3D-QSAR modeling and synthesis of new fusidic acid derivatives as antiplasmodial agents

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Wide spread Plasmodium falciparum (P. falciparum) resistance has compromised existing antimalarial therapies to varying degrees. Novel agents, able to circumvent antimalarial drug resistance, are therefore needed. Fusidic acid is a unique antibiotic with a unique mode of action, which has shown weak in vitro antiplasmodial activity. Toward identifying new fusidic acid derivatives with superior antiplasmodial activity, a 3D-QSAR model was developed based on the antiplasmodial activity of previously synthesized fusidic acid derivatives. The validated Hypo 2 model was used as the 3D-structural search query to screen a fusidic acid-based combinatorial library. On the basis of the predicted activity and pharmacophore fit value, eight virtual hit compounds were selected and synthesized, including C-21 amide and C-3 ether derivatives. All synthesized hit compounds showed superior antiplasmodial activity compared to fusidic acid. Two C-21 amide derivatives displayed significant activity against the drug-sensitive NF54 strain with IC; 50; values of 0.3 μM and 0.7 μM, respectively. These two derivatives also displayed activity against the multidrug-resistant K1 strain, with an IC; 50; value of 0.2 μM and were found to be relatively noncytotoxic.

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