Chapter 9
Computational Approaches for the Discovery of Novel Hepatitis C Virus NS3/4A and NS5B Inhibitors

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ABSTRACT

Nonstructural 5B (NS5B) polymerase and Nonstructural 3/4A (NS3/4A) protease have proven to be promising targets for the development of anti-HCV (Hepatitis C Virus) agents. The NS5B polymerase is of paramount importance in HCV viral replication; therefore, employing NS5B inhibitors was considered an effective way for the treatment of HCV. Identifying inhibitors against NS3/4A serine protease represents another attractive approach applied in anti-HCV drug discovery, which is evidenced by its crucial role of in the biogenesis of the viral replication activity. In this chapter, many different computational approaches including Quantitative Structure-Activity Relationship (QSAR) and virtual screening in anti-HCV drug discovery were considered and discussed in detail. Virtual Screening (VS) techniques, including ligand-based and structure-based, and QSAR have been utilized for the discovery of NS5B inhibitors. Moreover, using various in silico protocols and workflows, a number of studies have been conducted with an aim of identifying potential NS3/4A blockage agents.

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INTRODUCTION

Hepatitis C virus infection causes a global healthcare burden, which is likely to increase in the coming years. There are approximately 3 to 4 million new cases of HCV infection each year, and it is estimated that a minimum of 3% of worldwide population are chronically infected (Wasley et al., 2000). In most infected patients, this remarkable RNA virus causes the development of malignant chronic diseases, including cirrhosis and hepatocellular carcinoma, which often leads to liver failure and death (Alter, 1993; Hoofnagle, 1997). At present, neither an HCV vaccine nor an effective therapy against all genotypes of HCV is available. The current therapy, including pegylated interferon α, either alone or in combination with ribavirin, a broad spectrum antiviral agent, has not only limited efficacy, but also significant adverse effects (Feld et al., 2005; Fried, 2002). Hence, it is essential to develop novel agents with a high therapeutic efficacy, reduced side effects, and convenient administration to meet requirements for an anti-HCV agent.

Perceiving that urgent need, scientists around the world have conducted various research to identify as many novel HCV antiviral agents as possible. Currently, different targets for HCV therapeutic intervention encompass both structural and non-structural proteins. The structural protein is processed by host and viral proteases into four structural (core, E1, E2, and p7) and six nonstructural proteins (NS2, -3, -4A, -4B, -5A, and -5B) (Shimakami et al., 2009; Tanji et al., 1994). Non-structural protein 3/4A (serine protease - helicase) and non-structural protein 5B (RNA-dependent RNA polymerase - RdRp) have attracted the attention of medicinal chemists as targets for drug development because they play a vital role in HCV replication and the host lacks functional counterparts of them (Shimakami et al., 2009; Wang et al., 2000). This chapter will generally point out certain conducted computational approaches and virtual screening, which could be employed in combination with QSAR to build a robust model, with the goal of identifying new effective antiviral drugs utilizing NS3/4A and NS5B as principle targets.

HCV GENOME AND STRUCTURE

HCV Genome

HCV is an enveloped, positive-sense and single-stranded RNA virus approximately 9600 nucleotides in length. The significant genetic diversity was exhibited in HCV genome due to its highly error prone RNA polymerase, which makes difficulties for vaccine development and the discovery of anti–HCV agents (Francesco et al., 2005). 6 major HCV genotypes have been identified with the difference of over 30% in nucleotide sequences among each of them (Simmonds et al., 2005). RNA of HCV includes one continuous open reading frame bounded by two nontranslated regions (NTRs) at 5’ and 3’ ends. 5’ NTR constitutes the internal ribosome entry site (IRES), which plays the role as a starting point of cap-independent translation of HCV genome to produce a single polyprotein (Honda et al., 1996). The polyprotein is in turn split by both host cell and virus proteases into 10 different viral proteins with various functions and characteristics (Alvisi et al., 2011).