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RESEARCH PAPER

STUDIES OF ANTI-HYPERTENSIVE ACTIVITY OF 1, 4-DIHYDROPYRIDINE DERIVATIVES: COMBINATIONS OF DFT-QSAR AND DOCKING APPROACHES

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1,4-Dihydropyridine (1,4-DHP) derivatives have been recognized as calcium channel blocker (CCB) agent. In this research, a series of 1,4-dihydropyridine (1,4-DHP) derivatives were theoretically examined for inhibitory activity against hypertension using density functional theory (DFT), quantitative structure activity relationship (QSAR) and docking approaches. The calculated molecular descriptors from DFT were used to develop QSAR model that related the descriptors to the bioactivity (IC_{50}). The QSAR analysis indicated that the energy of highest occupied molecular orbital (HOMO), dipole moment, solvation energy and average of electronic charges on heteroatoms are crucial parameters for the observed biological activity. The QSAR model predicted bioactivity (IC_{50}) agreed well with the experimental IC_{50}. All these compounds were docked against hypertensive cell receptors (PBD: 1IMT) and the binding free energy of ligand-receptor interactions agreed with the observed bioactivity (IC_{50}) of the 1, 4-DHPs with the receptor.

Key words: 1, 4-Dihydropyridine derivative, Calcium channel blocker, DFT, QSAR, Docking.

INTRODUCTION

Calcium channel blockers (CCBs) are drugs with heterogeneous set of compounds, categorized according to chemical structure such as dihydropyridines and diphenylalkylamines. CCBs also known as calcium antagonists help in the treatment of hypertension. CCBs act through voltage-dependent Ca^{2+} channel by preventing the entrance of calcium ions into cardiac and vascular smooth muscle cells (Lip and Beevers, 2001).

Hypertension, a diastolic blood pressure with BP greater than 90 mmHg and systolic blood pressure with BP greater than 140 mmHg, is the only risk factor that develops stroke, congestive heart failure, chronic kidney disease, and coronary artery disease and eventually leads to deaths (Ogah and Rayner, 2013). Hypertension is easily identified and can be managed if the patients undergo effective treatment but yet to be effectively controlled especially with people that as advanced in age (Havas *et al* 1993; Whitworth, 2003).

Chemotherapy is one of effective ways of managing hypertension and among CCBs, 1, 4-dihydropyridines (DHPs) are well known for their effectiveness. DHP is a pyridine based molecule and the parent to a set of molecules which are semi-saturated with two substituents that replace one double bond. They are well recognized in pharmacology as L-type calcium channel blockers, as well as in the treatment of hypertension. Therefore, the structural features of 1, 4-DHPs are well recognized as essential descriptors for their bioactivity as drugs that treat hypertension. Several DHPs class L-type