Data-based Virtual Screening for Selective Drug Discovery

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Traditional drug development takes a lot of time and money, but recently, computer-based drug design has been attempted to reduce time and cost by using computer development and accumulated pharmacological activity data of compounds. New drug design research using computer studies the relationship between 2D/3D quantitative structure and activity of target protein, derives pharmacophore model, which is essential for pharmacological activity that substrate should have, proceed screening to select the optimal inhibitor. There are two types of computer-aided drug design studies: structure-based methods and ligand-based methods. The structure-based drug design method is to design a pharmacophore model for amino acid residues of the active sites based on the three-dimensional structure of the target protein under study. Ligand-based drug design methods use information from compounds known to be active on target proteins to design pharmacophore models and quantitative structure-activity relationship models to predict the activity of new candidate compounds.

In this study, selective inhibitors were designed using both methods. Ligand-based pharmacophore model consisting of ring aromatic, positive ionizable, negative ionizable, and hydrogen bonding receptors were generated from known active inhibitors. In addition, by analyzed the binding modes of known target proteins and ligands, we generated a structure-based pharmacophore model with the addition of hydrogen bonding donors. In order to increase bioavailability from a total of 4,508,836 drug databases collected from Enamine, Asinex, Chembridge, and Chemdiv, 305,452 compounds were filtered using Lipinski's 5th law, which is utilized in chemical-based drug design, and ADMET analysis sequentially. After that, 20 selective inhibitors were finally selected through the process of selecting compounds with a fit value of 10.6 or higher and eliminating duplication.