Abstract

Virtual Screening of Multi-target Inhibitors by Combinatorial Support Vector Machines

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Virtual screening (VS) methods have been increasingly explored for searching multi-target agents. In this work, we evaluated the performance of combinatorial support vector machines (C-SVM) in searching dual inhibitors of 29 target pairs from 8 biochemical classes and of different similarity levels between their drug-binding domains. C-SVMs, trained by 68-1894 individual-target inhibitors for the 29 target pairs, were tested on 9-230 dual-target inhibitors collected from literature and produced dual inhibitor yields in the range of 17.65%-77.80% for low similarity target pairs, 14.63%-73.10% for intermediate similarity target pairs, and 38.26%-75.00% for high similarity target pairs. And the dual inhibitor virtual-hit rates identified by C-SVM in screening 168,000 MDDR compounds were as low as 0.00%-0.28% for low similarity target pairs, 0.02%-0.12% for intermediate similarity target pairs, and 0.03%-0.12% high similarity target pairs. In comparison with the other two VS tools k-Nearest Neighbor (k-NN) and Probabilistic Neural Network (PNN), C-SVM produced comparable dual-inhibitor yields and significantly lower false-hit rates in screening large chemical database, regardless of the similarity level of the target pairs. Combinatorial SVM showed promising capability in searching multi-target inhibitors of target pairs with varying similarity levels.

Keywords multi-target inhibitors, high-throughput screening, computer aided drug design, support vector machines, virtual screening