The use of machine learning for generation of *Plasmodium falciparum* hsp90 selective inhibitors

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Introduction: Human malaria is responsible for over half a million deaths every year, mainly affecting children in sub-Saharan Africa. Existing therapeutic interventions are threatened by the development of resistance, particularly *P. falciparum*. The ATP dependent molecular chaperone heat shock protein 90 (Hsp90) plays critical roles in fundamental processes of cell signaling and, cell cycle control involving the folding and maturation of client proteins in *P. falciparum*. Therefore, *P. falciparum* Hsp90(PfHsp90) is an attractive drug target for antimalarial agents, because its inhibition interferes with essential cellular functions. PfHsp90 is implicated in drug resistance, therefore its targeting might circumvent resistance mechanisms

Methodology: This study implemented pathfinder to generate novel compounds in synthetically accessible chemical space and have affinity towards pfHsp90 using a retrosynthetic analysis from a reference compound with proven activity towards PfHsp90. The chEMBL database was explored to enable the discovery of more potent hit compounds and unlock new areas of a chemical space using machine learning models. An active learning-based protocol supported and enhanced by molecular docking, was used to train and test models that were used to screen for compounds in different chemical spaces and have selectivity towards PfHsp90 was employed. Synthetically tractable compounds were prioritized based on their induced fit docking energies and visual inspection.

Results & Discussion: The AutoQSAR active learning model shows that the PfHsp90 chemical space is well distributed with high and low scoring molecules mixed. The training of the models using an active learning approach yielded models with an average R^2 of 0.6925, Q^2 of 0.5836, SD of 0.4497 and RMSE of 0.4767. The results obtained suggests that the protocol implemented produced highly potent novel inhibitors with selectivity towards PfHsp90, which will be subjected to biophysical and biochemical analysis as well as cytotoxicity assays.

References

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