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Computer-aided Drug Design Method for Anti-hepatitis C Drug Design

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Abstract

Hepatitis C is ***a*** *disease caused by the hepatitis C* ***virus and can cause*** *serious liver damage. There is* ***currently*** *no vaccine for this* ***disease*** *and the number of* ***infections*** *continues to increase worldwide. Currently used antiviral drugs are interferon alfa-2a and ribavirin, but about half of patients do not respond to therapy. Therefore,* ***new drugs that protect against hepatitis C need*** *to* ***be investigated.*** *Computational drug methods have been instrumental in finding drug candidates. This review is devoted to the role of computational drug development methods in the development of new hepatitis C drugs Additionally, we propose a QSAR model as a binding method to simulate in vivo anti-hepatitis C activity and use homology modeling and ab initio modeling to generate protein 3D structure conformations as identification of pockets in proteins. Pocket druggable ligands were developed using novel drug design method. Designing effective ligands requires considering the geometry of the target protein's pocket. Recent advancements have led to the development of new drugs tailored specifically for each Hepatitis C Virus (HCV) protein. By meticulously matching the ligand structure to the protein pocket's unique shape, these drugs promise enhanced specificity and efficacy in combating HCV.*

Keyword: Anti-HCV agents, QSAR, 3D-QSAR, structure-based drug design, linear discriminant analysis, fragments

INTRODUCTION

Hepatitis C (HC) is an infectious disease that affects the liver. It is caused by the hepatitis C virus (HCV), which is the only known member of the family of hepatitis viruses of the family Flaviviridae [1]. Although the disease is often asymptomatic, once established, chronic disease can cause scarring (fibrosis) and scarring (cirrhosis) of the liver and often lasts for years. Some people with cirrhosis develop liver failure or other complications of cirrhosis, including liver cancer, and in other cases, life-threatening varices in the esophagus and stomach. HCV infection is now believed to be both parenteral and hospital acquired, and it is estimated that nearly 200 million people worldwide become infected with HCV, with an additional 2-3 million each year. Therefore, HC may be the next pandemic [2, 3]. Spontaneous clearance of the virus is highly variable, and 10-60% of HCV-infected individuals clear the virus during the acute phase, as indicated by elevated levels of liver enzymes (alanine transaminase (ALT) and aspartate transaminase AST) and plasma HCV Purification of RNA (this is called spontaneous virus purification) *However*, persistent *infection is* common and most patients develop hepatitis C [4]. The prevalence of HCis higher in Asian and African countries where health condition very unfavorable. The *worst case is Egypt,* where HC is thought to be linked to

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discontinued *large-scale* treatment for *schistosomiasis, which* is endemic in the country [5]. An important factor of HCV is its ability to cause co-infection with humans. Human immune deficiency virus (HIV) [6] which is a major cause of death in immunocompromised patients.

Today, dealing with HC is very difficult. Current treatment is a combination of pegylated *interferon-a-2a [7] (peginterferon-a-2b* can also be used) *and the* antiviral drug ribavirin for 24 or 48 weeks, depending on the genotype of *HCV [8, 9].* Interferon alpha-2a is a protein released by lymphocytes in response to the presence of pathogens such as viruses, *bacteria, viruses, or brain tumors* (Figure 1). It is one of the proteins that allow cell-to-cell communication to trigger defense mechanisms of the immune system that destroy pathogens or tumors. The pegylated form (40 KDa; trade name Pegasus) is an antiviral drug discovered by the pharmaceutical company F. Hoffmann-La Roche; it hasa dual mode of action-both antiviral and immunomodulatory. Adding polyethylene glycol to interferon through a process known as pupylation increases the half-life of interferon compared to its original form.

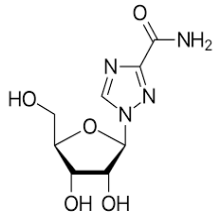

Figure 1. Structure of ribavirin.

On the other hand, ribavirin is a nucleoside antimetabolite used as an antiviral agent that inhibits the synthesis of nucleic acid and is used against both RNA and DNA viruses (Figure 1). This drug inhibits the activity of the RNA-dependent RNA polymerase enzyme because it resembles the building blocks of RNA molecules. *Oral forms are used* together with interferon *drugs to treat HC.* In any case, this treatment is generally recommended for patient with established chronic HCV infection and persistent abnormalities in liver function tests. However, approximately 50% of patients do not respond to antiviral therapy. There is generally no vaccine against HC. Therefore, the search for effective antiviral treatment against HCV is a challenge for the scientific community to find compounds with anti-HCV activity in a more rational and effective way. In this sense, computer-aided drug design (CADD) methodologies play an important role in the fields of chemoinformatic [10, 11] and bioinformatics which have been important to better understand infinity. chemical, biochemical and biological processes to perform rational drug design in less time and with significant resource savings. This is because they focus on the use of multiple computational methods that allow the processing of biological data related to chemical structure at different levels of complexity and diversity. This review focuses on the current state of CADD methods for the development of new anti-HCV agents. Here, we confirm the great importance of CADD by introducing a model based on structural approaches to design new antiviral agents with potent in vivo HC activity [12, 13].

CADD METHODOLOGIES FOR THE DISCOVERY OF DRUGS AND TARGETS

Today, CADD methodologies for the development of new anti-HCV agents and generally for each drug class can be divided into two broad categories. The first category refers to methods *for obtaining information about* the three-dimensional structure of *chemical receptors through experiments* such as X-ray crystallography or *nuclear magnetic resonance* spectroscopy. If the receptor structures are not available, homology model of the biological receptor can be generated. This first class of methods is often called structure-based drug design. The second category includes methodologies that do not consider the three-dimensional structure of the receiver. They are based on the *detection of molecular structures* in molecular *structures and* have biological activity due *to interactions* with *receptors.* The commonly accepted name for such methods is ligand-based drug design. Mainly the second category, but (recently) the first includes models known as quantitative structure-activity relationship (QSAR)

models. In all these cases we. Can find models that use structural parameters of molecular systems as input to predict the properties of such a system, such as drugs, protein structure, RNA secondary structure, protein-protein interaction networks (PINs), genes network). Therefore, the editor González-Díaz extended the discussion to various groups of authors who edit special issues on CADD techniques (including QSAR and others) published in publications such as Current Issues. in medicinal chemistry, current proteomics, current drug metabolism current pharmaceutical design and current bioinformatics [14–19].

Structure-Based Drug Design

In general, structure-based drug design is strongly related to bioinformatics, which concerns the application of statistics and computer science to the field of molecular biology and has been a crucial factor in achieving a better understanding. of biochemical and biological processes. Methods such as molecular docking, homology modeling, structure-based virtual screening, and many others comprise a select group of molecular modeling techniques (MMT)in structure-based drug design [20–23].

Several *efforts* using MMT have been reported in the field of HCV *vaccination [24]*. In general, almost all work has focused on finding effective anti-HCV agents by inhibiting NS5B and NS3 proteins. This viral RNA replicase shows about a million times lower fidelity than replicative prokaryotic or eukaryotic DNA polymerase removal. This is in part because NS5B does not contain an exonuclease or proofreading region [20–21]. In NS5B, two *different* cations coordinated by *the* carboxyl *group* (as seen in DNA polymerases) catalyze the polymerization of RNA triphosphate monomers to extend the primer *chain from* the *beginning. The* residues *serving different* cations *(Mg 2+ or Mn 2+* in vitro) *in NS5B are* three *functional* aspartates (220, 318, and 319). Another resin *examined* is NS3 serine *protease. An important study resulting from in silico screening combining LB)* and structure-based (SB) *approaches* for *novel allosteric inhibitors* of HCVNS5B polymerase *has been.*

Described. In this instance, the Combining a comprehensive computational process with biological research produced novel molecular scaffolds that had never been tested with NS5B polymerase. NS5B non-nucleoside inhibitors (NNIs), whose binding conformations were easily accessible from the protein database (PDB), were used to create structure-based 3D-QSAR models. Depending on which of the two training sets of structurally distinct NS5B NNIs they bound—the thumb (15 NNIs) or palm (10 NNIs) domains of the enzyme—these were categorized.

This is why LB and SB alignments were thoroughly examined to evaluate the accuracy of the molecular alignment for an unidentified binding mode [20–21].

24 Experimental Binding Conformity Error Minima for the Experimental Allosteric NS5B Inhibitor Binding conformations 81 (thumb) and 223 (blanket) were taken from the data for LB and SB and used as an external reference to build a 3D QSAR model. The low prediction error indicated that 3-D QSARs are useful scoring functions for an in-silico screening procedure. Finally, virtual screening of thence diversity resulted in the selection of the top 20 scoring molecular enzymatic assays for each final model. Among the 40 selected molecules, initial data yielded four derivatives with IC50 values ranging from 45 to 75micro meter [22–23].

On the other hand, promising efforts to identify novel HCV-NS5B inhibitors using pharmacophore-based virtual screening and in vitro assays have been reported. NS5B polymerase inhibitor. Based on new data identifying the NS5B pocket, which is distinct from the nucleoside-binding domain but well-received among various HCV isolates, a virtual analysis of this combination was performed. A library of 3.5 million countries. The inhibitory activity of 119 compounds selected in silico was evaluated in vitro by RNA-dependent RNA polymerase (RdRp) assay. 4) and kinetic analysis showed that these compounds were not competitive. ribonucleotide substrate. In addition, mutation of a conserved residue in the NS5B binding pocket led to a decrease in RdRp activity; this suggests that the binding pocket proposed here may be essential for HCV treatment intervention. These new inhibitors will help develop

effective anti-HCV drugs. Another reported study also focused on the search for new NS5B inhibitors using pharmacophore-guided virtual screening [22]. To achieve this goal, the method was applied to identify new HCV-NS5B inhibitors. A pharmacophore model generated from previous binding mode analysis and structure-based 3D-QSAR studies of arylides acid analogs was used. In this pharmacophore-driven virtual screening, 40 compounds were selected as new candidates for HCV-NS5B inhibitors from 37,447 compounds in the chemical library LeadQuest and evaluated for their biological activities. This fact was because this compound was very active against HCV-NS5B.

Ligand-Based Drug Design

Relative to these methods based on knowledge of receptor structure, quantitative structure-activity relationship techniques (including 3D-QSAR approaches) have played a crucial role. These.

Methods were strongly supported by chemometric methods such as multiple linear regression (MLR) linear discriminant analysis (LDA) artificial neural networks (ANNs), partial least squares (PLS). and many other techniques. On the other hand, complex network theory (CNT) during the past 10 years allowed deeper convergence between ligand-based and structure-based drug design and contributed to a better understanding of several biological phenomena. different levels of chemical diversity and complexity.

Several works have been published using SAR techniques to discover new anti-HCV compounds. Many of these works used 3D-QSAR as a method to model anti-HCV activity. The goal was to find the most active molecules that can provide more information about molecule-receptor interactions.

*Therefore***,** comparative molecular *response* analysis *(CoMFA) and* comparative molecular similarity index *(CoMSIA) were performed on* 67 HCV-NS5B polymerase inhibitors using two methods. First, **a** ligand-based 3D QSAR *study was performed* based on the lowest *energy configuration* using *atomic model fitting. The result is a predictable connection.* The predictive ability of the *model was* validated using a *different* set of 22 compounds that were not included in the original 45 compound *training*. The *estimated R2 values for* the ligand-based CoMFA and CoMSIA models were 0.734 and 0.800, while the corresponding *estimated R2 values for* the receptor-based CoMFA and CoMSIA models *were 0.538* and 0.639. Tryptophan derivatives showed stronger effects than tyrosine derivatives and interpreted from CoMFA steric and electrostatic contour maps. The CoMSIA results showed that significant inhibitory activity of the NS5B inhibitor required hydrogen bond donor and acceptor groups at the 5-position of the indole ring and an R-substitution at the chiral carbon. Interpretation of the CoMFA and CoMSIA contour maps in the context of NS5B allosteric binding topology provided insight into NS5B inhibitor interactions. Taken together, these 3D-QSAR models accurately predicted the inhibitory activity of the different HCV-NS5B polymers tested. Reliable guidelines are given for further optimization of these benzimidazole derivatives. Another promising work was based on the activity of CoMFA and CoMSIA as triazolone derivatives as allosteric inhibitors of hepatitis C virus NS5B polymerase [22]. For this purpose, 3D-QSAR models of thiazolone derivatives were developed as novel inhibitors binding to the allosteric site of HCV-NS5B polymerase. Predictions of CoMFA and CoMSIA models. CoMFA and CoMSIA models with the best predictive power were obtained using the Xray crystal structure.

Many new inhibitors with better activity have been developed. Finally, an ANN analysis was performed to predict the antigenic activity of the major conformational epitope of hepatitis C virus NS3 protein This fact arises from a lack of understanding of the principles underlying the true quantitative inference of biological properties. Sequences are a major obstacle to the rational design of proteins with predetermined activity. Because of this disadvantage, protein engineering is often based on the use of computational methods that focus on identifying structure-activity relationships (SAR) for each specific task. This work developed a computational model to determine the SAR of the most important conformational antigenic epitope of HCV non-structural protein 3 (NS3) to facilitate the rational design of HCV antigens in an improved diagnostically relevant manner. Functions. In this sense, an ANN model was developed to incorporate changes in the immunological properties and structure of HCV-

NS3 recombinant proteins representing all six HCV genotypes. An artificial neural network can predict enzyme-linked immunoassay (EIA) signal/cleavage (S/Co) spectra with 89.8% accuracy based on single junction data. Amino acid positions and physicochemical properties closely related to the antigenic properties of HCV NS3 were determined. The 3D model of NS3 marked the areas that had the greatest impact on the model. The location of these functions confirmed the importance of the relationship between antigenicity and the structure of the HCV-NS3 protein found by the ANN model.

QSAR FRAGMENT-BASED APPROACH TOWARD THE DESIGN OF ANTI-HCV AGENTS

All the computational approaches and methods discussed so far have been instrumental in the search for and development of new anti-HCV agents. However, a disadvantage remains, viz. a compound can be very active against any target, which is currently continuously researched, but this is a necessary and sufficient condition to ensure that the same compound that wasa very potent receptor blocker already is. active in HCV-infected cells? To address this problem, we present here a QSAR model based on a fragment-based approach [22].

Methods

Atom-Centered Fragments

Atom-centered fragments have proven to be very useful descriptors and have been used in some Quartiles. They provide useful information on hydrophobic and diffusive interactions involved in both drug transport and distribution across the membrane and drug-receptor interactions. These exponents are defined as the number of fragments containing certain types of atoms in a molecule and are calculated from the molecular composition and atomic bonds. Thus, each type of atom in a molecule is described by its neighboring atoms. Hydrogen and halogen atoms are classified according to the degree of hybridization and oxidation of the carbon atom to which they are attached, and for hydrogen atoms are considered the heteroatoms attached to the carbon atom in the position. Carbon atoms are classified according to their hybridization state and whether their neighbors are carbon atoms or heteroatoms.

Functional Group Counts

These are other types of explanations that indicate some poor performance. These are simple molecular descriptions defined as the number of specific positions in the molecule that can be calculated from the molecular composition and atomic bonds. Functional groups defined in these figures are traditionally used in organic chemistry.

The Spectral Moments of the Bond Adjacency Matrix

This method involves calculating the spectral time of the bond adjacency matrix and is called the TOPS MODE (topological substructure molecular DE representation) method, which is used to model some physicochemical properties. organic compounds. This description also covers QSAR studies and toxicological properties. To calculate the spectral range, the edge adjacency matrix E (also called the bond adjacency matrix B) is used to encode the molecular structure [23]. The matrix E is a square matrix of order m whose elements are equal to 1 if bonds i and j are next to each other, for example if they encounter one more atom (m is the number of chemical bonds in the molecular diagram). and 0 more. year. To encode heteroatom information, the TOPS MODE method uses a weight matrix transformation. Weight is an important factor in properties such as long-distance bonds, dipole bonds, polarization bonds, or mathematical expressions involving atomic weight. Therefore, the spectral period of the bond in the matrix can be used as a molecular fingerprint in QSAR studies and molecular design [24].

Selection of the Dataset: Calculation of the Descriptors and Development of the Model

The dataset contained 1958 compounds (see Additional material file 1, available from the corresponding authors upon request; Supplementary Information and 937 of them were found to be active against HCV. The requirement for the compound to be active was to have an EC50 of 2.5 M, which is an EC50half of the maximum effective concentration. The inactive group consisted of compounds, many of which were compounds with EC50 > 2.5 M and also drugs belonging to different therapeutic classes. This dataset was split into training and prediction sets. The Education Series

contained 1469 compounds: 703 active and 766 inactive, while the prediction consisted of 489 compounds:234 active and 255 inactive. Numerical plots of atom-centered fragments and functional groups were calculated using the program DRAGON (version 5.3). The spectral moments of the weighted edge adjacency matrix were calculated using the Mode slab software (version 1.5). In this case, the spectral moments were weighted by dipole moments, soft refractive indices, and Abraham soft refractive indices. As a modeling technique, we chose linear-discriminant analysis (LDA), which has been widely used in QSAR studies to find a classification model which best describes the anti-HCV activity (AHCV) as a linear combination of the predictive X variables (molecular descriptions Dk) with coefficients Ak. Such coefficients are optimized by LDA, specifically the LDA technique implemented in the software STATISTICA (version 6.0) using only compounds from the training set [25].

During model development, active and inactive compounds were assigned AHCV values of +1 and 1, but posterior probabilities were used instead to confirm model classification of compounds. Specifically, if the probability of being active did not differ by more than 5% from the probability of being inactive, the case was considered unclassified in the model. Forward stepwise (FS) was used as a procedure to select molecular descriptors (X variables) with the greatest effect on anti-HCV activity. In addition, the principle of impartiality was followed in the selection of FS. Thus, a classification model with high statistical significance but with as few descriptors as possible was selected.

The statistical quality of the model is evaluated by examining various test parameters such as Wilkslambda, Mahala Nobis squared distance (D2), Fisher ratio, p level, and percentage of good distribution. The Wilks statistic is a measure of group differences in various variables and can take values from 0 (exact difference) to 1 (no difference). Data D2 is also a measure of the difference between active and inactive groups and indicates whether the model has sufficient discriminatory power to distinguish these groups.

Structural Interpretation of the Descriptors

They consider different physicochemical properties. The accessibility of molecules in regions of different sizes (coded μ15(Ab-R2) andμ2(MR)) is very important, because its inclusion means that the molecule has several regions with which it can correctly to interact a biological receptor that causes enzymatic inhibition and reduction of viral proliferation. These descriptors are also somehow related to the increase in hydrophobicity that causes the molecule to pass through the membrane. On the other hand, decreasing the polarity of the bond (coded byμ2(Dp)) improves the activity of the molecule against, because the van der Waals interaction increases between the molecule and the corresponding receptor.

Atom-centered fragments and descriptions of functional group count are easy to interpret because they indicate certain types of atomic groups that form moieties and/or functional groups. In this sense, the information given by these descriptors depends on the structure of the fragment or functional group and therefore has a strong relationship with reactivity (acidity, nucleophilic and electrophilic properties, hydrolysis capacity) or specific relationship. physicochemical properties not encoded by the spectral moments. Although it is not possible to determine exactly which property has the greater influence in the fragment coded by the atom-centered fragment and functional group number descriptors, the signs of the corresponding coefficients of these descriptors are. The equation gives an idea of the desirability of different fragments, ie. whether the fragment is favorable or unfavorable against- for the formation of HCV activity. The main advantage of this model is the ability to calculate the quantitative contribution of any fragment to the anti-HCV activity. In this sense, we have chosen some fragments that are present in the molecules, and we were able to calculate the quantitative contribution of these fragments to the studied activity [26].

Calculation of the ratio of fragments provides useful information about molecular patterns that can be decisive for the development of anti-HCV activity, and which are those that negatively affect the

potency of the compound used. Anti-HCV agent Thus, it is possible to design new molecules from these fragments with a positive contribution, and such molecules should in principle be very active as HCV inhibitors.

CONCLUSIONS

Computational drug design methods have been instrumental in the discovery and development of HCV drugs. However, there is a need to expand existing drug design techniques to find new targets for HCV antiviral therapy, for example using molecular modeling techniques such as homology modeling. Further efforts should be made to develop new molecular units with possible in vivo activity. Our model, based on infrastructure and a large library of heterogeneous compounds, attempts to solve this problem. We also believe that powerful and promising concepts such as complex network theory should be considered to better understand biological and biochemical processes, including investigating the mechanism of Christine. We believe that in the future the development of new and effective HCV drugs should take more into account the following aspects:

Develop and/or implement new approaches based on QSAR model to combining the used strategies graph theoretical description. Others predict the in vivo anti-HC activity of several compounds easily, quickly and reasonably.

Broaden and increase the application of structure-based drug design methods such as homology modeling to discover more connections between HCV and other viruses at the biomolecular level.

Apply complex web-based approaches that enable the development of new strategies to control hepatitis C.

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