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In silico structure-based screening of versatile P-glycoprotein inhibitors using polynomial empirical scoring functions

Sergey Shityakov
University of Würzburg, Germany

P-glycoprotein is an ATP-binding cassette transporter that causes multidrug resistance of various chemotherapeutic substances by active efflux of them from mammalian cells. P-gp plays a pivotal role in limiting drug absorption and distribution in different organs including intestines and brain. Thus, the prediction of P-gp-drug interaction is of vital importance for assessing drug pharmacokinetics and pharmacodynamics properties. In order to aid in the discovery of strongest P-gp blockers, we performed an in silico structure-based screening of P-gp inhibitor database (1300 molecules) by genetic algorithm using polynomial empirical scoring functions (polscore). We report the strong correlation ($r2 = 0.80$, $F = 16.27$, $n = 6$, $p < 0.0157$) of inhibition constants (Kiexp/pKiexp) converted from experimental IC_{50} values with polscore-predicted constants (Kipolscore/pKipolscore) using a linear regression fitting technique. The hydrophobic interactions between P-gp and selected drug substances were detected as main forces responsible for the inhibition effect. The results show that this scoring technique might be useful in virtual screening and filtering of databases of drug-like compounds at the early stage of drug development process.

Keywords: P-glycoprotein, molecular docking, polynomial empirical scoring functions.

shityakoff@mail.ru