BENZOPHENONE-BASED FARNESYLTRANSFERASE INHIBITORS AS NOVEL ANTI-MALARIALS

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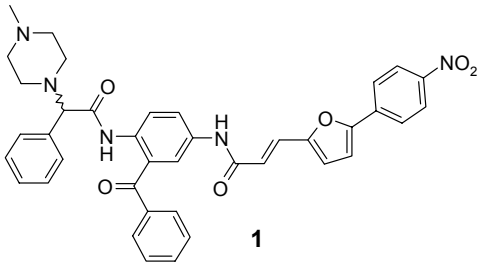
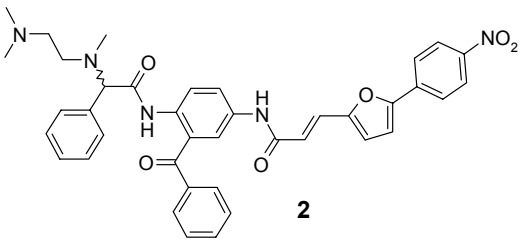
Malaria tropica, caused by the infection with *Plasmodium falciparum*, is one of the most important infectious diseases. Approximately 40% of the world population live in areas with malaria risk, and 2 to 3 million people die each year from malaria. Due to the increasing spread of parasites resistant against the common anti-malarials there is an urgent need for novel malaria therapeutics.

The development of farnesyltransferase inhibitors directed against *P. falciparum* has been generally accepted as a new strategy towards new drugs against malaria. Previously, we described benzophenone-based farnesyltransferase inhibitors with high *in vitro* anti-malarial activity but no *in vivo* activity.

Through the introduction of a methylpiperazinyl moiety we obtained the first farnesyltransferase inhibitors (e.g. **1**) for which *in vivo* anti-malarial activity was described [1]. Subsequently, a structure-based design approach was chosen to further improve the anti-malarial activity of this type of inhibitors.



1



2

Since no crystal structure of the farnesyltransferase of the target organism is available, homology modelling was used to reveal differences between the active sites of the rat/human and the *P. falciparum* farnesyltransferase. Based on flexible docking results, the piperazinyl moiety was replaced by open chain amines (e.g. the *N,N,N'*-trimethylethylenediamine moiety). This modification resulted in an inhibitor (**2**) with significantly improved *in vitro* and *in vivo* anti-malarial activity. Currently, this compound represents the farnesyltrasferase inhibitor with the highest anti-malarial activity known. Furthermore, inhibitor **2** displayed a notable increase in selectivity towards malaria parasites compared to human cells.

[1] Wiesner, J.; Kettler, K.; Sakowski, J.; Ortmann, R.; Katzin, A. M.; Kimura, E. A.; Silber, K.; Klebe, G.; Jomaa, H.; Schlitzer, M. Farnesyltransferase-Inhibitoren hemmen das Wachstum von Malaria-Erregern in vitro und in vivo. *Angewandte Chemie* **2004**, *116*, 254-257; Farnesyltransferase Inhibitors Inhibit the Growth of Malaria Parasites In Vitro and In Vivo. *Angew. Chem. Int. Ed.* **2004**, *43*, 251-254.