02-5

Redesigning the low-molecular weight SHP2 inhibitors with Computational Chemistry.

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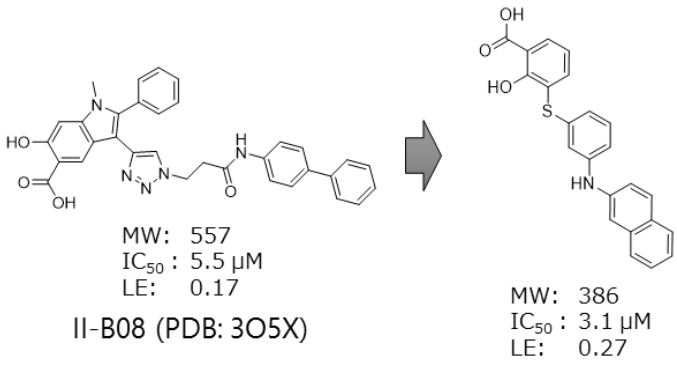
In recent years, thanks to the epoch-making improvement of structural analysis technology supported AI, various protein-ligand complexes have been revealed and have been available for structure-based drug design. In this study, we obtained novel active compounds based on the co-crystalized X-ray structures of anti-cancer target protein SHP2 which is related to the immune checkpoint pathway associated with PD-1 [1].

Method is as follows:

1) Analyze the SHP2 protein-ligand interactions of PDB structures [2-4] and design novel compounds with the same interactions using OPMF™ [5], our in silico FBDD technology.
2) Check the synthetic accessibility and the charged state of the experiment and calculation conditions.
3) Evaluate and select the compounds.
   - The binding stabilities calculated by MD simulation
   - The differences of the conformation energies between the complex form and free form calculated with molecular mechanics (MM) and quantum mechanics (QM)
   - The binding free energy calculated by MAPLECAFEE ™ V2
4) Synthesize the compounds and their analogues and evaluate SHP2 inhibitory activities.



We synthesized 10 of 18 selected compounds and 3 of 10 compounds showed IC_{50} < approximately 3 μM. The molecular weight, activity value and ligand efficiency (LE) of the three compounds were improved than the values of the PDB structure which we used for the drug design.

These results indicate that combination of the crystal structure of existing active compounds and our design technology could accelerate the development of novel low-molecular drugs.

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