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Research Article

Identification of novel human renin inhibitors through a combined approach of pharmacophore modelling, molecular DFT analysis and in silico screening

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ABSTRACT

Renin is an aspartyl protease of the renin–angiotensin system (RAS) and the first enzyme of the biochemical pathway for the generation of angiotensin II – a potent vasoconstrictor involved in the maintenance of cardiovascular homeostasis and the regulation of blood pressure. High enzymatic specificity of renin and its involvement in the catalysis of the rate-limiting step of the RAS hormone system qualify it as a good target for inhibition of hypertension and other associated diseases. Ligand-based pharmacophore model (Hypo1) was generated from a training set of 24 compounds with renin inhibitory activity. The best hypothesis consisted of one Hydrogen Bond Acceptor (HBA), three Hydrophobic Aliphatic (HY-Al) and one Ring Aromatic (AR) features. This well-validated pharmacophore hypothesis (correlation coefficient 0.95) was further utilized as a 3D query to screen database compounds, which included structures from two natural product repositories. These screened compounds were further analyzed for drug-likeness and ADMET studies. The compounds which satisfied the qualifying criteria were then subjected to molecular docking and Density Functional Theory (DFT) analysis in order to discern their atomic level interactions at the active site of the 3D structure of rennin. The pharmacophore-based modelling that has been used to generate the novel findings of the present study would be an avant-garde approach towards the development of potent inhibitors of renin.

1. Introduction

Renin is an aspartyl protease of the renin–angiotensin system (RAS) or the renin–angiotensin–aldosterone system (RAAS) and is secreted by the renal juxtaglomerular cells in the kidneys. It is involved in the regulation of the mean blood pressure and the electrolyte balance of the body (Pratt et al., 1988). Unlike other hormones which require peripheral receptors to achieve a physiological effect and to mediate signal transduction, renin functions as a hydrolyzing enzyme. Human renin is composed of 340 amino acid residues and possesses a mass of 37 kDa (Imai et al., 1983). It circulates in the blood stream and is involved in catalytically influencing the first and rate-limiting step of the RAS hormone system i.e., the conversion of angiotensinogen to angiotensin I and is therefore also classified as an angiotensinogenase with aspartyl protease activity (Mori et al., 1997). Subsequently angiotensin I is transformed into a highly vasoactive peptide, viz., angiotensin II, through the catalytic activity of the angiotensin-converting enzyme (ACE) that is primarily present in the extracellular fluids, viz., blood plasma, lymph and interstitial fluid, and which affects arterial vasoconstriction. Thus, the enzymatic activity of renin is the rate-limiting step in the regulation of the blood pressure, thirst and urine output of the body (Fujino et al., 2004).

An impaired RAS is often associated with a risk of high blood pressure (hypertension), cardiac infarction, renal failure and diabetes. A hyperactive RAS also affects hypertension which is instigated by vasoconstriction and the retention of sodium and water. This condition can be detected and evaluated by the Plasma Renin Activity (PRA) a.k.a. the renin (active) assay or the random plasma renin assay (Ram, 2009). PRA measures renin activity in blood plasma which is significantly involved in regulation of the

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mean arterial blood pressure. PRA is flagged as a critical prognostic biomarker for hypertension or hypotension-associated disease/disorders. Renin inhibitors can be hence, forwarded for the treatment of hypertension (Ram, 2009). ACE, though a key enzyme of the RAS system, is also associated with several other pathways which are important for homeostasis- hence its inhibition may result in side effects. Renin, which is highly specific in its action, is speculated to have lesser unwanted interactions and hence, fewer side effects. Moreover, inhibition of renin would imply the inhibition of the foremost rate-limiting step of RAS.

Abnormal levels of renin are often seen to occur in young patients with kidney-related cancers e.g. juxtaglomerular cell tumour (reninoma), Wilms' tumour, and renal cell carcinoma (Mendez et al., 2011). Therapies targeting renin have promising prospects for treatment of the aforementioned risks of high blood pressure (hypertension), cardiac infarction, renal failure and diabetes (Lindsay and Skrydstrup, 2006). 'Pepstatin' – a synthetic drug of microbial origin was previously forwarded as a prospective drug candidate for the inhibition of renin (Gross et al., 1972). However, due to disappointing outcomes in preliminary experiments, attributed to its high hydrophobicity and low solubility in blood serum – leading to weak interactions with renin, further interest in it waned (Eid et al., 1981). Peptide analogues (Webb et al., 1985; Szelke et al., 1982) and peptide mimetics were also found to be highly effective in inhibiting renin in controlled experiments and are under investigation (Wood et al., 1985).

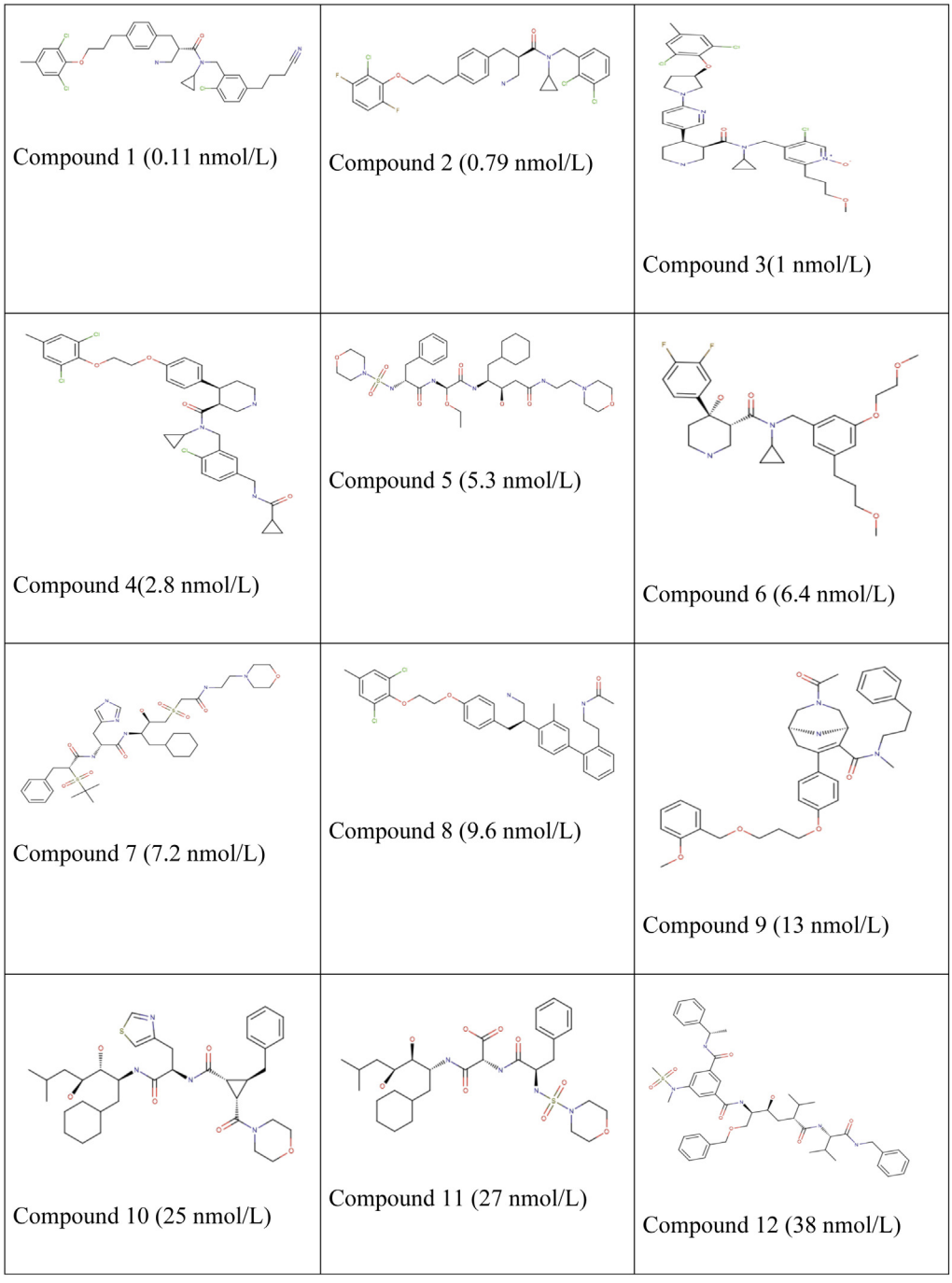

Fig. 1. Chemical structures of renin inhibitors in the training set – experimental activity in nmol/L is indicated within the parentheses.