Machine learning approach to discovery of small molecules with potential inhibitory action against vasoactive metalloproteases

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Abstract
Abstract: With the advancement of combinatorial chemistry and big data, drug repositioning has boomed. In this sense, machine learning and artificial intelligence techniques offer a priori information to identify the most promising candidates. In this study, we combine QSAR and docking methodologies to identify compounds with potential inhibitory activity of vasoactive metalloproteases for the treatment of cardiovascular diseases. To develop this study, we used a database of 191 thermolysin inhibitor compounds, which is the largest as far as we know. First, we use Dragon's molecular descriptors (0-3D) to develop classification models using Bayesian networks (Naive Bayes) and artificial neural networks (Multilayer Perceptron). The obtained models are used for virtual screening of small molecules in the international DrugBank database. Second, docking experiments are carried out for all three enzymes using the Autodock Vina program, to identify possible interactions with the active site of human metalloproteases. As a result, high-performance artificial intelligence QSAR models are obtained for training and prediction sets. These allowed the identification of 18 compounds with potential inhibitory activity and an adequate oral bioavailability profile, which were evaluated using docking. Four of them showed high binding energies for the three enzymes, and we propose them as potential dual ACE/NEP inhibitors for the control of blood pressure. In summary, the in silico strategies used here constitute an important tool for the early identification of new antihypertensive drug candidates, with substantial savings in time and money. Graphic abstract: [Figure not available: see fulltext.]

Author keywords
Angiotensin-converting enzyme; Artificial intelligence; Docking; Machine learning; Neutral endopeptidase; Thermolysin; Virtual screening