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In silico design and pharmacokinetics investigation of some novel hepatitis C virus NS5B inhibitors: pharmacoinformatics approach

Stephen Ejeh*, Adamu Uzairu, Gideon A. Shallangwa, Stephen E. Abechi and Muhammad Tukur Ibrahim

Abstract

Background: Hepatitis C virus (HCV) is a contagious disease that damages the liver over time, eventually leading to cirrhosis and death. Chronic HCV infection is regarded as a serious health problem worldwide, impacting up to 3% of the populace and killing over 300,000 people annually. Quick reproduction driven by non-structural protein 5B (NS5B), which is a possible target spot for the development of anti-HCV vaccines, causes genomic diversity. Sofosbuvir, a new oral NS5B inhibitor, was recently licensed by the US Food and Drug Administration for the cure of HCV. Unfortunately, it has received a lot of attention due to its financial concerns and adverse effects. As a result, there is a pressing need to explore alternative HCV treatments that are both cost-effective and free of adverse effects. In this study, we used a Pharmacoinformatics-based strategy to identify and design bioactive molecules that are anti-HCV NS5B. The simulation outcomes are compared to Sofosbuvir simulation outcomes.

Results: Based on docking simulation, the proposed molecules have high-binding energies at the range of − 41.71 to − 39.90 kcal/mol against − 30.34 kcal/mol of Sofosbuvir. Furthermore, when compared to Sofosbuvir, which has a drug score of 0.31 (31% performance), the ADMET analysis of the lead compound demonstrates superior performance with a drug score of 0.88 (88% performance).

Conclusions: The findings revealed that alternative bioactive molecules vary substantially in docking rankings at a range of − 41.71 to − 39.90 kcal/mol against − 30.34 kcal/mol of Sofosbuvir, the FDA-approved NS5B enzyme inhibitor, and when compared to Sofosbuvir, which has a drug score of 0.31, the ADMET analysis of the chosen compound (**1c**) demonstrates superior performance with a drug score of 0.88.

Keywords: In silico design, NS5B inhibitors, Pharmacoinformatics approach, Drug discovering

Background

Hepatitis C virus (HCV) is a contagious disease that damages the liver over time, eventually leading to cirrhosis and death. Chronic HCV infection is regarded as a serious health problem worldwide, impacting up to 3% of the populace and killing over 300,000 people annually (Abuelizz et al. 2020; Ejeh et al. 2021a; Zając et al. 2019). Its gradual spread and difficulty in detection make it a hidden pandemic, and the majority of infections proceed into a persistent condition that lasts for years. About 60–80% of people who are infected with HCV suffer persistent hepatitis, with 20% developing cirrhosis, and about 2–5% of patients dying from liver cirrhosis and malignancy (Hajarizadeh et al. 2013; Li et al. 2016).

In 2019, there were approximately 58 million severe recorded cases in the globe, with 75% of them occurring in low- and middle-income countries (LMICs) (World Health Organization 2021a). New HCV infections are occurring in high-risk populations around the world, including drug users and men who have sex with males (World Health Organization 2021b). HCV is primarily transmitted in Sub-Saharan Africa through improper

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medical practices and infected blood transfusions. Needlestick injuries in healthcare professionals, mother-to-child transmission (MTCT), and societal behaviors like piercing and tattooing are also possible transmission routes for males (World Health Organization 2019, 2021b).

The hepatitis C virus gene contains a polyprotein with around 3000 amino acids that are separated into two groups: The structural and non-structural (NS) proteins are the key targets for anti-viral drug development because of their critical role in HCV virus propagation (Ejeh et al. 2021a; Qin and Yan 2020). In recent times, a number of promising anti-viral targets for HCV have emerged (Bianculli et al. 2020). The majority of attempts, similar to HIV, have focused on blocking key viral enzymes. Inhibitors of one of these targets, the HCV NS5B enzyme, have been demonstrated to be the most effective anti-viral agents (Asiri et al. 2020). Current HCV treatment has a poor sustained viral chance of success, the rapid development of drug resistance, and significant side effects, all of which lead to treatment discontinuation (Therese et al. 2014). As a response, more effective anti-HCV drugs having minimal adverse effects are desperately required. The discovery of the most critical information to facilitate the identification of unique bioactive compounds that could be utilized to cure HCV infection and then provide medically successful therapy is certainly a key global health priority (Algamal et al. 2017).

Structure-based drug design, which involves docking small compounds into biomolecules, notably enzyme targets, is an important subject in computer-aided drug design (CADD). Protein–ligand or protein–protein docking is a computer technique that predicts how a ligand will behave when bonded to a target molecule or enzyme. The method entails using a rating system to determine the possibility that a ligand would bind to a protein with strong potential, allowing for future pharmacological research and development (Gurung et al. 2021).

Pharmaceuticals can be designed in silico using molecular docking by enhancing lead candidates targeted against specific receptors. A docking method can be used to find the best small molecule (ligand) binding mode to a receptor active domain. As a result, the goal of drug research is to generate molecules that are bound to a receptor more strongly than the native ligand (Ejeh et al. 2021b). The biological reaction catalyzed by the target molecule can be modified or inhibited in this way. High-throughput screening techniques that employ in vitro tests to determine the biological responses of a variety of molecules toward a specific macromolecule are often used to identify drugs by chance in a trial-and-error procedure. This is a lengthy and expensive process. If the target's 3D structure is known, a program to mimic docking can help in drug discovery. This in silico study identifies promising therapeutic candidates more quickly and at a lower cost by virtual screening of drug repositories. Following that, laboratory investigations (synthesis), cytotoxic screening, clinical trials, and other procedures could be utilized to investigate the drug molecules discovered using the in silico approach. Most docking approaches employ an energy-based ranking system to find optimum thermodynamically stable ligand orientation when a ligand is attached to a target. Lower energy scores are assumed to indicate stronger protein–ligand bindings when related to higher energy scores. Consequently, docking can indeed be conceived of as an iterative algorithm aiming at finding the ligand-binding formation with the least amount of energy (Shao et al. 2006). The goal of this study is to find potential ligands that can act as HCV NS5B enzyme inhibitors through high-throughput virtual screening of PubChem database compounds using a structure-based approach, to find lead (hit) molecules as templates for designing enhanced HCV NS5B enzyme inhibitors, and to screen the new compounds depending on their docking rating and binding modes. The novel compounds were further tested for oral bioavailability, drug-likeness, synthetic accessibility, pharmacokinetic profiles, and druggability using Lipinski's rule of five, and compared to the reference inhibitor (Sofosbuvir), the FDA-approved NS5B enzyme inhibitors.

Methods

Collection of small molecules and optimization

A sequence of 69 molecules offered in Additional file 1: Table S1, as potential HCV NS5B enzyme inhibitors, were retrieved from the PubChem online data source (https://pubchem.ncbi.nlm.nih.gov/). Additional file 1: Table S1 contains the 2D structure of the molecules along with PubChem compound identification number (CID) and energy score (E_{score}). The 2D structure of the retrieved molecules was drawn with ChemDraw V12.0 and imported into Spartan software which converts the 2D structure to 3D form for onward geometry optimization by implementing the DFT concept at the B3LYP standard of principle and 6-31G** as the basis set (Ejeh et al. 2021b; Shao et al. 2006). The optimized structures were followed by docking in the PDB file.

Preparation of target and docking process

The HCV NS5B enzyme was retrieved from the protein data bank uploaded on February 11, 2015, by Appleby and co-workers containing the required details: The ID is 4WTG, the resolution is 2.90 Å, *R*-value free is 0.232, the *R*-value work is 0.179, and the R-value observed is 0.181

(Appleby et al. 2015). The native ligand (Sofosbuvir as a reference inhibitor) attached was separated after which the HCV NS5B enzyme was loaded through the ICM-pro (Molsoft ICM) software for docking and the native ligand was re-dock for comparison. We used a comprehensive docking method as described in our earlier work (Arthur et al. 2020). Figure 1 shows the HCV NS5B enzyme.

The theoretical background of the energy terms in the docking Algorithm

To describe the free energy of binding, most current techniques use an enlarged "master equation," which includes entropic parameters in the molecular mechanics models (Huai et al. 2021). Equation 1 shows the energy variables that make up the binding free energy scoring function, ΔG (1)

$$\Delta G = \Delta G_{\text{vdw}} + \alpha_1 \Delta G_{\text{hbond}} + \alpha_2 \Delta G_{\text{elec}} + \alpha_3 \Delta G_{\text{conform}} + \alpha_4 \Delta G_{\text{tor}} + \alpha_5 \Delta G_{\text{sol}} + \alpha_6 T \Delta S_{\text{tor}} \quad (1)$$

where ΔG_{vdw}, ΔG_{hbond}, ΔG_{elec}, $\Delta G_{\text{conform}}$, ΔG_{tor}, and ΔG_{sol} are free energy terms for van der Waals, hydrogen bonding, electrostatic, conformational strain penalty, restriction of internal rotors, global rotation, and translation, and the desolvation penalty associated with binding, respectively. While the added entopic energy terms ΔS_{tor} is based on rotatable torsion count which is a constant when poses of the same ligand are considered. Also α_1–α_6 are ligand and biomolecules parameter coefficients and T is the temperature term. All molecules were docked to the enzyme binding site, and the weighted portion of the ICM scoring algorithm was used to provide a score to each molecule (Huai et al. 2021).

Design of new potent inhibitors

Potentially great inhibitors are developed by picking a suitable template molecule (2-amino-9-((2R,3R,4R,5R)-3,4-dihydroxy-5-(hydroxymethyl)-3-methyltetrahydrofuran-2-yl)-1H-purin-6(9H)-one) with outstanding docking scores and passing pharmacokinetics screening from a dataset (see Additional file 1: Table S1 Compound 1). Evaluation of the docking model indicated that the helicase domain can offer an interface over the tetrahydrofuran moiety, including a region to incorporate the methanol substituent. Hence, the interior surface slot should be occupied to give improved binding efficacy and more interactions, which can be accomplished if the chosen drug is tailored with some favorable substituents. As a result of the alteration, the 3-methyl attached to the tetrahydrofuran moiety was substituted with certain favorable moieties to yield a variety of novel compounds, and the position of 3-methyl was labeled **R** as a point of attachment as illustrated in Fig. 2.

Screening the designed entities

In silico ADMET analysis methodologies have been introduced as an extra means to facilitate pharmaceutical chemists in the design and analysis of leads. Using in silico tools to find novel drug candidates minimizes the set of numerical research studies and improves the performance level. We employed Lipinski's rule of five for drug-likeness as an initial assessment step for oral bioavailability and synthetic accessibility utilizing the SwissADME (www.swissadme.ch/) online resource. The newly developed entities, template, and reference

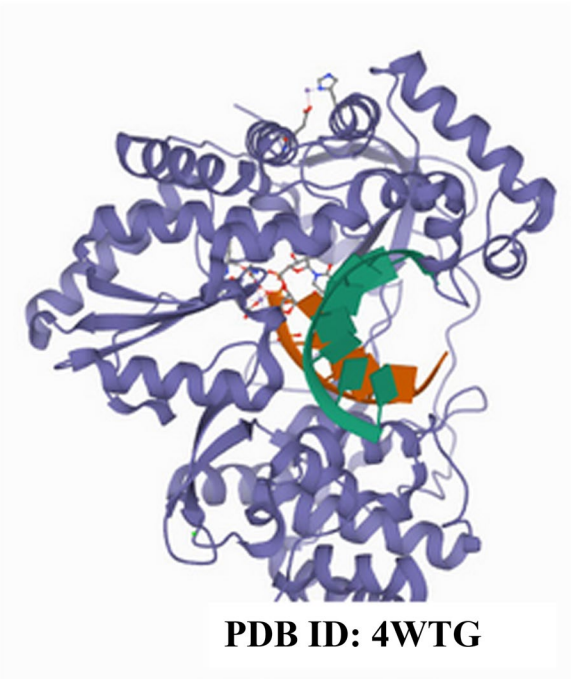


Fig. 1 The structure of HCV NS5B enzyme in interaction with Sofosbuvir

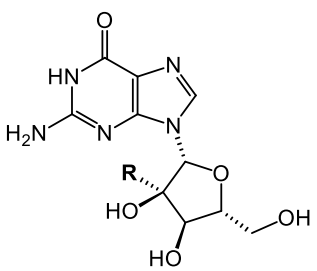


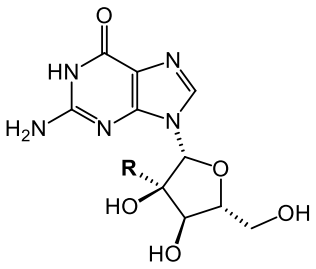
Fig. 2 Structural skeleton of compound **1** showing **R** position as a point of attachment

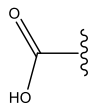
chemicals were then subjected to secondary screening using OSIRIS Property Explorer to calculate the pharmacological characteristics as a measure of pharmacokinetics (Madariaga-Mazón et al. 2021).

Results

The PubChem SID, PubChem CID, compound structure, and binding scores of the full datasets are listed in Additional file 1: Table S1, while Additional file 1: Table S2 shows the docking scores in the form of an ICM score in kcal/mol and various contributions of interaction energy to the binding affinity. The majority of the tested candidates were effective in inhibiting the HCV NS5B RNA enzyme, and the best HCV NS5B RNA enzyme inhibitors were ranked based on the lowest docking score. We also looked at the binding of the more potent inhibitor (compound 1) with the HCV NS5B RNA enzyme to have a deeper understanding of the outstanding docking score. Compound 1's docked pose is displayed in Fig. 3 and is used as a template to create new molecules, as demonstrated in Fig. 2, where the **R** position is a point of attachment, whereas Fig. 1 displays the target receptor in a complex with a native inhibitor (Sofosbuvir). Table 1 shows the structures and docking outcomes of the predefined template (molecule **1**), new molecules (**1a**–**1c**), and Sofosbuvir as reference inhibitors (**R**), while Table 2 presents the natures of interactions intricate in the template

Table 1 The structures and docking outcomes of the predefined template (molecule **1**), new molecules (**1a**–**1c**), and Sofosbuvir as reference inhibitors (**R**)



S/N	R	Binding score (kcal/mol)	Hbond (kcal/mol)	Hphob (kcal/mol)
1 (T)		− 37.46	− 14.56	− 2.329
1a		− 39.98	− 15.76	− 1.730
1b		− 39.90	− 15.59	− 1.864
1c		− 41.71	− 16.52	− 2.306
R		− 30.34	− 10.54	− 2.954

^{Hbond} Hydrogen bond energy, ^{Hphob}hydrophobic energy in exposing a surface to water

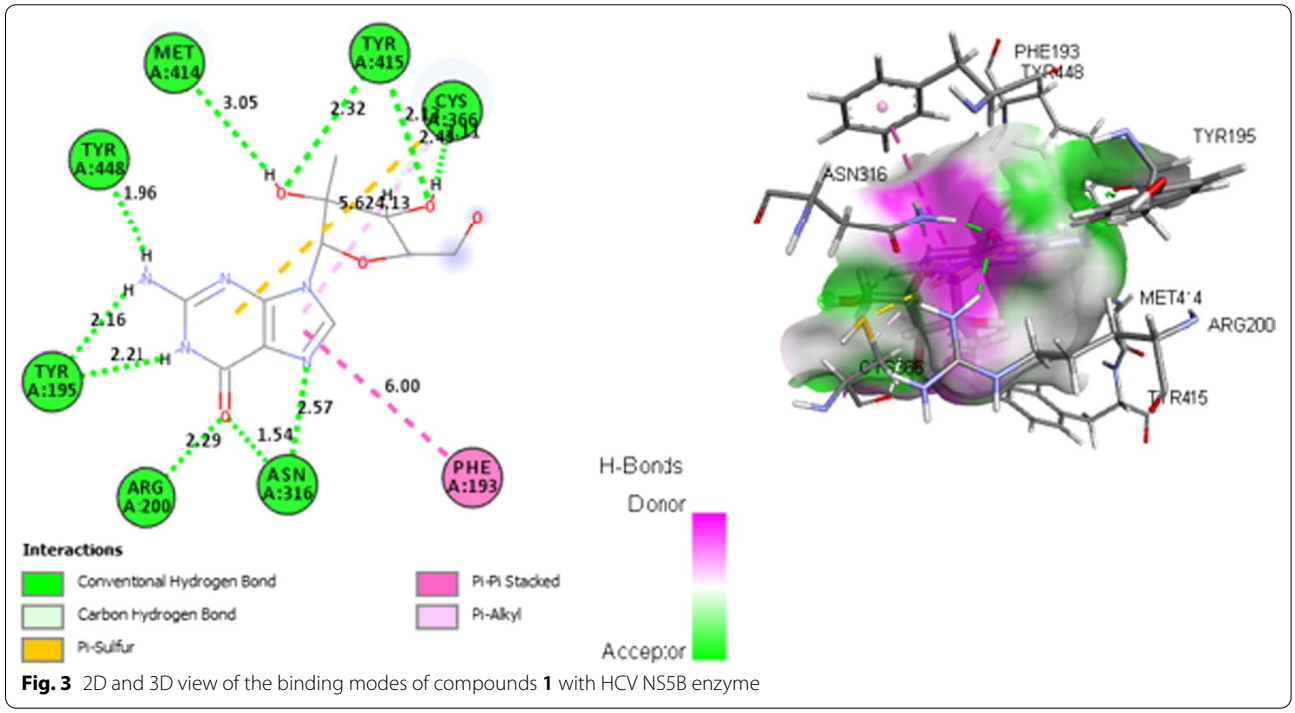


Fig. 3 2D and 3D view of the binding modes of compounds **1** with HCV NS5B enzyme

Table 2 The natures of interactions intricate in the template (molecule 1), new molecule (1c), and Sofosbuvir (R)

Compound	Ligand	Receptor	Interaction	Distance
1	NH	TYR195	H-donor	2.21
	NH	TYR195	H-donor	2.16
	NH	TYR448	H-donor	1.96
	OH	MET414	H-donor	3.05
	HO	TYR415	H-acceptor	2.32
	OH	CYS366	H-donor	3.11
	HO	TYR415	H-acceptor	2.13
	O	ARG200	H-acceptor	2.25
	O	ASN316	H-acceptor	1.54
	N	ASN316	H-acceptor	2.57
	6-ring	CYS366	π-Sulfur	5.62
	5-ring	CYS366	π-Alkyl	4.13
	5-ring	PHE193	π–π Stacked	6.00
1c	NH	TYR195	H-donor	2.23
	NH	TYR195	H-donor	2.18
	NH	TYR448	H-donor	1.96
	O	ARG200	H-acceptor	2.25
	O	ASN316	H-acceptor	1.58
	N	ASN316	H-acceptor	2.73
	OH	MET414	H-donor	2.80
	OH	TYR415	H-donor	2.18
	HO	TYR415	H-acceptor	2.00
	HO	TYR415	H-acceptor	2.21
	OH	CYS366	H-donor	2.35
	H	CYS366	Carbon–hydrogen bond	2.35
	6-ring	CYS366	π-Sulfur	5.61
	5-ring	CYS366	π-Alkyl	4.04
R	O	TYR415	H-acceptor	1.72
	NH	TYR415	H-donor	2.51
	HO	ARG200	H-acceptor	2.67
	HO	GLY192	H-acceptor	1.82
	OH	ASN316	H-donor	1.95
	O	TYR448	Van der Waals	2.69
	CH	TYR195	Carbon–hydrogen bond	2.56
	6-ring	TYR195	Amide π-stacked	3.85
	6-ring	M	Alkyl	5.24
	5-ring	PHE193	π–π T-shaped	4.57
	6-ring	CYS366	π-Alkyl	5.13

(molecule **1**), new molecule (**1c**), and Sofosbuvir as reference inhibitors (**R**).

Figures 4 and 5 show the docked poses of the proposed compound (**1c**) and Sofosbuvir with the HCV NS5B RNA enzyme in 2D and 3D, respectively. Because the main causes of drug development failure are unfavorable pharmacokinetics and toxicity of candidate compounds, it is commonly accepted that ADMET should be examined as soon as possible. As a result, the drug-likeness, pharmacokinetics, ADMET characteristics, and drug score of the proposed compounds were evaluated using Sofosbuvir as the reference. Table 3 shows the results of using the SwissADME online tool to forecast drug-likeness qualities, and Table 4 shows the results of using the OSIRIS Property Explorer to predict ADMET properties such as druggability (drug score) and toxicity risk. On the OSIRIS Property Explorer interface, Figs. 6 and 7 show side views of the representation of physicochemical characteristics (Toxicity Risks, cLogP, solubility, drug-likeness, and drug score) of molecules **1c**, and reference inhibitor, respectively, and the focus is on Toxicity Risks. Prediction findings from OSIRIS Property Explorer are valued and color-coded. Properties having a significant risk of unintended consequences, such as mutagenicity or poor intestinal absorption, are highlighted in red. The green color represents drug-adherent behavior, whereas a red color suggests non-adherent conduct.

Discussion

The docking modeling was used repeatedly to find the best inhibitors for the HCV NS5B RNA enzyme. The number of hydrogen bonds within the complex's studied ligands is thought to indicate the ligand's stability when it interacts with the HCV NS5B RNA enzyme. Increases in hydrogen bonding are expected to indicate increased docking system stability (Saleh and Elshemey 2017).

The native inhibitor (Sofosbuvir) is utilized as a benchmark against which the binding affinity of other recommended drugs is measured. As illustrated in Fig. 5, the native inhibitor establishes five hydrogen bond interactions with the NS5B RNA enzyme residues (TYR415, ARG200, GLY192, TYR415, and ASN316) and other interactions such as van der Waals, carbon–hydrogen bond, amide π-stacked, Alkyl, π–π T-shaped, and π-alkyl with the TYR448, TYR195, MET414, PHE193, and CYS366 amino acid residues of the target, respectively, by docking modeling. The total energy of the docking system with the native inhibitor is − 30.34 kcal/mol, hydrogen bond energy is − 10.54 kcal/mol, and hydrophobic energy is − 2.954 kcal/mol, according to Table 1. As shown in Fig. 3 and Table 1, the most potent inhibitor (compound **1** in the dataset) forms ten H-bonds interaction with the HCV NS5B enzyme residues (TYR195, TYR448, MET414, TYR415, CYS366, ARG200, and ASN316 and other interactions such as π–π stacked, π-sulfur, and π-alkyl with the PHE193, and CYS366 amino acid residues of the target, respectively, by docking modeling. The total energy of the docking system with compound **1** is − 37.46 kcal/mol, hydrogen bond energy is − 14.56 kcal/mol, and hydrophobic energy

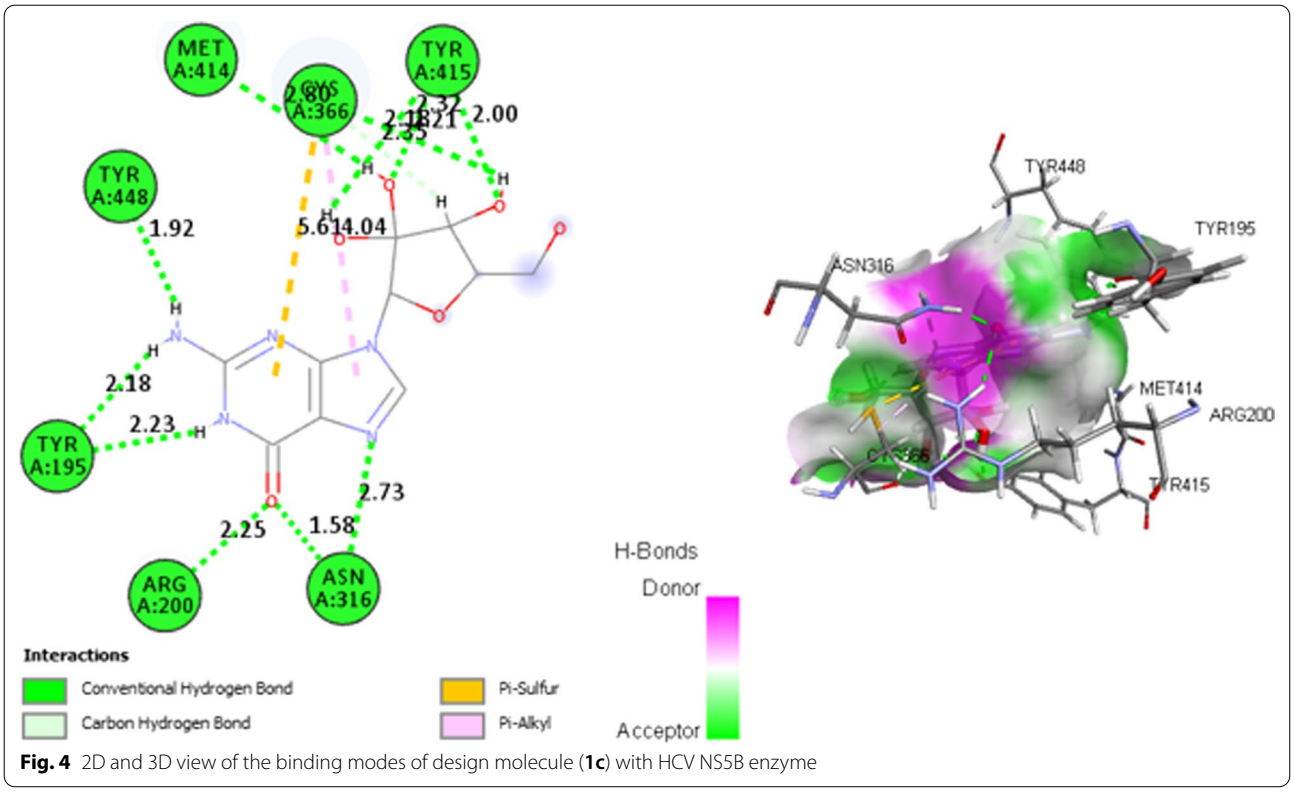


Fig. 4 2D and 3D view of the binding modes of design molecule (**1c**) with HCV NS5B enzyme

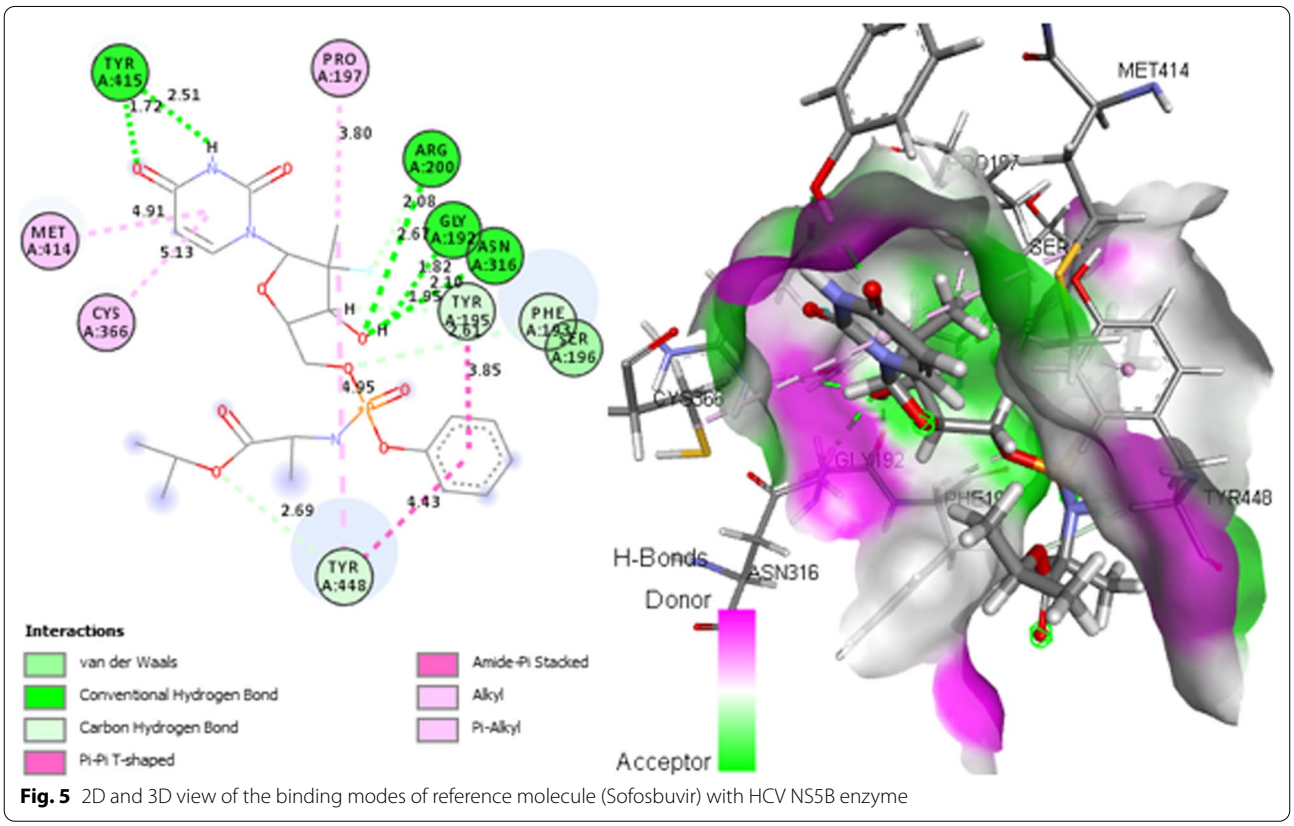


Fig. 5 2D and 3D view of the binding modes of reference molecule (Sofosbuvir) with HCV NS5B enzyme

Table 3 The drug-likeness for molecule **1**, designed molecules (**1a**–**1c**), and Sofosbuvir as reference inhibitor (**R**)

CID	M W (g/mol)	HA	HD	Log p	TPSA (Å^2)	Lipinski #violations	Bioavailability score	Synthetic accessibility
Lipinski's rules of 5: M W (g/mol) < 500; HA ≤ 10; HD ≤ 5; Log p ≤ 5; and TPSA (Å^2) < 140								
1	299.24	7	5	0.14	179.74	1	0.17	3.76
1a	297.27	8	6	− 0.35	159.51	2	0.55	4.00
1b	298.26	8	6	− 0.91	185.53	2	0.17	3.99
1c	327.25	9	6	− 0.74	196.81	2	0.11	4.04
R	529.45	11	3	3.31	167.99	2	0.17	6.02

is − 2.329 kcal/mol, according to Table 1. This indicates that compound **1** is more potent than the native inhibitor.

After that, several favorable substituents were added to the designated template **R** location after assessing the docking and molecular properties. This was done automatically in the current study utilizing the Scaffold Grow module in Discovery Studio, followed by docking screening with ICM-pro. When comparing the designed compounds to the template and reference inhibitors, it was discovered that the docking score of the designed compounds (**1a**–**1c**) ranges from − 41.71 to − 39.90 kcal/mol, as shown in Table 1, indicating that the designed compounds have lower binding energy and form more stable systems. As a result, these new compounds are novel inhibitors of the HCV NS5B RNA enzyme, and their docking results are compared to compound 1's docking results and Sofosbuvir's docking results as a positive control. The interaction of the suggested compounds was also investigated to provide a clearer interpretation of the outstanding docking scores reported. Tables 1 and 2 show the comprehensive docking data as well as the types of interactions involved. Furthermore, the developed compounds had a binding score of less than − 39.90 kcal/mol, which implies that the novel inhibitors can bind the target efficiently and create a more thermodynamically stable system than the reference inhibitor.

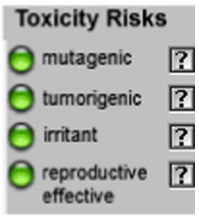
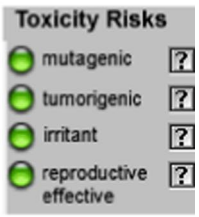
As shown in Fig. 4 and Table 1, the most potent inhibitor (compound **1c**) of the designed molecules forms eleven hydrogen bond interactions with the NS5B RNA enzyme residues (TYR195, ARG200, TYR448, ASN316, MET414, TYR415, and CYS366) and other interactions such as carbon–hydrogen bond, π-alkyl, and π-sulfur with the CYS366 amino acid residues of the target, by docking modeling. The total energy of the docking system with the novel inhibitor is − 41.71 kcal/mol, hydrogen bond energy is − 16.52 kcal/mol, and hydrophobic energy is − 2.306 kcal/mol, according to Table 1. In comparison, these values outperform both the template and the reference molecule. A virtual evaluation was performed using Discovery Studio software, which revealed more information about the interactions of molecules **1**, **1c**, and **R** with the target receptor (HCV NS5B enzyme with PDB ID: 4WTG). Molecule **1c** has a higher degree of favorable interaction with the target receptor than the reference molecule.

The H-bond is the key force driving interactions between the molecule and the target receptor, according to this research, and the interaction energy of the molecules increases as the number of hydrogen bonds increases (Ejeh et al. 2021a; Umar et al. 2020). The number of amino acids participating in the H bond discovered with the proposed compounds was found to be better than Sofosbuvir, as shown in Figs. 4 and 5, respectively, and there are obvious similarities. This may help to provide the chosen compounds with more accurate binding scores for the HCV NS5B enzyme. As a result, as evidenced by the molecular docking data, these new compounds will be effective inhibitors of the HCV NS5B enzyme, demonstrating competitive inhibition with Sofosbuvir. Furthermore, the drug-likeness and pharmacokinetics ADMET features of the proposed compounds were assessed using Sofosbuvir as a reference to ensure that they are feasible drugs.

Because of ADMET risks, many prospective medications never make it to the clinical stage. Due to their importance, ADMET qualities are now being examined in early-stage pharmaceutical research, resulting in a significant reduction in the number of molecules that failed in clinical trials due to poor ADMET properties (Daina et al. 2017; Pires et al. 2018). Computational virtual screening of selected compound (1), designed molecules, and the reference inhibitor was used to assess drug-likeness, including oral bioavailability and synthetic accessibility, utilizing Lipinski's Ro5 (Table 3).

The proposed molecules are regarded to pass Lipinski's requirements because none of them violate more than two and hence can be categorized as drug-like molecules. In addition, an evaluation was carried out using the ABS criterion (Filipovich et al. 2005), with all of the proposed molecules receiving a bioavailability score in the range of 0.55 to 0.11. This standard was based on a probability level of a molecule having an optimal profile of permeability and bioavailability, where 0.55 indicates total

Table 4 The pharmacological characteristics drug scores and toxicity risks for molecule **1**, designed molecules (**1a**–**1c**), and Sofosbuvir as reference inhibitor (**R**)

CID	clogp	Solubility (LogS)	Drug-likeness	Drug score	Toxicity risks
1	−2.39	−1.83	2.54	0.91	
1a	−3.10	−1.40	1.00	0.82	
1b	−3.50	−1.48	1.31	0.84	
1c	− 3.70	−1.30	1.99	0.88	
R	0.36	− 3.78	− 29.3	0.31	

obedience of the Lipinski rule of five (Umar et al. 2020), and the rat bioavailability value is 55%, which is a higher probability value than 10%, confirming the designed molecules' drug-likeness.

The synthetic accessibility score is based on a mix of component contributions and a complexity penalty to measure the ease of synthesis of drug-like compounds. The score ranges from 1 (easy processing) to 10 (tough to synthesize) (Ejeh et al. 2021a). Table 3 shows that the proposed inhibitors have synthetic accessibility in the range of 3.99–4.04, indicating that they are easy to synthesize, as opposed to the reference molecule, which has synthetic accessibility of 6.02, indicating that it is difficult to synthesize.

Again, using OSIRIS Property Explorer software, the pharmacological characteristics and drug scores of

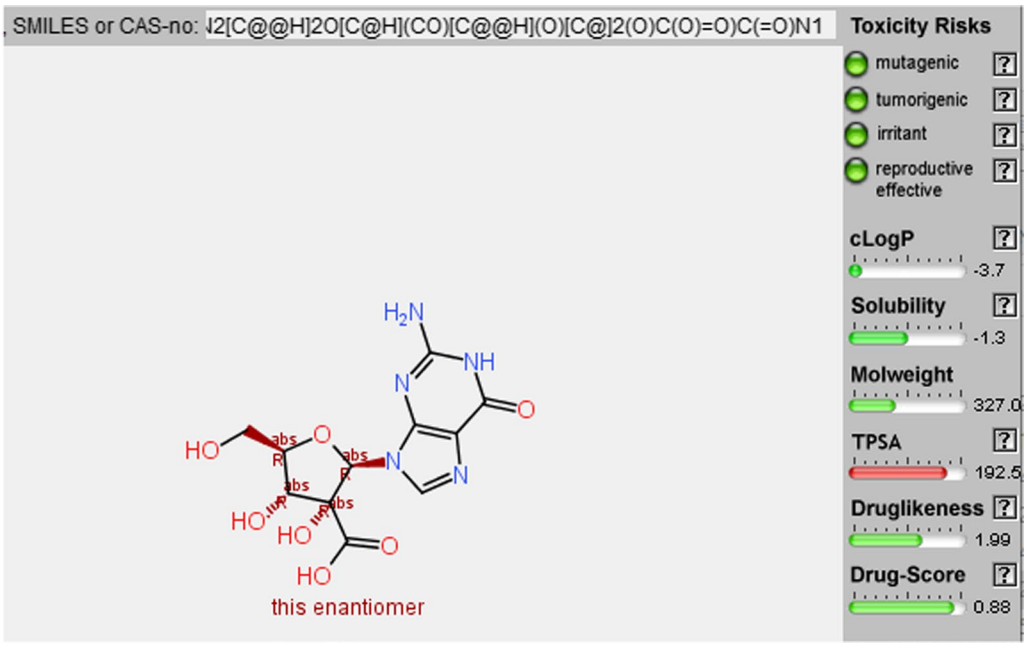


Fig. 6 Side view of the compound **1c** on the OSIRIS Property Explorer interface showing physicochemical characteristics including Toxicity Risks

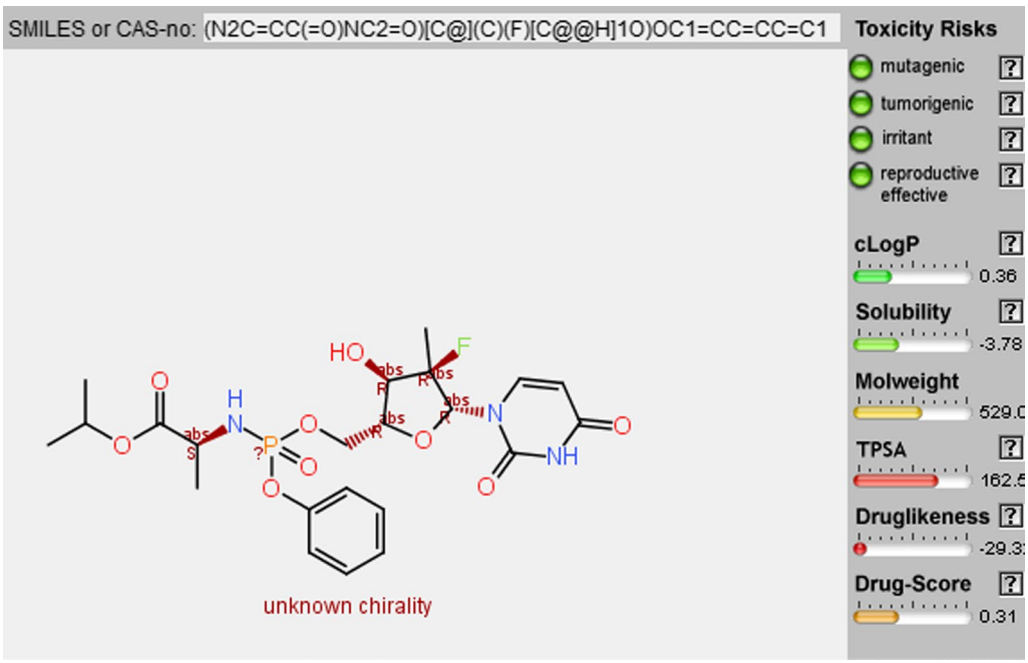


Fig. 7 Side view of the reference molecule on the OSIRIS Property Explorer interface showing physicochemical characteristics including Toxicity Risks

molecule 1, designed molecules (**1a**–**1c**), and Sofosbuvir as reference inhibitors (**R**) were analyzed, with the results given in Table 4. To compute compound hydrophilicity, the software used the logarithm of the partition coefficient between n-octanol and water (cLogP). A high cLogP score indicates poor absorption; compounds with a cLogP value less than 5.0 are more likely to be well absorbed. All of the designed compounds in the current

study have cLogP values of less than 5.0, indicating a high likelihood of being well absorbed. Because a compound's water solubility has a significant impact on its absorption and distribution features, it is a useful metric for evaluating drug transport features. The breakdown of the tablet or capsule is the initial step in the drug absorption process, followed by the dissolution of the effective drug. Low solubility is detrimental to good and efficient oral absorption, and measuring this quality early in the drug development process is critical. The logarithm of the molar concentration (log mol/L) is used to calculate a compound's estimated solubility. Acceptable compounds are those with a log mol/L value between − 4 and 0.5. All the molecules considered have values within this range (Table 4). As a result, the logS values of the designed molecules are appropriate for druggability compounds.

The drug score (ds) integrates drug-likeness, cLogP, logS, molecular weight, and toxicity concerns into one useful score that can be utilized to measure the molecule's total impact to qualify for therapy, which is used to determine the dependability of these proposed entities. The analysis of the proposed molecules in Table 4 reveals that they have ds values in the range of 0.82 to 0.88 (about 82% to 88% of total performances) which are better compared to Sofosbuvir the reference inhibitor with a ds value of 0.31 (31% of total performance). Figures 6 and 7 show side views of the representation of physicochemical characteristics of molecules **1c** and reference, respectively, and indicate the performance of those molecules as **1c** has a value close to 1 (0.88) as compared to the reference which is not closed to 1 (0.31). Prediction findings from these figures reveal that molecules **1c** and Sofosbuvir did not show any toxicity risk alert as displayed in Figs. 6 and 7 in green, respectively, indicating drug-adherent behavior.

Conclusions

Using ICM-Pro software, a cheminformatics approach via molecular docking studies was effectively done between NS5B enzyme (PDB ID: 4WTG) and several anti-HCV agents. The molecule with the lowest docking value for the enzyme of interest was used to develop new analogues, improving the parent substance's potency. Because of the incorporation of a specific hetero-containing moiety that can enhance the final docking performance by boosting the percentage of H-bond interactions observed in their docking systems, the novel compounds designed vary substantially in docking rankings at a range of − 41.71 to − 39.90 kcal/mol against − 30.34 kcal/mol of Sofosbuvir. All of the developed compounds were discovered to block the receptor by filling the protein target's binding domain. Compound **1c** was found to be the most effective inhibitor of the NS5B enzyme, outperforming Sofosbuvir, the FDA-approved NS5B enzyme inhibitor. Furthermore, when compared to Sofosbuvir, which has a drug score of 0.31, the ADMET analysis of the chosen compound (**1c**) demonstrates superior performance with a drug score of 0.88. As a result, future research should include the synthesis, in vivo, and in vitro evaluation of these compounds to confirm our assumption.

Abbreviations

HCV: Hepatitis C virus; NS: Non-structural proteins; FDA: Food and Drug Administration; PDB: Protein Data Bank; ds: Drug score; CADD: Computer-aided drug design; 2D: Two dimensional; 3D: Three dimensional.

Supplementary Information

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Additional file 1. Table S1: The Pubchem_SID, Pubchem_CID, Compound Structure and docking scores of the entire datasets. **Table S2**: The Docking results of the entire datasets.

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Author contributions

SE and AU were in charge of selecting the research tool. SE, AU, GAS, SEA, and MTI were involved in the study design, paper writing, and subject selection and data collecting. The statistical analysis was carried out by SE, AU, GAS, SEA, and MTI who also revised the final text. All authors read and approved the final manuscript.

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Declarations

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