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Fragment-based Approach to the Discovery of Novel Plasmepsin II Inhibitors by NMR Screening and Molecular Modelling

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Malaria, one of the major re-emerging parasitic diseases, is caused by protozoal parasites belonging to the genus plasmodia [1]. To date, resistance has emerged towards all classes of antimalarial drugs, except artemisinins [2]; however, artemisin-resistant parasites are starting to appear in some regions [3]. Hence, drugs with novel mechanisms of action are desperately needed to combat the disease [4].

We chose plasmepsin II, an aspartic protease essential in ensuring *Plasmodium falciparum* life cycle [2], as a target for the development of new antimalarial drugs. In our study we used a fragment-based approach – a concept that proper optimization of each unique interaction in the inhibitor binding site and subsequent incorporation of the identified fragments into a single molecular entity should yield a compound with a binding affinity that is the sum of the individual interactions [5]. Thus, a fragment-based approach enables one to explore a dramatically larger portion of chemical structure space with considerably fewer compounds [6].

Our fragment library, which was obtained from a commercial supplier, consists of 1000 fragment-like compounds including 50 compounds selected from virtual screening of the fragment-like subset of the ZINC database [7]. We employed NMR spectroscopy to detect binding of the fragments to plasmepsin II, as it is well suited for detection of relatively weak binding.

We proved that our approach was successful by identifying micromolar fragment hits against plasmepsin II. The actives were confirmed using surface plasmon resonance and/or biochemical assay, and the binding pose was determined by molecular docking to guide further hit optimization.

Thus, the fragment-based NMR screening followed by molecular modelling enabled us to develop novel plasmepsin II inhibitors with IC_{50} values in high nanomolar range.

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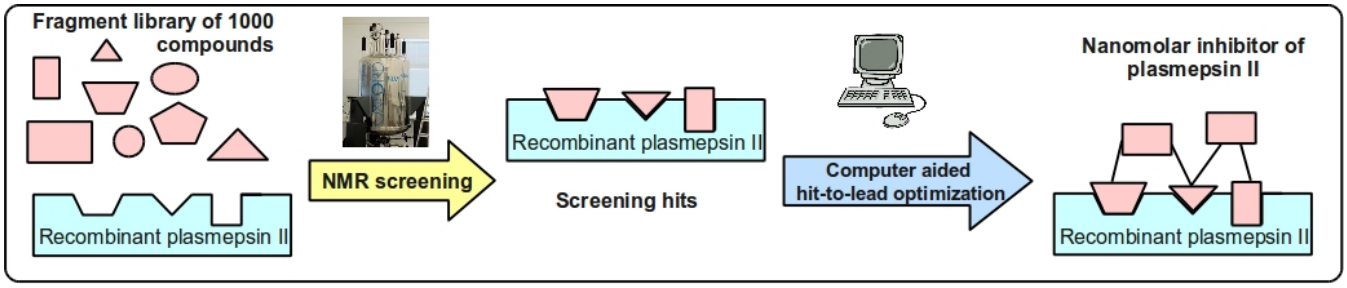

Figure 1. Discovery of plasmepsin II inhibitors by fragment-based approach