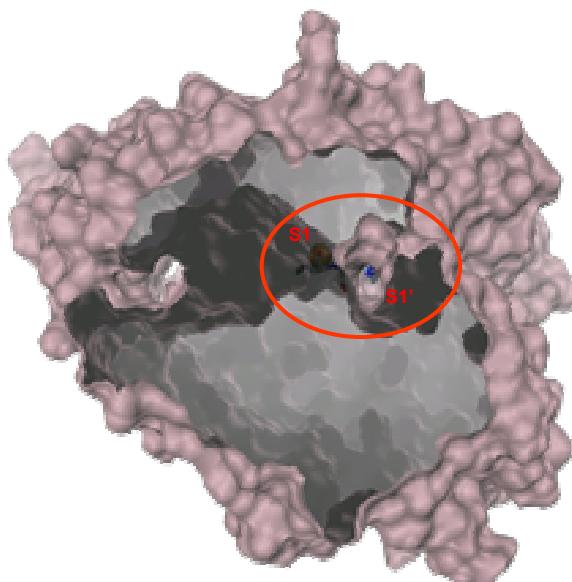


Strategies for ACE2 structure-based inhibitor design

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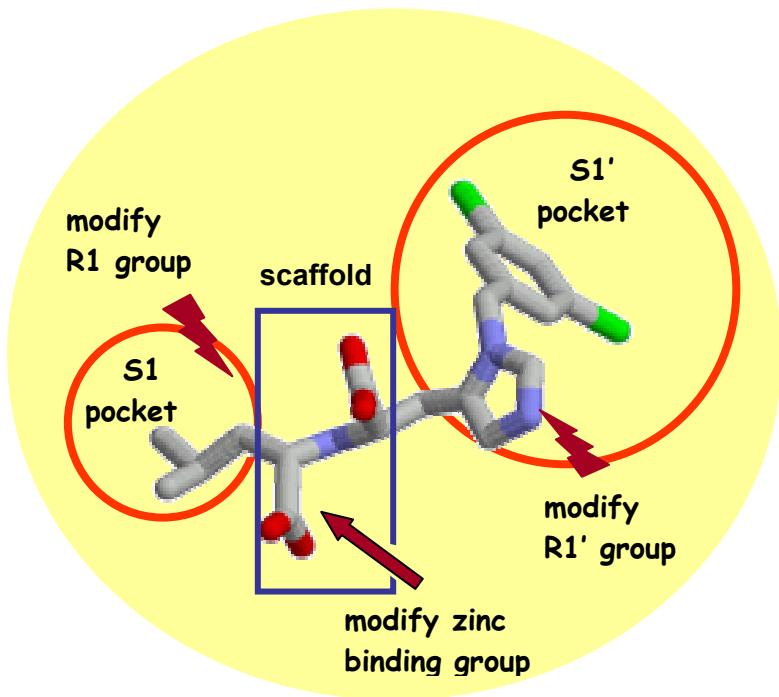
Angiotensin-Converting Enzyme (ACE) is an important drug target for hypertension and heart disease. Recently, a unique human ACE homologue termed ACE2 has been identified in the School of Biochemistry and Microbiology, which has been linked to hypertension, heart and kidney disease. In addition, ACE2 was shown to function as SARS-CoV-2 receptor. This surprising role and its assumed counter-regulatory function to ACE make ACE2 an interesting new cardio-renal disease target.

With the recently resolved ACE2 structure in complex with an inhibitor available, a structure-based drug design project has been undertaken to identify novel potent and selective inhibitors. The general long-term strategy comprises computational structure-based drug design approaches, as well as chemical synthesis of promising candidates, or purchase of existing compounds and bioassay-based potency evaluation by our collaborators. Computational approaches involve combinatorial library design and docking as well as pharmacophore-based virtual screening of large compound databases.



Cross-sectional view of the ACE2 substrate-binding site in form of a channel that stretches the whole protein. The protein is displayed as sliced surface to exhibit the interior and the translucent channel which is formed upon inhibitor binding. The inhibitor is sitting in the narrow bottleneck connecting the left (S1) and right (S1') active site pockets. The size of S1 is limited to the side chain of the inhibitor, whereas S1' is more spacious. The zinc metal ion is shown in spacefill.

A small number of synthetically accessible fragments were selected and individually evaluated for improved interaction energy using our in-house rigid-body docking tool Q-fit. In a second step, the *de novo* design tool, SynSPROUT, was applied for replacing the original side chain of the core structure with each fragment, and docking the whole molecule. Currently, we are preparing a combinatorial library on a larger scale by mimicking a synthetic reaction that involves synthetic starting material such as boronic acid derivatives and any naturally occurring amino acid. R-groups suitable for chemical synthesis will be assessed and prioritised via docking as described above.



Scaffold-based design strategy for new ACE2 inhibitors using the bioactive conformation of the ACE2 inhibitor. A combinatorial library is designed by replacing both R-groups on a common scaffold with suitable synthetic starting material that should satisfy both active site pockets (S1, S1'). In addition, alternative zinc binding groups can be screened for.

In a complementary approach, a protein-based pharmacophore model was created manually comprising several chemical features such as hydrogen bonding, electrostatic and hydrophobic interactions aligned in 3D, resembling specific drug-receptor interactions. Selectivity of the model was ensured by initial screening for ACE inhibitors and enrichment enhanced through repeated optimisation cycles. The final model is currently used to search 2.5 million unique compounds for matching features. Hits will further be evaluated and prioritised via docking and the most promising candidates proposed for purchase and biological testing.

Collaborators

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Funding

The author wishes to acknowledge support for this work by the University of Leeds Research Scholarship.