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Abstract

Modeling of New VHR Inhibitors Based on 4*H*-1,3,5-Oxadiazine Derivatives †

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Abstract: *Vaccinia* H1-related phosphatase (VHR) is a dual-specific phosphatase that is a promising potential target for the treatment of many human diseases. In this work, we have proposed a series of 6-(4-chlorophenyl)-*N*-aryl-4-(trichloromethyl)-4*H*-1,3,5-oxadiazin-2-amines as potential VHR inhibitors. The SuperPred online server predicts VHR inhibition for the studied compounds with a probability of 88.88–98.51%. To establish the efficiency of binding of 4*H*-1,3,5-oxadiazine derivatives to the active site of VHR (PDB ID: 3F81) in the AutoDock Vina program, we have carried out molecular docking studies. According to the results, the studied compounds effectively interact with the hydrophobic region of the VHR active site due to aromatic rings and the trichloromethyl group, but the polar catalytic cavity is not involved, and therefore inhibition cannot be effective. In this regard, we have built a number of model compounds containing a sulfate group and its derivatives (methyl ester and amide) in the *para*-position of the arylamine fragment. According to the results of molecular docking, these compounds effectively bind to the polar catalytic cavity of the enzyme due to hydrogen bonds, but due to the relative rigidity of their molecules, hydrophobic interactions are not fully realized. Therefore, in these model compounds between the arylamine fragment and the sulfo group, we introduced a spacer with a length of one to three methylene groups. Hit compounds have been selected—2-(4-((6-(4-chlorophenyl)-4-(trichloromethyl)-4*H*-1,3,5-oxadiazin-2-yl)amino)phenyl)ethane-1-sulfonic acid and its amide.

Keywords: 4H-1,3,5-oxadiazine; molecular docking; VHR; cancer; inhibitor

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