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Homology modeling and QSAR analysis of 1,3,4-thiadiazole and 1,3,4-triazole derivatives as carbonic anhydrase inhibitors

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Carbonic anhydrase (CA) inhibitors are very interesting target for designing anticancer (hypoxic) and antiglaucoma drugs. In the present study, a 3D homology modeling of human carbonic anhydrase-IX *(*hCA-IX*)* isozyme, based upon the crystal structure of murine CA-XIVA (PDB CODE 1RJ5) was performed, as no experimental 3D structures are available. A homology model of hCA-IX was developed and validated. To explore the responsible physicochemical properties of 1,3,4-thiadiazole and 1,3,4-triazole derivatives for carbonic anhydrase inhibition, a quantitative structure activity relationship (QSAR) study was performed having hCA-II and hCA-IX inhibitory activity respectively. In hCA-II and hCA-IX inhibitory activities, four significant models with good correlations (≥ 0.945 & ≥ 0.926) were obtained; two models (models 1 and 3) were selected based on statistical criterion. The QSAR study revealed that in case of hCA-II, overall increase in size and volume of molecule, introduction of electropositive surfaces might increase the inhibitory activity, whereas in case of hCA-IX, decreasing the hydrophobicity and introduction of electron releasing substituents might increase the hCA-IX inhibitory activity.

Keywords: Carbonic anhydrase inhibitor, QSAR, Anti-tumor, Homology, Modeller 9v2

Sixteen isozymes of α-carbonic anhydrase (CA) are discovered till now; the main difference is in their subcellular location and catalytic activity[1]. Among these four CAs are cytosolic (CA-I, III, VII and XIII), two are mitochondrial (CA-VA and CA-VB), one is secreted (CA-VI), and others are membrane bound (CA-IV, IX, XII and XIV). Three non-catalytic forms (CA-VIII, X and XI) are also reported and defined as carbonic anhydrase-related proteins[2,3]. A novel application of the CA inhibitors is their potential use in the treatment of hypoxic tumors[4-11].

In tumor conditions, CA-IX and CA-XII are highly expressed in tumor cells, but not in normal cells[12-15]. CA-IX is explicit in only a few normal tissues, but it is found in high concentration in many tumor types, due to its transcriptional activation by hypoxia via transcription factor hypoxia-inducible factor. These properties make CA-IX a useful marker and prognostic indicator for many types of tumors. In addition, it is also involved in regulation of pH and cell adhesion processes caused by tumor metabolism. Therefore, CA-IX and CA-XII inhibitors are interesting and potential targets for design of anticancer drugs[16].

Most CA inhibitors directly bind by deprotonated sulfonamide/sulfamate moiety to the catalytically critical Zn^{2+} ion of the active site of the enzyme, taking part in a large number of polar and hydrophobic interactions with amino acid residues of the active site cavity[17-23]. Supuran et al[24] studied the interactions of a small series of meracaptens with isozymes CA-I, II and IV. They suggested that -SH moiety of such derivatives may act as a zinc-binding function in the design of CA inhibitors, even though the potency of such compounds was lower than that of the sulfonamide derivatives.

In the present study, to better understand the relationship between catalytic site of CA-IX and their inhibitors a homology modeling technique has been used to generate the 3D structure of human carbonic anhydrase-IX (hCA-IX), due to the unavailability of crystallographic structure of hCA-IX. The developed homology model could be further exploited through docking studies for search of better selective

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Abbreviations: hCA-II, human carbonic anhydrase-II; hCA-IX, human carbonic anhydrase-IX; BLAST, basic local alignment search tool; MOE, molecular operating environment; AMBER, assisted model building with energy refinement; MMFF, Merck molecular force field.