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IDX-184 is a superior HCV direct-acting antiviral drug: a QSAR study

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Abstract Quantitative structure–activity relationship (QSAR) parameters are good indicators for the reactivity of direct-acting antiviral drugs. Since molecular structure is related to molecular function, careful selection of molecular substitutions will result in more drugs that are potent. In this work, QSAR parameters are selected in order to compare the four drugs used as nucleotide inhibitors (NIs) for non-structural 5B (NS5B) RNA-dependent RNA polymerase (RdRp) of hepatitis C virus (HCV). These drugs are: ribavirin (widely used over the last 20 years), sofosbuvir (approved on December 2013 by FDA), and finally IDX-184 and R7128 (phase IIb of clinical trial drugs). The nucleotide analogues uracil (U), guanine (G), and cytosine (C) from which these drugs are fabricated are also compared to that group of drugs. QSAR parameters suggested that the drug IDX-184 is the best among all of the studied NIs. It also shows that NIs are always more reactive than their parent nucleotide.
Graphical Abstract The active site environment of 12 amino acids coordinated with IDX-184 through two Mg^{2+}. The interaction with HCV subtypes 1a, 2b, and 3b is better than 4a subtype.

Keywords QSAR · NS5B · Sofosbuvir · IDX-184 · Nucleotide inhibitors

Introduction

Quantitative structure–activity relationship (QSAR) is important in studying direct-acting antiviral (DAA) drugs (Ibrahim *et al.,* 2013). The use of mathematical models describing the effectiveness of a drug as a potent activator or inhibitor of specific enzyme has been given a growing attention for drug design in the last decade. Structure-specific properties that could be modeled using a mathematical equation is the key for fabrication of novel antiviral drugs for human immunodeficiency virus (HIV) and hepatitis C virus (HCV) (Ibrahim *et al.,* 2012; Mostafa *et al.,* 2014; Saleh *et al.,* 2014).

HCV was discovered by Choo *et al.* (1989). It was named non-A non-B hepatitis. Those who made injections using unsterile or non-disposable needle or carried out blood transfusion before 1992 (the start of HCV blood screen tests) in the USA were subject to HCV infection

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(Das *et al.,* 2011; Firpi and Nelson, 2007; Lemon *et al.,* 2010; Yang *et al.,* 2011). Hepatitis C virus is one of the major causes of hepatocellular carcinoma (Massariol *et al.,* 2010). More than 200 million were infected by HCV worldwide with some countries such as Egypt having infection percentages over 14 % of the population. HCV is transmitted by blood-to-blood contact. This was the case for high percentage in Egypt where the focus was to invade the schistosomiasis using unsterile needles during 1980s–1990s (De Francesco *et al.,* 2003; Lemon *et al.,* 2010).
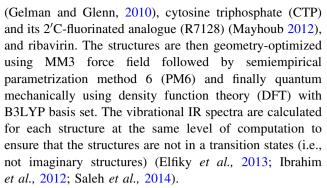
The genome of HCV (positive RNA) translates into 3000-amino acid polyprotein inside infected liver cells. This polyprotein is cleaved using viral and host cell proteases into 10 proteins: envelope proteins 1 and 2, core protein, p7 (structural proteins), and NS2, NS3, NS4A, NS4B, NS5A, and NS5B (non-structural proteins) (De Francesco *et al.,* 2003; De Francesco and Carfí 2007; Lemon *et al.,* 2010).

The widely used antiviral drug ribavirin was the seed for HCV treatment in combination with interferon alpha during the last two decades until the first DAA protease inhibitor drugs (boceprevir and telaprevir) were approved by Food and Drug Administration (FDA) in 2011 (Beaulieu *et al.,* 2011; De Francesco *et al.,* 2003). These drugs worked in competition with the substrate of the viral enzyme (NS3 serine protease). In December 2013, FDA approved sofosbuvir for HCV treatment in combination with ribavirin with and without interferon (Asselah 2014). Different DAA drugs now are in clinical trials, and in the coming years one would expect to find different interferon-free drug formulations in order to avoid the adverse side effects of interferon (Asselah 2014; Beaulieu *et al.,* 2011).

Molecular modeling was used frequently to study drug–protein interactions (Elshemey *et al.,* 2010; Saleh *et al.,* 2014). It was used in conjunction with QSAR parameters to study HIV, HCV, SARS, and other viral proteins and succeeded in the suggestion of new drugs that inhibit certain proteins via interference with viral replication (Mostafa *et al.,* 2014; Saleh *et al.,* 2014, 2015). Our previous studies suggested the formation of weak interactions between the active site environments (the 5 Å region around the active site of NS5B) and the drug (Elfiky *et al.,* 2013, 2015).

Computational details

Computational chemistry integrated platform, SCIGRESS 3.0 software is utilized to draw the structures of: uracil triphosphate (UTP) and its 2′C-methyl, 2′fluorinated analogue (sofosbuvir, formally called PSI-7977) (Elfiky *et al.,* 2013, 2015; Murakami *et al.,* 2010), guanine triphosphate (GTP) and its 2′C-methylated analogue (IDX-184)

(Gelman and Glenn, 2010), cytosine triphosphate (CTP) and its 2′C-fluorinated analogue (R7128) (Mayhoub 2012), and ribavirin. The structures are then geometry-optimized using MM3 force field followed by semiempirical parametrization method 6 (PM6) and finally quantum mechanically using density function theory (DFT) with B3LYP basis set. The vibrational IR spectra are calculated for each structure at the same level of computation to ensure that the structures are not in a transition states (i.e., not imaginary structures) (Elfiky *et al.,* 2013; Ibrahim *et al.,* 2012; Saleh *et al.,* 2014).

Selected QSAR parameters are used to compare between the different drugs and the nucleotides from which these drugs are fabricated. These parameters include: dipole moment, log P, electron affinity, molar refractivity, ionization potential, solvent-accessible surface area, volume, total energy, heat of formation, highest occupied molecular orbitals (HOMO), lower unoccupied molecular orbitals (LUMO), and the frontier energy gap ($\Delta E =$ LUMO − HOMO).

Results and discussion

In the liver cell, the mechanism of interaction between HCV NS5B RdRp and nucleotides or NIs is competitive (Klumpp *et al.,* 2006). The ability of nucleotides or NIs to interact with the polymerase active site can be predicted from its QSAR parameters. Table 1 shows the QSAR parameters for the activated (triphosphate) NIs (sofosbuvir, IDX-184, and R7128), their activated parent nucleotides (UTP, GTP, and CTP, respectively), and ribavirin.

From Table 1, the best QSAR values among all nucleotides and NIs are as follows: GTP possesses the highest electron affinity (−5.426 eV), lowest ionization potential (4.503 eV), and lowest frontier energy gap ($\Delta E = 0.923$ eV) all implying reactivity of GTP with the active site of the viral polymerase. The UTP possesses the lowest log P (−2.185) implying higher water solubility which is important for the interaction that involved divalent cations in the active site of the polymerase and lowest final heat of formation (−567.566 kcal/mol) which means higher stability. On the other hand, activated IDX-184 has the lowest total energy (−190,434.6 kcal/mol) which indicates the stability of the drug, highest molar refractivity (97.136), and highest solvent-accessible surface area (440.056 Å^2) which all would help in increasing the interaction possibility with the two aspartic acids of the polymerase. Ribavirin in its active form has the highest dipole moment (65.378 debye) illustrating the reactivity of the compound used more than 20 years ago against HCV. It is very surprising that activated sofosbuvir (approved by FDA in December 2013) and R7128 both show no best values compared to all the active drugs and NTPs.

Table 1 Quantitative structure–activity relationship (QSAR) descriptors for phosphorylated nucleotide inhibitors [sofosbuvir (PSI-7977), IDX-184, and R7128], their parent phosphorylated nucleotides (UTP, GTP, and CTP, respectively), and phosphorylated ribavirin

QSAR descriptors	Sofosbuvir	IDX-184	R7128	Ribavirin	Uracil (U)	Guanine (G)	Cytosine (C)
Dipole moment (debye)	63.72	60.15	37.485	**65.378**	51.337	62.016	41.229
Log P	−1.504	<u>−2.036</u>	−1.223	−1.795	**−2.185**	−2.114	−1.904
Electron affinity (eV)	−6.322	<u>−5.616</u>	−8.962	−6.148	−6.713	**−5.426**	−7.126
Molar refractivity	83.643	**97.136**	88.39	81.888	80.697	92.499	85.445
Ionization potential (eV)	4.952	4.598	<u>4.521</u>	4.9	4.675	**4.503**	4.612
Solvent-accessible surface area ($Å^2$)	406.165	**440.056**	383.178	404.767	387.171	435.459	386.396
Volume ($Å^3$)		354.82			303.35	335.55	309.31
Total energy (kcal/mol)	−180,219.1	**−190,434.6**	−178,678.92	−173,008.91	−173,446.15	−185,978.18	−171,689.3
Heat of formation (kcal/mol)	<u>−557.107</u>	−485.679	−524.417	−479.155	**−567.566**	−480.085	−516.462
HOMO (eV)	4.952	4.598	4.521	4.9	4.675	4.503	4.612
LUMO (eV)	6.322	5.616	8.962	6.148	6.713	5.426	7.126
Frontier energy gap (eV)	1.37	<u>1.018</u>	4.441	1.248	2.038	**0.923**	2.514

The best values for nucleotide inhibitors are underlined, while the best values among all (nucleotides and nucleotide inhibitors) are bold

Comparing the four nucleotide inhibitors, sofosbuvir, IDX-184, R7128, and ribavirin, Table 1 shows that IDX-184 triphosphate reports best values for six important QSAR descriptors: log P (−2.036), electron affinity (−5.616 eV), molar refractivity (97.136), solvent-accessible surface area (440.056 $Å^2$), total energy (−190,434.6 kcal/mol), and frontier energy gap (1.018 eV). These parameters imply the stability and higher reactivity of the drug IDX-184 among all drugs studied. Hence, IDX-184 is probably the most favored for HCV NS5B RdRp inhibition compared to the other investigated NIs. The other NIs each shows a best value for only one QSAR descriptor: heat of formation (−557.107 kcal/mol), ionization potential (4.521 eV), and dipole moment (65.378 debye) for sofosbuvir, R7128, and ribavirin, respectively.

Moreover, from Table 1 one can find that all NIs are better than their parent nucleotides in some parameters such as: total energy, heat of formation, and molar refractivity. Activated sofosbuvir and IDX-184 are better than UTP and GTP, respectively, in frontier energy gap and solvent-accessible surface area parameters. Activated sofosbuvir is better than UTP also in electron affinity parameter. R7128 is better than CTP in ionization potential parameter.

These QSAR results show that the NI IDX-184 is probably the best DAA in comparison with sofosbuvir, R7128, and ribavirin to compete with native nucleotide GTP for the inhibition of HCV NS5B RdRp.

Conclusion

Direct-acting antiviral drugs sofosbuvir, IDX-184, and R7128 are better than their parent nucleotides uracil, guanine, and cytosine, respectively, and ribavirin. IDX-184 is the best DAA drug among the group of drugs investigated in this study. It is thus recommended that IDX-184 should be given more attention in future investigations as a promising anti-HCV drug.

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