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Interaction analysis of AKR1C3-inhibitor complexes using fragment molecular orbital method and molecular dynamics simulation

Hikari Yoshimoto[1]
2033310131k@kindai.ac.jp

Norihito Kawashita[2]
nkawashita@life.kindai.ac.jp

[1] Graduate School of Science and Engineering, Kindai University, 3-4-1 Kowakae, Higashiosaka-shi, Osaka,577-8502, Japan
[2] Faculty of Science and Engineering, Kindai University, 3-4-1 Kowakae, Higashiosaka-shi, Osaka, 577-8502, Japan

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AKR1C3 belongs to the aldehyde-reductase (AKRs) family and has high-homology with AKR1C1, C2, and C4 [1]. Therefore, there is concern that side effects due to cross-inhibition may occur. In AKR1C3, it is expected that a more potent and selective inhibitor can be obtained by binding the inhibitor to the SP1 region consisting of Ser118, Asn167, Phe306, Phe311, and Tyr319 [2].

In this study, we performed interaction analysis of AKR1C3 inhibitor complexes and AKR1C2 inhibitor complexes by fragment molecular orbital (FMO) method and molecular dynamics (MDs) simulations to develop inhibitors with high selectivity for AKR1C3.

The crystal structures of AKR1C3 and AKR1C2 inhibitor complex which IC_{50} have been known in the literature [3-5] were downloaded from Protein Data Bank (PDB). Structural modifications and optimizations were performed using MOE. We also prepared the complexes that was not registered in the PDB by MOE Dock. 100 ns MD-simulations were performed using GROMACS for these structures, and a total of 10 structures were acquired in each complex, one for every 10 ns. FMO calculations were performed for the acquired structures and the inter-fragment interaction energies (IFIE) and PIEDA between each residue and inhibitor were calculated. ABINIT-MP was used as the FMO calculation, and MP2/6-31G* was used as the calculation level.

MD-simulations indicated that the interaction between SP1 in the ligand binding pocket and the inhibitor was weak in AKR1C2, and the inhibitor tended to approach Lys84 in many cases, so the interaction between the SP1 residue and the inhibitor is important. PIEDA also suggest that the dispersion energy (DI) of Phe306, Phe311 of SP1 contribute to the selectivity.

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