to have different chiralities with *ab initio* fragment molecular orbital (FMO) calculations. The FMO results reveal that two histidine residues in the VDR contribute significantly to the binding of the VDR with the derivatives and that their protonation states can affect these specific interactions. Therefore, the researchers considered the other possible protonation states of these histidine residues and determined the most stable states using the ab initio FMO calculations. The results illustrated, for the first time, the possibility that the difference in the chiralities of vitamin-D derivatives can induce changes in protonation states of the histidine residues in the VDR that exists near the derivative. Due to this change in the protonation state, the derivatives can bind more strongly to the VDR and can thus produce more stable complexes with it.

TOYOHASHI UNIVERSITY of TECHNOLOGY
Hibarigaoka, Tempaku, Toyohashi, Aichi, 441-8580 Japan
PHONE: +81-532-44-6577 FAX: +81-532-44-6557
E-mail: press@office.tut.ac.jp

This finding provides an important and essential warning for the molecular simulations to consider protonation states of histidine residues in proteins more precisely while investigating the specific interactions between proteins and ligands.

“We have used sophisticated molecular simulations and K-computer to find that the protonation states of the histidine residues in the VDR change significantly with alterations in the chirality of ligand”, explains Associate Professor Noriyuki Kurita, “Since histidine residues exist in many proteins involved in the pathogenesis of diseases, we should consider their protonation states more precisely via *in silico* drag design based on molecular simulations.”

The first author, graduate student Yuta Terauchi, said, “Our final goal is to develop novel potent medicines capable of activating VDR based on our *ab initio* molecular simulations, as well as on the basis of biomedical studies performed by our collaborators.”

The authors are participating in an *in silico* drug design consortium – the fragment molecular orbital drug design (FMODD) consortium - in which various researchers from universities, drug companies, and national institutes are investigating the specific interactions between disease-related proteins and many types of candidate drugs using *ab initio* molecular simulations based on the FMO method and K-computer. Similar molecular simulations are underway now for a huge number of vitamin-D derivatives in order to propose novel ligands for VDR, which can act as candidate for potent drugs against immunological diseases, such as cancer.

Funding agency:
A part of this research was undertaken during activities of the FMODD consortium. A part of the results was obtained using the K-computer (project ID: hp170183 and hp180147).

Reference:
Yuta Terauchi, Rie Suzuki, Ryosuke Takeda, Ittetsu Kobayashi, Atsushi Kittaka, Midori Takimoto-Kamimura and Noriyuki Kurita (2018).
Ligand chirality can affect histidine protonation of vitamin-D receptor: *ab initio* molecular orbital calculations in water.
Journal of Steroid Biochemistry and Molecular Biology, in press.
(DOI: https://doi.org/10.1016/j.jsbmb.2018.09.020).

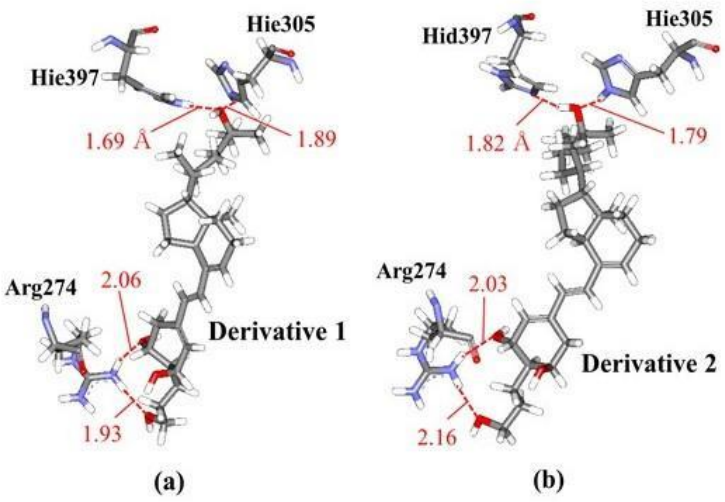
TOYOHASHI UNIVERSITY of TECHNOLOGY
Hibarigaoka, Tempaku, Toyohashi, Aichi, 441-8580 Japan
PHONE: +81-532-44-6577 FAX: +81-532-44-6557
E-mail: press@office.tut.ac.jp

Further information

Toyohashi University of Technology
1-1 Hibarigaoka, Tempaku, Toyohashi, Aichi Prefecture, 441-8580, JAPAN
Inquiries: Committee for Public Relations
E-mail: press@office.tut.ac.jp

Toyohashi University of Technology founded in 1976 as a National University of Japan is a research institute in the fields of mechanical engineering, advanced electronics, information sciences, life sciences, and architecture.
Website: https://www.tut.ac.jp/english/

Figure:



Title: Hydrogen bonding interactions between vitamin-D derivatives and amino acid residues in VDR
Caption: Hydrogen bonding interactions between vitamin-D derivatives and amino acid residues in VDR; (a) derivative 1 and (b) derivative 2 that have the same chemical structures but different chiralities. Our *ab initio* molecular simulations demonstrated that derivative 1 interacts with Hie397 and Hie305, while derivative 2 interacts with different protonated histidine residues, such as and Hie305, indicating that the difference in chirality of the derivatives can induce changes in histidine protonation states of the VDR protein.

Primary keyword: BIOCHEMISTRY, BIOINFORMATICS, BIOLOGY, BIOTECHNOLOGY,CANCER, CHEMISTRY/PHYSICS/MATERIALS SCIENCES, MEDICINE/HEALTH, MOLECULAR BIOLOGY, PHARMACEUTICAL CHEMISTRY, PHARMACEUTICAL SCIENCE