

Novel fragment-like PTR1 inhibitors discovered by virtual screening

C. P. Mpamhanga, L. Tulloch, E. Shanks, D. Robinson, W.N. Hunter P.W. Wyatt, R. Brenk
*Biological Chemistry and Drug Discovery, College of Life Sciences, University of Dundee, Dow St,
Dundee, DD1 5EH, U.K.*

It is not uncommon in the drug discovery process to find projects that have been ensnared into intractable ‘chemical cul-de-sacs’. This is often due to inherent poor physicochemical and ADMET properties of the existing hits or lead compounds. An increasingly popular method used to avoid this problem is fragment screening. The rationale being that identification of new fragments could provide new starting points for chemistry this process is now popularly referred to as ‘scaffold hopping’. Typically these methods use particularly sensitive biophysical methods such as NMR and X-ray which are able to identify even fragments with low binding affinities; however they come with one major disadvantage that of limited throughput. We therefore explored if virtual screening can be used as an initial step to screen rapidly vast fragment libraries for novel scaffolds.

To validate our strategy we chose the enzyme pteridine reductase 1 (PTR1), a short-chain dehydrogenase responsible for the salvage of pterins in, *Trypanosoma brucei*, a protozoan parasite. This parasite is the causative agent of sleeping sickness or Human African Trypanosomiasis (HAT), a human epidemic affecting large numbers in the Sub-Saharan region of Africa. The parasites are auxotrophic for foliates thus making PTR1 a desirable potential drug target.**(1)** So far all known PTR1 scaffolds retain high PSA and as a result may suffer from poor blood brain permeability, a crucial property required for effective HAT therapeutic agents.

Our strategy involved use of DOCK 3.5 **(2)**; DrugScore **(3)**, Interaction fingerprints **(4)** and the MAB force field **(5)**, to identify fragment-like compounds. This was followed by hit verification using appropriate biological-assays and X-ray crystallography to confirm the binding modes of the novel scaffolds. From an initial library of 25,000 commercially available fragments only 56 compounds were chosen for testing leading to the discovery of 15 compounds containing eight new scaffolds. One of these hits was subjected to crystal structure analysis and the predicted binding mode was confirmed. However, crystal structure analysis of two analogous revealed two distinct alternative binding modes. In these complexes, previously not observed protein movements and water-mediated protein-ligand contacts occur which prohibit prediction of the binding modes. This study demonstrates the power and pitfalls of using molecular docking for the discovery of fragment-like inhibitors.

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