Lead Antimalarial Identification Using In Silico Prediction Methods and Simulation

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Objectives. With increasing resistance to currently available antimalarials, new compounds with activity against resistant parasites are needed. Novel compounds were designed and first-in-human (FIH) simulations were performed, based on in silico predictions, to identify lead compounds. The most optimal lead compounds were then synthesized and in vitro experimental values were determined and compared with the in silico predictions.

Methods. Literature-based compounds known to inhibit dihydroorotate dehydrogenase were used to build a quantitative structure-activity model in ADMET Predictor™. Compounds active against Plasmodium falciparum (based on a phenotypic blood culture assay screen; PubChem Bioassay, AID 2306) were then used to identify attractive structural classes of antimalarials using MedChem Studio™. Novel compounds were generated by recombining substituents of the best compounds in the selected class. First-in-human plasma concentration (Cp) predictions in GastroPlus™, using the in silico predicted physicochemical properties, were used to select suitable lead compounds with acceptable dosage profiles. The selected compounds were synthesized and experimental versus in silico properties were compared.

Results. The synthesized lead compounds were determined to have more potent biological activity than the structurally related literature-based compounds, and the predicted and experimentally determined potencies were consistent. Experimental and predicted physicochemical properties were generally in agreement (RMSE of 0.6 log units).

Conclusion. In silico tools can be used to design, assess, and strategically identify potential antimalarial lead compounds with acceptable activity, risk, and human exposure profiles.

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