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Research Article

Quantum molecular modeling of hepatitis C virus inhibition through non-structural protein 5B polymerase receptor binding of C_5-arylidene rhodanines

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ABSTRACT

We have carried out high-level quantum chemical computations followed by molecular docking studies on a set of 17 C_5-arylidene rhodanine isomers to provide insights into the binding modes with different reported binding pockets of the nonstructural protein 5B (NS5B) polymerase that contribute to the hepatitis C virus (HCV) inhibition. We optimized the multi-target profile of the selected rhodanine analogs to investigate potential non-nucleotide inhibitors (NNIs) by quantum chemical optimization of the 18 isomers followed by docking with quantum chemically optimized structures of each isomer with NS5B polymerase at multiple binding pockets. The binding affinities of the PP-I, PP-II and TP-II pockets of NS5B polymerase were analyzed for all the 17 isomers of 2-[(5*Z*)-5-(2,4-*di*chlorobenzylidene)-4-oxo-2-thioxo-1,3-thiazolidin-3-yl]-3-phenylpropanoic acid. On the basis of binding propensity at the different pockets and inhibitor constants, we ranked these isomers as potential candidates for the HCV inhibition. We have identified four isomers as promising NNIs of NS5B polymerase with comparable binding and inhibition to the standard (1,3) *di*chloro substituted isomer that exhibits *in vitro* activity and several other isomers as candidates in a "multi-targeted drug" approach.

1. Introduction

The HCV virus is one of the major causes of chronic liver disease which results in the development of liver cirrhosis followed by hepatocellular carcinoma (Kapoor et al., 2011; Aman et al., 2012). Chronic HCV infection is a leading cause of morbidity and mortality across the world. As with many viruses, there are challenges in finding satisfactory therapeutic cure for the HCV infections. The available antiviral therapies can result in a sustained virological response (SVR) in a majority of patients (Dore and Feld, 2015). In 2013, Sofosbuvir (Sovaldi) a promising anti-HCV drug has been introduced and its long term results are much awaited (Kowdley et al., 2013; Bhatia et al., 2014). Many of the currently available HCV treatments do not have adequate efficacy especially to reduce the rise in End Stage Liver Diseases or HCV transmission (Harris et al., 2014; Wedemeyer et al., 2014; Martin et al., 2015). Since the last two decades, academic and pharmaceutical research have shown tremendous progress in understanding the HCV infection and developing new treatment options for infected patients. Early drug discovery efforts focus on the NS3/4A serine protease (Halfon et al., 2011) and the NS5B-RNA dependent polymerase (Coats et al., 2014) as HCV targets. The combined therapy of injectable pegylated interferon (pegIFNα) and ribavirin is a standard therapy and no preventive vaccination is available (Santantonio et al., 2005). The limitations of available therapies are toxicity, expensive treatment and their effectiveness only in 50% of the patients for the most common genotype.

Significant progress has been made in recent years to find suitable drugs for the treatment of HCV infection. Some of the recently approved anti-HCV anti-viral drugs are telaprevir, boceprevir, and simeprevir acting as viral NS3/4A protease or NS5B polymerase inhibitors (Wilby et al., 2012; Capuozzo et al., 2013; Butt and Kanwal, 2012; Lin et al., 2009; Cholongitas and Papatheodoridis, 2014; Yau and Yoshida, 2014). In 2014, Harvoni™, a combination of sofosbuvir and ledipasvir, and Viekira Pak™, a combination of ombitasvir, paritaprevir and dasabuvir were approved by the FDA (Link et al., 2014; Krishnan et al., 2015; DeGoey et al., 2014; Gentile et al., 2014). The binding mode for various heterocyclic nuclei comprising of imidazole, benzimidazole, thiouracil at the NS5B polymerase binding site along

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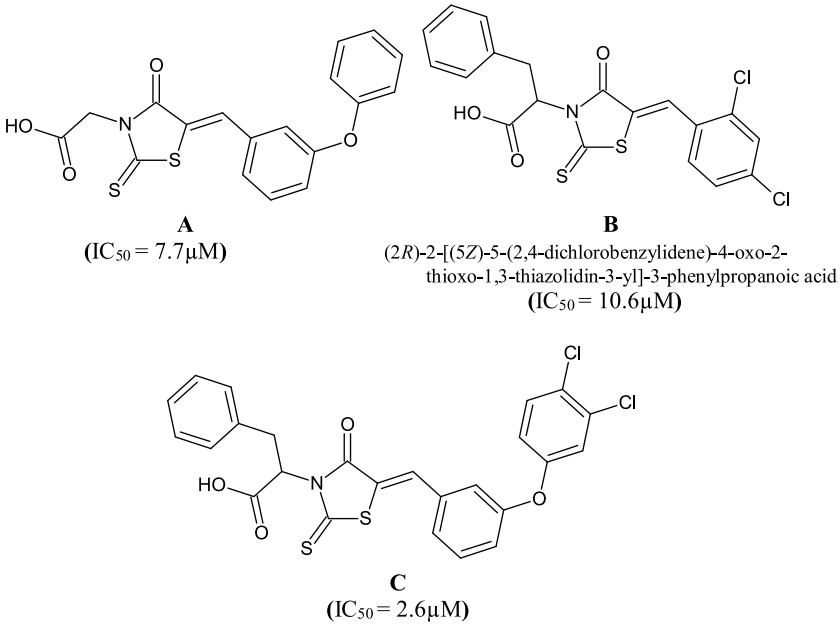
withquantitative structure-activity relationship (QSAR) studies has been well reported (Patil et al., 2010, 2012a, 2013, 2012b, 2011a). In order to develop biochemical targets against HCV, characterization of the HCV-RNA dependent RNA polymerase (RdRp) and the role of quantum molecular modeling of HCV inhibitors through nonstructural protein 5B polymerase receptor binding of C5-arylidene rhodanines and the role of recombinant NS5B polymerase in the synthesis of full length HCV RNA has been well reported (Hwang et al., 1997; Yamashita et al., 1998; Behrens et al., 1996; Lohmann et al., 1997; Ferrari et al., 1999). It has been established that HCV NS5B can unwind into stable secondary and tertiary RNA structures.

Rhodanines comprise a set of five-membered heterocyclic thiazole containing molecules that have a broad spectrum of activities. The role of rhodanine analogs as a potential drug candidate is questionable as it has been observed as non-selective and non-drug like compounds (Baell and Holloway, 2010). The non-selectivity at screening concentrations may be due to high density interaction sites offering polar and H-bond interactions. The biomolecular profile can be enhanced by applying special target affinity and selective criteria (Tomasić and Masic, 2009; Mendgen et al., 2012; Jain et al., 2013). The clinical success observed in the past few decades has attracted considerable attention of synthetic chemists for molecular modifications to generate new drugs with greater efficacy. Sudo et al. reported HCV protease inhibition activity of rhodanine derivatives (Sudo et al., 1997). An aryl methylidiene rhodanine derivative, LJ001, has been identified as a promising, broad-spectrum molecule with viral inhibition activity (Wolf et al., 2010). The antiviral potential of rhodanine is well established and it has been validated by the reported patents (Anon, 2018a, 2018d) and biological evaluation data (Wolf et al., 2010; Foye and Tovivich, 1997; Ramkumar et al., 2010; Kurbatov et al., 2014). Some anti-HCV rhodanine analogs have been reported as NS5B polymerase inhibitors (Talele et al., 2010; Powers et al., 2006). Talele et al. have reported optimization of two rhodanine lead molecules (**A** and **B**, shown in Fig. 1) which have IC_{50} of 7.7 μM and 10.6 μM, respectively compared to a hybrid compound that has an IC_{50} value of 6.7 μM. Furthermore, compound **C**, shown in Fig. 1, exhibits an IC_{50} value of 2.6 μM (Talele et al., 2010; Patel et al., 2013).

The combined use of crystallographic and biochemical studies has facilitated the exploration of the structural features of the HCV NS5B polymerase, an important therapeutic target. The NS5B polymerase adopts a topology analogous to a right hand having "palm," "fingers," and "thumb" subdomain. The non-nucleotide inhibitors (NNIs) inhibit the initiation/elongation phases of replication depending on their allosteric binding sites (Barakat et al., 2013). ElHefnawi et al. have investigated five NNI allosteric binding pockets namely, palm pocket-I (PP-I), palm pocket-II (PP-II), palm pocket-III (PP-III), thumb pocket-I (TP-I), and thumb pocket-II (TP-II) (all shown in Fig. 2) (ElHefnawi et al., 2012). The three important inhibitor categories of NS5B polymerase *i.e.* benzothiazoles, benzothiadiazines, and benzodiazepines binding at the PP-I site have been identified *in silico* (Beaulieu, 2007). Further studies have revealed that this site is located in close proximity to the active site, and it is at the junction of the thumb and palm domains (ElHefnawi et al., 2012). In recent work reported by Vrontaki et al. (Vrontaki et al., 2015a, 2016a) a combination of the computational methods such as molecular docking, 3-D Quantitative Structure Activity Relationship Comparative Molecular Field Analysis (3D-QSAR CoMFA), similarity search and virtual screening has been applied to identify new indole analogs and anthranilic acid-based inhibitors of HCV replication.

Some NNIs such as filibuvir, lomibuvir and GS-9669 that bind to the thumb pocket site II (TP-II) are in the clinical phase of development (Watkins et al., 2010) and GS-9669 has reported promising activity against diverse resistance mutations beyond NS5B TP-II (Fenaux et al., 2013; Patil et al., 2011b, 2016). Considering the *in vitro* activity of (2*R*)-2-[(5*Z*)-5-(2,4-dichlorobenzylidene)-4-oxo-2-thioxo-1,3-thiazolidin-3-yl]-3-phenylpropanoic acid (IC_{50} = 10.6 μM) (compound **B**, Fig. 1), in the present investigation we have quantum chemically optimized 17 isomers of the *di*-chloro substituted compound **B** and these together with the standard compound **B** provided us with a set of 17 isomers for our docking studies. The docking simulation and quantum mechanical studies of these C_5-arylidene rhodanine isomers for HCV polymerase binding sites have been carried out in this study in order to provide better insight into the essential residue interactions.



A
(IC_{50} = 7.7μM)

B
(2*R*)-2-[(5*Z*)-5-(2,4-dichlorobenzylidene)-4-oxo-2-thioxo-1,3-thiazolidin-3-yl]-3-phenylpropanoic acid
(IC_{50} = 10.6μM)

C
(IC_{50} = 2.6μM)

Fig. 1. Structures of Reported HCV Inhibitory Rhodanine Molecules.