Virtual Screening for novel ACE2 Inhibitors using Structure-based Pharmacophore Hypotheses

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Introduction

Angiotensin-Converting Enzyme (ACE) is an important drug target for hypertension and heart disease. Recently, a close and unique human ACE homologue termed ACE2 has been identified, involved in hypertension, heart and kidney disease [1]. In addition, ACE2 was found to be a functional receptor of the SARS-Coronavirus. This surprising role and its assumed counter-regulatory function to ACE make ACE2 an interesting new cardio-renal disease target.

Aims and Objectives

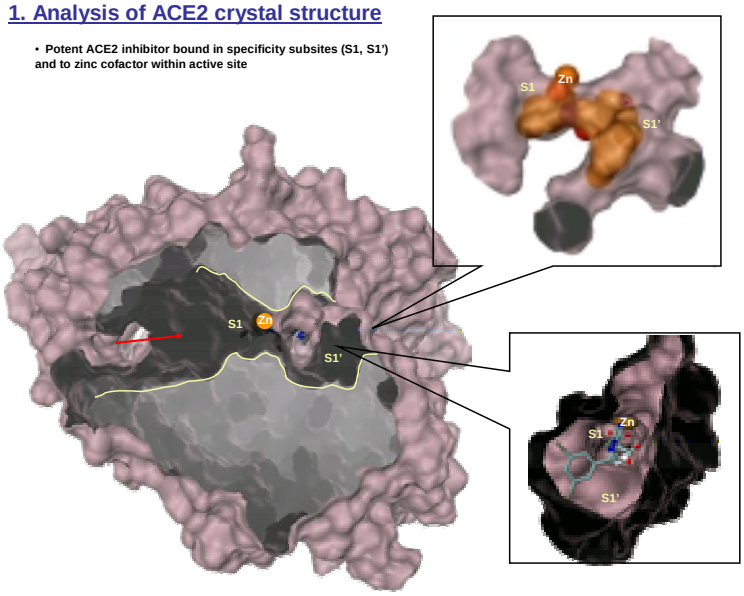
With the recently resolved ACE2 structure in complex with a potent inhibitor available [2], a structure-based drug design project has been undertaken to identify novel potent and selective inhibitors. The strategy comprises computational structure-based drug design approaches as well as chemical synthesis of promising candidates or purchase of existing compounds and bioassay-based potency evaluation. Computational approaches involve combinatorial library design and docking as well as pharmacophore-based virtual screening of large compound databases.

Methods

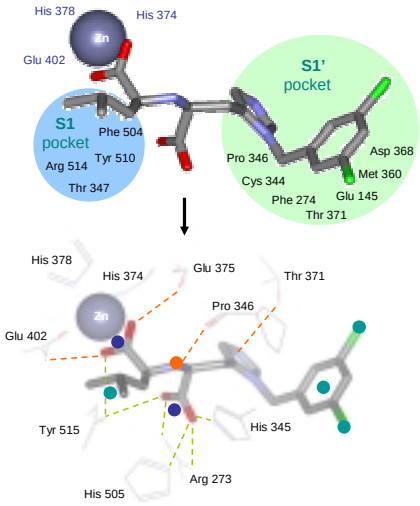
Various structure-based pharmacophore models were created with the software packages LigandScout [3] and Catalyst [4]. The strategy involved ACE2 active site analysis, identification and mapping of pharmacophore features such as hydrogen bond acceptors (HBA) hydrophobicity (H) and a zinc binding group (ZBG) aligned in 3D resembling specific drug-receptor interactions. Selectivity of the model was ensured by screening for ACE inhibitors and improved through repeated optimisation cycles. The final model was used for virtual screening of large 3D compound databases.

1. Analysis of ACE2 crystal structure

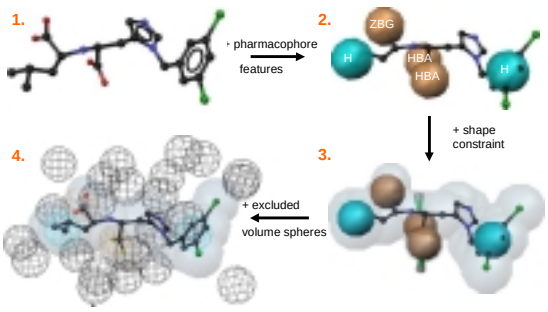
- Potent ACE2 inhibitor bound in specificity subsites (S1, S1') and to zinc cofactor within active site



2. Pharmacophore feature mapping

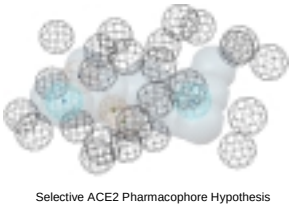


3. Design of a selective pharmacophore hypothesis

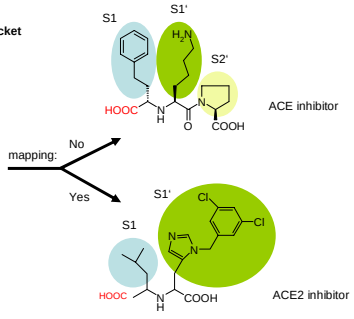


4. Selectivity test of hypothesis against ACE inhibitor mapping

- ACE and ACE2 related but distinct
- ACE inhibitors cannot inhibit ACE2 due to missing pocket



Selective ACE2 Pharmacophore Hypothesis



Results and Discussion

Screening of ~ 2.5 million unique compounds from 28 different commercial databases using various pharmacophore models with increasing selectivity resulted in restricted hit lists with an average retrieval rate of 0.36%. Top scoring hits were evaluated for structural diversity, "ACE2 drug likeness and ADME/Tox properties. Hits showed little diversity within and between databases and several compounds are identical among different vendors offered at competitive rates. A small number of most promising candidates were proposed for purchase and biological testing with the potential to become new lead structures for ACE2 inhibition.

Future Work

Experimental activity data will be employed for model refinement and improved database searching. Hit lists obtained by applying pharmacophore-based virtual screening will be used for a complementary *in silico* screening study based on the docking methodology.

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References

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[2] Towler P, Staker B, Prasad SG, Menon S, Tang J, Parsons T, Ryan D, Fisher M, Williams D, Dales NA, Patane MA, Pantoliano MW. *J Biol Chem.* 2004, 279(17):17996-8007.

[3] Wolber G, Langer T. *J Chem Inf Model.* 2005, 45(1):160-9.

[4] CATALYST Version 4.9, MSI, San Diego, CA, USA