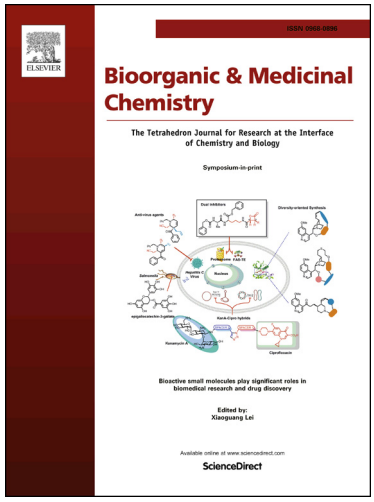

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Design, synthesis and biological evaluation of renin inhibitors guided by simulated annealing of chemical potential simulations

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ABSTRACT

We have applied Simulated Annealing of Chemical Potential (SACP) to a diverse set of ~150 very small molecules to provide insights into new interactions in the binding pocket of human renin, a historically difficult target for which to find low MW inhibitors with good bioavailability. In one of its many uses in drug discovery, SACP provides an efficient, thermodynamically principled method of ranking chemotype replacements for scaffold hopping and manipulating physicochemical characteristics for drug development. We introduce the use of Constrained Fragment Analysis (CFA) to construct and analyze ligands composed of linking those fragments with predicted high affinity. This technique addresses the issue of effectively linking fragments together and provides a predictive mechanism to rank order prospective inhibitors for synthesis. The application of these techniques to the identification of novel inhibitors of human renin is described. Synthesis of a limited set of designed compounds provided potent, low MW analogs (IC_{50}s < 100 nM) with good oral bioavailability (F >20-58%).

1. Introduction

Detailed investigations of the enormous costs and the extensive amount of time involved in drug discovery have called into question the benefits of early optimization efforts which were aimed at creating potent, single-digit nanomolar compounds.[1-3] There is substantial evidence that early efforts to drive hyper-potency typically lead to large and hydrophobic compounds.[4] Gleeson[5] argues that such compounds inherently possess a dichotomy between physicochemical parameters associated with potency and those associated with desirable ADME characteristics. Analysis by Wenlock[6] indicated that in the development pipeline, failure of oral drugs was associated with the higher MW and LogP candidates. Another analysis by Oprea[7] added solubility to Wenlock's analysis and confirmed that drug-like molecules are more likely to be low MW (<425) compounds.

A prominent and salient example of the tension between the early drive for very high potency and the difficulty of developing a real drug is the decades-long search for a renin inhibitor to treat hypertension. The Renin−Angiotensin−Aldosterone System (RAAS) plays a significant role in hypertension by regulating blood pressure and extracellular fluid volume.[8, 9] It has been shown that blockade of the RAAS, either with an angiotensin converting enzyme inhibitor (ACEi) or with an angiotensin II (AngII) AT1 receptor blocker (ARB) reduces blood pressure (BP). Another method for therapeutic intervention of the RAAS pathway would be directly target renin, the first and rate-limiting step in the system. After more than 20 years of research in the pharmaceutical industry, aliskiren, a sub-nanomolar compound with less than 3% oral bioavailability[10] in humans, was finally approved as the only marketed renin inhibitor to date. Aliskiren has a molecular weight of 551, which is a contributor to its poor *in vivo* properties and one of the reasons for the continuing research on better alternatives. Yokokawa[11] has comprehensively summarized the progress between 2009-2012 on investigations into creating renin inhibitors with a better balance of potency to physicochemical properties. While these efforts have produced promising new molecules, there is still no marketed alternative to aliskiren, which is a testament to how difficult it has been to achieve both potency and desirable physicochemical properties simultaneously.

The analyses of Gleeson,[5] Wenlock[6] and Oprea[7] suggest that a compound with MW<425 and a potency of around 50 nM promises to have the right characteristics for drug development. One approach adopted by the fragment-based drug design (FBDD) community[12, 13] has been to start with low affinity, small molecular weight compounds. Multiple distinct fragments predicted to bind in several adjacent pockets can be linked together to form higher molecular weight, higher affinity compounds. Ligand efficiency (LE),[14] a metric used to describe affinity per molecular unit, is very useful to compare different

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