[P15] Toward the computer-aided discovery of FabH inhibitors. Do predictive QSAR models ensure high quality virtual screening performance?

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Antibiotic resistance has increased over the past two decades. New approaches for the discovery of novel antibacterials are required and innovative strategies will be necessary to identify novel and effective candidates. Related to this problem, the exploration of bacterial targets that remain unexploited by the current antibiotics in clinical use is required. One of such targets is the β-ketoacyl-acyl carrier protein synthase III (FabH). Here, we report a ligand based modeling methodology for the virtual-screening of large collections of chemical compounds in the search of potential FabH inhibitors. QSAR models are developed for a diverse dataset of 296 FabH inhibitors using an in-house modeling framework [1]. All models showed high fitting, robustness, and generalization capabilities. We further investigated the performance of the developed models in a virtual screening scenario. To carry out this investigation, we implemented a desirability-based algorithm for decoys selection that was shown effective in the selection of high quality decoys sets. Once the QSAR models were validated in the context of a virtual screening experiment their limitations arise. For this reason, we explored the potential of ensemble modeling to overcome the limitations associated to the use of single classifiers. Through a detailed evaluation of the virtual screening performance of ensemble models it was evidenced, for the first time to our knowledge, the benefits of this approach in a virtual screening scenario. From all the obtained results, we could arrive to a significant main conclusion: at least for FabH inhibitors, virtual screening performance is not guaranteed by predictive QSAR models.

[1] Pérez-Castillo, Y.; Lazar, C.; Taminau, J.; Froeyen, M.; Cabrera-Pérez M.A.; Nowé, A. J. Chem. Inf. Model. (2012) 52(9):2366-86.