[P22] Prediction and Search for Biogenic Amine Receptor Antagonists Based on Electronic-Structure Informatics

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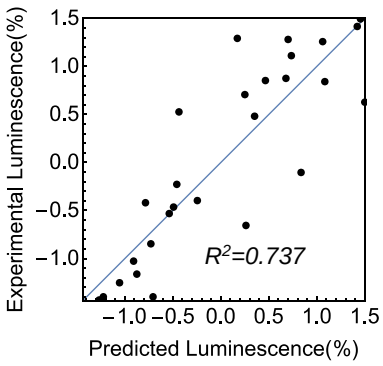
Biogenic amine receptors (BAR) have been known as targets to develop new pesticides because they control eating behavior of insects [1]. In order to understand and predict structure-activity relationships of the BAR-targeting pesticide molecules, it is desired to derive a statistical model which would facilitate their quantitative description. In this study, we focus on 35 antagonists to silkworm dopamine receptor (BmDopR2) experimentally investigated by Ohta et al. [1]. In our statistical modeling, 18 descriptors of molecules are evaluated through electronic-structure calculations since electronic interaction is considered to be a key in formation of ligand-receptor complexes. Herein the DFT(M06-2X)/6-31G** method was used in electronic-structure calculations.

In order to derive a regression model that explains and predicts experimental values representing biological activity, we used a multiple regression analysis. An objective variable is an experimental value describing the formation of 3',5'-cyclic adenosine monophosphate (cAMP) triggered by the interaction with the G protein-coupled receptor (GPCR), while explanatory variables are electronic descriptors. Through the regression analysis, we obtained

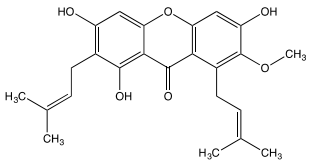
$$y = 0.88\delta\varepsilon_{H\text{-}L} - 0.30\lambda_{A\rightarrow N} - 0.29\lambda_{S\rightarrow T} - 0.60V_{mol} + 0.82\Delta E_{solv} \quad (1)$$

where $\Delta\varepsilon_{H\text{-}L}$ is the energy gap between HOMO and LUMO. $\lambda_{A\rightarrow N}$ and $\lambda_{S\rightarrow T}$ are the structure relaxation energies upon de-excitation from the electron-attached and T_1 states, respectively. V_{mol} and ΔE_{solv} are the molecular volume and solvation energy, respectively, evaluated by the DFT calculations. A good correlation between the experimental and predicted values was obtained by eq. (1) as shown in Figure 1. the coefficient of determination is 0.737 (see Figure 1).

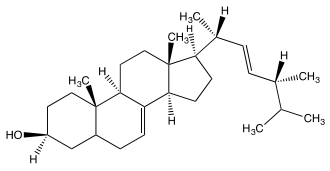


By referring to the regression model established herein, we searched for highly active compounds from a database which stores electronic-structure information on 6000 secondary metabolites of plants [2]. As a result, 31 compounds were predicted to have high activity. A part of the structures is shown in (Figure 2). The present study shows that statistical analysis based on electronic-structure calculations ("electronic-structure informatics") would be promising in screening potential antagonists.

Mangostin



Ergosterol



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