Development of a Quantitative Index for Early-Stage Screening of Compounds Targeting Protein-Protein Interactions

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There are indexes to score compounds to develop drugs, Lipinski’s rule of five (RO5) and QED are very famous. Protein-Protein Interaction (PPI) is a recent drug discovery target, but it’s very difficult to develop drugs, there are no indexes to score whether to target PPI.

What is the score?

Introduction

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Methodology

1. Introduction

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Methods (Difference from QED)

QEPPI was calculated using essentially the same procedure as that of the original QED, except for a few points. The differences from the original QED are as follows:

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It is basically the same as the modeling procedure for QED.

Plotting histograms

The same procedure as that of the original QED

Fitting of ADs function

The ADs function (Eq. (11)) by implementing the Levenberg-Marquard algorithm in SciPy

Normalization of All fitting functions

All fitting functions (Eq. (19) to Eq. (25)) were divided by the maximum value and normalized to give a value 0-1. The normalized function (Eq. (26) to Eq. (32)) was used as the desirability function.

Weighted desirability functions

The QEPPI score of compound # was assigned as the weighted geometric mean of all desirability functions (Eq. (38)).

Assignment of weights

The seven weights were thoroughly tested from 0 to 1 in increments of 0.25, and the average of the 1,000 combinations of weights that resulted in the highest Shannon entropy was adopted. The Shannon entropy of the model was calculated by the following formula (Eq. (39)).

Peak and weight of descriptors in QEPPI

QEPPI score: 0.79

Results

Both ROC-AUC and PR-AUC values are higher than 1- QED (QED, inv.). Additionally, F-score is also higher than RO4. These results suggest that QEPPI performs better than other indexes.

Interestingly, when each value of RO4 was plotted on the ROC and AUC curves of QEPPI, they were very close to each other, suggesting that RO4, an index of discrete value, could be extended to an index of continuous value. The results suggested that QEPPI is a general extension of the RO4 concept.

Our application of QEPPI to the 30 clinical candidates used by Truong et al. showed a median value of approximately 0.59, which is higher than that of commercially available PPI modulators. The QEPPI, modeled from IPP1-DB has the potential to be adapted to more recent PPI modulators.

Conclusion

In this study, we solved these problems by developing a quantitative index called QEPPI (Quantitative Estimate Index for Compounds Targeting Protein-Protein Interactions), specifically for early-stage screening of PPI-targeting compounds.

QEPPI performs better than other conventional indexes such as RO4 and QED, inv. QEPPI was also considered to be an extension of the concept of RO4. QEPPI has the potential to be more suitable for more recent PPI-targeting compounds.

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