ASSESSMENT OF THE INHIBITORS OF CONNEXINS-43 USING QUANTITATIVE STRUCTURE-ACTIVITY RELATIONSHIP (QSAR) MODEL

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INTRODUCTION

Gap junctions (GJs) are transmembrane channels which are crucial for electrical interaction between cardiac myocytes. They consist of connexin family proteins, connexin-43 (Cx43) is the most prevalent isoform expressed in human heart tissue. QSAR is one of the most widely used computational modeling method to detect connections between structural characteristics of chemical compounds and biological activities. Activation or inhibition of Cx43 could be useful for the future treatment of cardiac arrhythmias and dysfunction.

METHODS

From other studies we managed to find 13 different substances and their half maximal inhibitory concentrations (IC_{50}) on GJs made of Cx43. We used the Avogadro molecular editor program to construct 3D structures with molecular mechanics and PaDEL Descriptor program to receive information about chemical and physical properties of those 13 substances. Then we used the QSAR model and managed to find correlation between those 13 molecules and their IC_{50} using Excel data analysis. The total of 1443 descriptors were obtained and 2 of them were chosen as they strongly correlated with the IC_{50} of the molecules we studied. We used multiple regression statistics in Microsoft Excel and calculated R^2 values.

CONCLUSIONS

IC_{50} of Cx43 inhibitors can be assessed by counting the number of nitrogen-hydrogen, oxygen-hydrogen bonds, heavy atoms and entering values into our predicted equation.

AIM

The aim is to find a method to assess the activity of the connexins-43 inhibitors using the QSAR model.

RESULTS

Descriptor-1 (nHBDon_Lipinski) value is counted as the number of nitrogen–hydrogen and oxygen–hydrogen bonds, descriptor-2 (nHeavyAtom) value is the count of all the atoms in the substance that are not hydrogen. The experimental IC_{50} was used from previous studies and converted into Log(IC_{50}). The predicted Log(IC_{50}) was calculated using multiple linear regression equation: (x_1 x descriptor-1 value) + (x_2 x descriptor-2 value) + b, where x_1=-0,425, x_2=-0,027, b=3,715 (x_1, x_2 and b values counted from regression analysis). Linear regression between experimental and predicted Log(IC_{50}) was calculated (R^2=0,809). The study data represents that the substance which had the highest hydrogen bonds count (nHBDon_Lipinski) and heavy atoms count (nHeavyAtom) inhibited Cx43 with the lowest IC_{50} value (phorbol-12,13-dibutyrate) and vice versa.