

Abstract

Machine-Learning QSAR Model for Predicting Activity against Malaria Parasite's Ion Pump PfATP4 and In Silico Binding Assay Validation [†]

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Malaria is a mosquito-borne infectious disease caused by parasitic protozoans of the genus *Plasmodium*. Although different effective antimalarial medicines have been developed, there is serious concern that parasites are developing widespread resistance to these drugs. To avoid this, now the efforts are concentrated on treating the malaria inside the *Anopheles* mosquito.

Several academic groups and companies are working worldwide to develop new compounds that fight the disease without provoking drug resistance. Within this context and making use of the Open Source Malaria project (<http://opensourcemalaria.org/>) which provides a large collection of molecules and 3D models of the targets with which they interact, we developed a machine learning-based QSAR model that predicts which molecules will block the malaria parasite's ion pump, PfATP4. The model was then employed to screen and classify the DrugBank database molecules and compounds coming from a proprietary marine molecules library. Finally, by means of an *in silico* binding assay, the predicted behavior was validated in the positive cases.

Summarizing, we have created a new set of repositioned drugs and marine molecules against malaria, establishing a good starting point for further studies and highlighting the key role that computational methods can have in the rational design of new drugs against infectious diseases.

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Author Contributions: A.L.-D.R. constructed the machine learning model and realized the QSAR experiments. L.L-P conducted the *in silico* binding experiments. A.P-L supervised the model generation, A.P-L and M.S-M supervised the QSAR experiments, A.N-C, C.A and M.S-M supervised the *in silico* binding experiments. All the authors analyzed and discussed the results. A.P-L and M.S-M conceived the study and designed the experiments. A.L.-D.R and L-L.P wrote the abstract whereas A-N.C, C.A, A-P.L and M.S-M corrected it.

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