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Manikandan A, Pearl Moharil, M. Sathishkumar, R.C. Muñoz-Garay, A. Sivakumar

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Therapeutic investigations of novel Indoxyl-based indolines: A drug target validation and Structure-Activity Relationship of angiotensin-converting enzyme inhibitors with cardiovascular regulation and thrombolytic potential

Manikandan A\textsuperscript{1}, Pearl Moharil\textsuperscript{1}, Sathishkumar M\textsuperscript{2}, R.C Muñoz-Garay\textsuperscript{2}, and Sivakumar A\textsuperscript{1}\textsuperscript{*}.

\textsuperscript{1}Dept. of Biotechnology, School of Bio-Sciences and Technology, VIT University, Vellore-632014, Tamil Nadu, India.
\textsuperscript{2}Institute of Physical Sciences, National Autonomous University of Mexico. Chamilpa, 62210 Cuernavaca, Morelos, Mexico.

*Corresponding Author, Email: siva_kumar.a@vit.ac.in

Abstract

A family of 12 members of Naphthalene-2-ol-indolin-2-one-thiocarbamides (5a-l) with pharmacological potentials of cardiovascular modulator were efficiently synthesized and evaluated. These compounds show inhibitory activity on angiotensin-converting enzyme (ACE), which is a principal constituent of the renin–angiotensin system and causative source for hypertension (HTN) (elevated blood pressure) and congestive heart failure (CHF), a parameter that was tested in this report. Prior to this, to get more insight into the binding mode and inhibition of human ACE C-domain (PDB ID: 2XY9) and N-domain (PDB ID: 3NXQ) compounds 5a-l was docked into the active site of them. The established inhibitory constant (\(K_i\)) (range 40-500 nM) and least binding affinities (-18.52 to -30.57 kcal/mol) indicated the therapeutic selectivity of compounds 5a-l towards ACE C-domain inhibition over ACE N-domain. The cytotoxicity effect of most potent compounds among 5a-l were tested in normal breast cells and MCF-7 cell lines. Simultaneously, \(H_2O_2\) induced antioxidant and DNA damage assessment was executed. Eventually, a thrombolytic activity followed by a human red blood cell (HRBC) membrane stabilization study to ensure the relaxation of blood and stabilization of RBC was executed. Structure-Activity Relationship (SAR) study discloses the potential of 5c, 5h, and 5k as cardiovascular protective therapeutic agents among 5a-l.

Keywords: Naphthalene-2-ol-indolin-2-one-thiocarbamides; ACE inhibitors; Angiotensin; hypertension; congestive heart failure; Molecular docking; Cardiovascular protection; Antioxidant; Cytotoxicity
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