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Exploring the binding mechanism of Heteroaryldihydropyrimidines and Hepatitis B Virus capsid combined 3D-QSAR and molecular dynamics

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ABSTRACT

The non-nucleoside drugs have been developed to treat HBV infection owing to their increased efficacy and lesser side effects, in which heteroaryldihydropyrimidines (HAPs) have been identified as effective inhibitors of HBV capsid. In this paper, the binding mechanism of HAPs targeting on HBV capsid protein was explored through three-dimensional quantitative structure-activity relationship, molecular dynamics and binding free energy decompositions. The obtained models of comparative molecular field analysis and comparative molecular similarity indices analysis enable the sufficient interpretation of structure-activity relationship of HAPs-HBV. The binding free energy analysis correlates with the experimental data. The computational results disclose that the non-polar contribution is the major driving force and Y132A mutation enhances the binding affinity for inhibitor **2** bound to HBV. The hydrogen bond interactions between the inhibitors and Trp102 help to stabilize the conformation of HAPs-HBV. The study provides insight into the binding mechanism of HAPs-HBV and would be useful for the rational design and modification of new lead compounds of HAP drugs.

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1. Introduction

The chronic Hepatitis B Virus (HBV) infection can lead to hepatocellular carcinoma and cirrhosis (Hwang and Cheung, 2011; Zeisel et al., 2015). HBV is an enveloped DNA virus with an icosahedral capsid, and has only a specific effect to human liver. At present, Food and Drugs Administration (FDA) approved seven drugs for the treatment of chronic hepatitis B infection (Manzoor et al., 2015). The majority of these seven drugs are the recombinant α-interferon (Isorce et al., 2015) and the nucleoside-analog drugs such as Lamivudine (Eron et al., 1995) and Hepsera (Ho et al., 2015). Unfortunately, the application of nucleoside-analogs is certain limited, for their serious side effects including the interferon or the substantial resistance of virus (Delaney et al., 2001; Dusheiko, 1997; Perrillo et al., 1990; Wong et al., 1993). The non-nucleoside drugs have been developed and are hopeful to replace the current treatments with the promise of increased efficacy, lesser side effects and shorter duration of healing (Katen et al., 2013; Lu et al., 2003; Wang et al., 2011; Zhang and Wang, 2014; Zlotnick et al., 2002). The HAPs are the kinds of non-nucleoside drugs (Bourne et al., 2006) that binds the HBV core proteins and misdirects the assembly of the capsid in vitro, instead of disturb the protein synthesis (Deres et al., 2003; Stray et al., 2005), and also have been identified as potent inhibitors of capsid maturation (Hacker et al., 2003). Many HAP derivatives have been discovered to decrease the production or accelerate the loss of HBV capsid protein. The advantage of HAPs supplies insight and correlates in vitro assembly with HBV replication in culture (Bourne et al., 2008). The found that the HAPs substituted by a heteroaryl ring (named Bay41-4109 and Bay36-5493) inhibited HBV replication by blocking the normal formation of nucleocapsids, and Bay41-4109 had good drug pharmacokinetic properties (Deres et al., 2003; Weber et al., 2002). NVR-010–001-E2 and GLS4 (Wu et al., 2013) were also potent inhibitors of HBV replication. Cp149-Y132A mutant will co-assemble with wild-type protein to generate extremely fragile capsids but does not poison nucleation (Bourne et al., 2009). Functionally similar HAPs and Y132A mutants may play a distinct critical roles in having antiviral effects on any self-assembling virus (Alexander et al., 2013; Klumpp et al., 2015; Packianathan et al., 2010). Currently, although a series of novel HAP derivatives have been

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designed and synthesized as inhibitors of HBV capsid assembly, the binding mechanism between these drugs and HBV core protein is still not clear, which maybe keep back the development of such drugs.

Computational chemical biology is increasingly essential in HBV study (Morgnanesi et al., 2015). The mechanisms of HBV polymerase resistance to lamivudine and emtricitabine were explored by the technologies of sequence alignments, homology modeling and molecular docking. The results shown that nucleotide analogs have the sulfur substituted or modified by a smaller atom or acyclic ring systems may retain activity against lamivudine-resistant mutant (Das et al., 2001). Several anti-HBV nucleoside drugs were studied by molecular docking (Sharon and Chu, 2008). Furthermore, the three-dimensional quantitative structure-activity relationship (3D-QSAR) methods have been developed to explore the influence of structural characteristics of drugs to their biological activities (Chai et al., 2011; Ma et al., 2016; Zhao et al., 2006), in which comparative molecular field analysis (CoMFA) and comparative molecular similarity indices analysis (CoMSIA) have been widely applied. Docking and molecular dynamics (MD) studies were used for characterization of entecavir targeting on HBV protein (Ismail et al., 2013). By means of the combination of 3D-QSAR and MD simulation methods, the more reliable conclusions could be obtained owing to the supports each other (Huang et al., 2011; Sheng et al., 2006).

In this work, the performed 3D-QSAR, molecular docking and MD including binding free energy calculation and decomposition to elucidate the binding mechanism in the complexes of Y132A Mutant HBV Core Protein and HAPs. Furthermore, the effect of Y132A mutation on binding mode of HAPs-HBV were investigated, which maybe provide some helpful suggestions for the development of such drugs.

2. Material and methods

2.1. Data sets

The data set was composed of 32 complex aromatic substituted HAP drugs derived from the references (Goldmann et al., 2001, 2006; Li et al., 2007a; Li et al., 2007b; Stoltefuss et al., 2002), which was randomly separated into two subsets: the training set with 24 compounds was used to establish CoMFA and CoMSIA models, and the test set with 8 compounds (indicated with * in Table 1) was employed to evaluate the predictive ability of the established models as external independent samples. The activity values of these HAPs were denoted as the 50% inhibitory growth concentration (IC_{50}). The IC_{50} values in the micro molar unit were transformed to in a molar unit and then to negative logarithmic scale marked as pIC_{50} (-logIC_{50}). The molecular structures of HAP drugs and their experimental pIC_{50} (Exp. pIC_{50}) values are listed in Table 1.

In SYBYL software, the structures of all drug molecules were constructed, and their geometrical conformations were optimized using the standard Tripos force field with the Powell conjugate gradient minimization algorithm, in which a convergence criterion was set to 0.05 kcal/mol Å. The net atomic charges were calculated with Gasteiger-Hückel method.

2.2. CoMFA and CoMSIA modeling

By means of SYBYL package, the molecule with the highest activity in data set served as template molecule, and the alignment of molecular skeletons was adopted (Hu et al., 2009). Then the analyses of 3D-QSAR were carried out. The CoMFA descriptors, including steric (Lennard-Jones 6-12 potential) and electrostatic (Coulomb potential) field energies between the probe atom and the aligned molecule, were calculated at each lattice with grid spacing of 1 Å and extending to 4 Å units beyond the aligned molecules in all three dimensions within defined region. The step was 2 Å, and the probe atom was a sp^3 carbon atom with van der Walls radius of 1.52 Å and a charge of $1e^-$. The CoMFA fields generated automatically were scaled by the CoMFA-STD method with default 30 kcal/mol. For CoMSIA method, the five different fields (steric, electrostatic, hydrophobic, hydrogen bond donor and hydrogen bond acceptor) were calculated using the same probe atom in CoMFA analysis. The attenuation factor was the default value of 0.3. To speed up the analysis and reduce the noise, the column filtering was set to 2.0 kJ/mol.

Partial least-squares (PLS) (Wold et al., 2001) regression analysis was carried out using SYBYL software, in which the CoMFA or CoMSIA descriptors served as independent variables and the experimental pIC_{50} values denoted a dependent variable. Then the two 3D-QSAR models (CoMFA and CoMSIA) were established, respectively. The predictive ability of the models was evaluated by leave-one-out (LOO) cross validation, and the cross-validated coefficient q^2 was calculated using Eq. (1):

$$q^2 = 1 - \frac{\sum \left(Y_{pred} - Y_{\exp}\right)^2}{\sum \left(Y_{\exp} - Y_{mean}\right)^2} \tag{1}$$

where, Y_{pred}, Y_{exp} and Y_{mean} are predicted, experimental and mean values of the target property (pIC_{50}), respectively. The optimum number of components in model was ascertained according to its highest LOO cross-validated q^2 and the lowest standard error of prediction in training set.

The predictive correlation coefficient R^2_{pred}, based on the test set, was defined as Eq. (2):

$$R^2_{pred} = \frac{(SD - PRESS)}{SD} \tag{2}$$

where SD is the sum of squared deviations between the biological activities of the test set molecules and the mean activity of the training set molecules, and $PRESS$ is the sum of squared deviations between the observed and the predicted activities of the test molecules.

The CoMFA and CoMSIA results were also graphically interpreted by field contribution maps (contour maps) using the "STDEV*COEFF" field type.

2.3. MD simulations

2.3.1. Molecular docking

Molecular docking is defined as the computer simulation of how ligands bind to a receptor of the known 3D structure. The crystal structure of human HBV core protein in complex with inhibitor **2** (PDB ID: 5E0I (Klumpp et al., 2015)) and **HAP18** (PDB ID: 5D7Y (Venkatakrishnan et al., 2016)) were downloaded from RCSB Protein Data Bank (www.rcsb.org/). 5E0I is Y132A mutant HBV core protein. Schrödinger 9.0 software package (Sherman et al., 2006) was employed to dock the drug molecules into the active pocket of HBV capsid protein. The preparation of HBV protein was accomplished through the Protein Preparation Wizard. Firstly, repaired missing residues, removed all crystallographic water molecules, added all hydrogen atoms and adjusted the ligand bond orders and formal charges. Secondly, B and C chains were retained in 5D7Y (A, B, C and D chains) and 5E0I (A, B, C, D, E and F chains), and were submitted to restrain minimization to release steric clashes using the OPLS_2005 force field (Shivakumar et al., 2010). Finally, the

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