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Abstract

The metallopeptidase Angiotensin Converting Enzyme (ACE) is an important drug target for the treatment of hypertension, heart, kidney, and lung disease. Recently, a close and unique human ACE homologue termed ACE2 has been identified and found to be an interesting new cardiorenal disease target. With the recently resolved inhibitor-bound ACE2 crystal structure available, we have attempted a structure-based approach to identify novel potent and selective inhibitors. Computational approaches focus on pharmacophore-based virtual screening of large compound databases. Selectivity was ensured by initial screening for ACE inhibitors within an internal database and the Derwent World Drug Index, which could be reduced to zero false positives and 0.1% hit rate, respectively. An average hit reduction of 0.44% was achieved with a five feature hypothesis, searching 3.8 million compounds from various commercial databases. Seventeen compounds were selected based on high fit values as well as diverse structure and subjected to experimental validation in a bioassay. We show that all compounds displayed an inhibitory effect on ACE2 activity, the six most promising candidates exhibiting IC50 values in the range of 62–179 μM.