A study of the allosteric inhibition of HCV RNA-dependent RNA polymerase and implementing virtual screening for the selection of promising dual-site inhibitors with low resistance potential

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Abstract

Structure-based pharmacophores were generated and validated using the bioactive conformations of different co-crystallized enzyme-inhibitor complexes for allosteric palm-1 and thumb-2 inhibitors of NS5B. Two pharmacophore models were obtained, one for palm-1 inhibitors with sensitivity = 0.929 and specificity = 0.983, and the other for thumb-2 inhibitors with sensitivity = 1 and specificity = 0.979. In addition, a quantitative structure activity relationship (QSAR) models were developed based on using the values of different scoring functions as descriptors predicting the activity on both allosteric binding sites (palm-1 and thumb-2). QSAR studies revealed good predictive and statistically significant two descriptor models (r2 = .837, r2adjusted = .792 and r2prediction = .688 for palm-1 model and r2 = .927, r2adjusted = .908 and r2prediction = .779 for thumb-2 model). External validation for the QSAR models assured their prediction power with r2ext = .72 and .89 for palm-1 and thumb-2, respectively. Different docking protocols were examined for their validity to predict the correct binding poses of inhibitors inside their respective binding sites. Virtual screening was carried out on ZINC database using the generated pharmacophores, the selected valid docking algorithms and QSAR models to find compounds that could theoretically bind to both sites simultaneously.

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