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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

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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 (*Ki*) (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