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SBDD of MDM2 inhibitors using FMO and data mining method

MDM2 (Mouse double minute 2 homolog) is known as a protein which is a significant negative regulator of p53. MDM2 is also considered to be E3 ubiquitin-protein ligase recognizing the N-terminal TAD (trans activation domain). Thus, MDM2-p53 interactions is proposed to be a promising therapeutic strategy for tumors. Previously, we reported a part of the FMO (Fragment Molecular Orbital) calculation results of MDM2 and its inhibitors at Chem-Bio Informatics Society (CBI). However, we could not obtain sufficient correlation between calculated and observed activities of the inhibitors. In this study, we added some FMO results and tried to obtain better correlation using data mining methods, such as PLS. First, we selected significant 53 amino acids from 85 ones for interactions between MDM2 and inhibitors considering the IFIE values. Then we obtained two latent variables as a result of PLS and cross validations. Resulted scatter plot between observed and calculated pIC50 of MDM2 is shown in Figure 1. we could obtain better correlation coefficient, R2=0.879. We are now calculating PIEDA of the complexes.

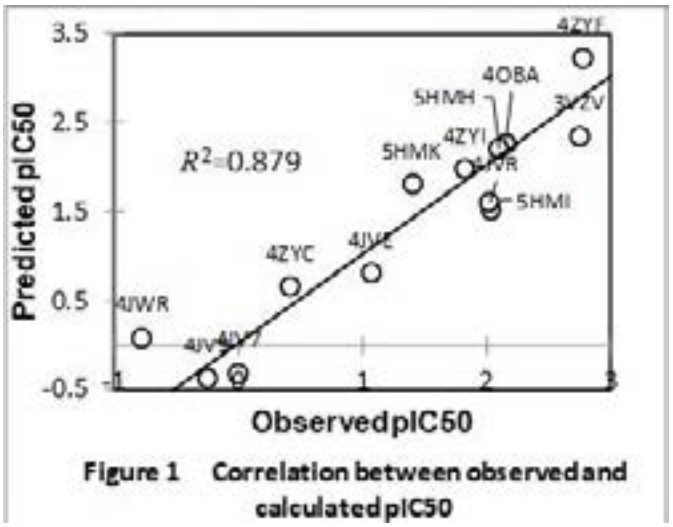

Figure 1 Correlation between observed and calculated pIC50

Biography

Tatsuya Takagi has completed his PhD from Osaka University. He had been an Assistant Professor of School of Pharmaceutical Sciences, Osaka University for 5 years. Then, since 1993, he had worked for the Genome Information Research Center, Osaka University as an Associate Professor until he became a Professor of Graduate School of Pharmaceutical Sciences, Osaka University in 1998. He has published more than 150 papers in reputed journals and had served as Chairman of Division of Structure-Activity Relationship of the Pharmaceutical Society of Japan for three years (until March 2017).

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