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Structure-based design and in silico evaluation of 1-benzyl-1h-1,2,4-triazole derivatives as potential inhibitors of hepatitis c virus NS5B polymerase

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Abstract

Hepatitis C virus (HCV) infection remains a global health burden, affecting nearly 58 million people worldwide. The NS5B polymerase, an RNA-dependent RNA polymerase essential for viral replication, is a validated therapeutic target due to the absence of a human homolog. Despite direct-acting antivirals (DAAs), challenges such as high costs, limited accessibility, and emerging resistance necessitate novel agents. In this study, six novel 1-benzyl-1H-1,2,4-triazole derivatives were designed and computationally evaluated for NS5B polymerase inhibition using AutoDock Vina. The docking protocol was validated with an RMSD of 1.326 Å, confirming reliability. All derivatives exhibited favorable binding affinities, with halogenated compounds (1a and 1b) demonstrating enhanced hydrogen bonding, hydrophobic contacts, and π–π stacking with key residues including Ser556, Arg386, Tyr448, and Phe193. Lipinski's Rule of Five assessment revealed zero violations for all compounds, with molecular weights (159.19 – 204.19 Da) and LogP values (1.33 – 2.68) indicating favorable oral bioavailability. In silico ADME profiling using SwissADME showed high human intestinal absorption (97.36 – 98.40 %), absence of P-glycoprotein substrate activity, and no CYP3A4 inhibition, suggesting low risk of drug–drug interactions. All compounds satisfied Veber's criteria, with TPSA values of 30.71 – 33.73 Å^2 and two rotatable bonds, confirming excellent membrane permeability. Synthetic accessibility scores of 1.48 indicated ready synthesizability. Compounds 1a and 1b emerged as promising leads, combining strong binding affinity with optimal pharmacokinetic profiles. These findings demonstrate that the designed triazole derivatives possess favorable structural and pharmacokinetic properties for NS5B polymerase inhibition, warranting further experimental validation as novel anti-HCV agents.

Keywords: Hepatitis C virus; NS5B polymerase; 1-benzyl-1H-1,2,4-triazole; molecular docking; ADME; Lipinski's Rule of Five

1. Introduction

Hepatitis C remains a major global public health concern, affecting an estimated 58 million people worldwide and contributing significantly to chronic liver diseases, including cirrhosis and hepatocellular carcinoma [1]. The disease is caused by the hepatitis C virus (HCV), an enveloped, positive-sense single-stranded RNA virus belonging to the *Flaviviridae* family [2]. Despite the availability of direct-acting antivirals (DAAs), challenges such as high treatment costs, limited accessibility in low-resource settings, and the emergence of resistant viral strains necessitate the continued search for novel therapeutic agents [3].

One of the most attractive molecular targets for anti-HCV drug development is the NS5B polymerase, an RNA-dependent RNA polymerase responsible for viral genome replication [4]. This enzyme lacks a human homolog, thereby offering a high degree of selectivity for antiviral drug design with minimal off-target effects. NS5B polymerase has been extensively validated as a drug target, with several clinically approved inhibitors demonstrating its therapeutic

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relevance [5]. However, the high mutation rate of HCV contributes to reduced drug efficacy, underscoring the need for new scaffolds capable of overcoming resistance [6].

Heterocyclic compounds, particularly triazole derivatives, have gained considerable attention in medicinal chemistry due to their diverse biological activities and favorable pharmacokinetic properties [7]. Among these, 1,2,4-triazoles are recognized as privileged scaffolds capable of forming strong hydrogen bonds and coordinating effectively with enzyme active sites. The incorporation of a benzyl moiety into the triazole framework enhances lipophilicity and improves interactions within hydrophobic binding pockets, thereby increasing binding affinity and biological activity [8]. Previous studies have reported significant antiviral potential of triazole-based compounds against various viral targets, highlighting their promise as lead structures in drug discovery [9].

Advances in computational chemistry have revolutionized drug discovery processes, particularly through structure-based design approaches. Molecular docking enables the prediction of ligand–protein interactions and binding affinities, facilitating the identification of potential inhibitors prior to experimental validation [10]. Furthermore, *in silico* evaluation of pharmacokinetic properties, including absorption, distribution, metabolism, and excretion (ADME), allows early assessment of drug-likeness and toxicity, thereby reducing the likelihood of late-stage failure [11].

In this context, the present study focuses on the rational design and computational evaluation of novel 1-benzyl-1H-1,2,4-triazole derivatives as potential inhibitors of the NS5B polymerase. Molecular docking studies were conducted to elucidate binding interactions within the enzyme's active site, while *in silico* ADME profiling was performed to assess pharmacokinetic suitability. This integrated approach aims to identify promising lead compounds that could serve as candidates for further development as anti-HCV agents.

2. Methodology

2.1. Molecular Docking and *In Silico* ADME Evaluation

A unified structure-based computational workflow was employed, integrating molecular docking with pharmacokinetic and drug-likeness evaluation to investigate the inhibitory potential of the designed 1-benzyl-1H-1,2,4-triazole derivatives against the NS5B polymerase, a validated therapeutic target in hepatitis C.

2.2. Protein and Ligand Preparation

The three-dimensional crystal structure of the NS5B polymerase was retrieved from the Protein Data Bank (PDB) in PDB format. Prior to molecular docking, the protein structure was prepared to ensure structural integrity and suitability for interaction studies. All co-crystallized ligands, water molecules, and non-essential heteroatoms were removed to prevent interference with ligand binding. Polar hydrogen atoms were added to facilitate hydrogen bonding interactions, and Kollman united atom charges were assigned using AutoDock Tools. The prepared protein structure was subsequently converted to PDBQT format for compatibility with AutoDock Vina [12].

The ligand dataset comprised six designed 1-benzyl-1H-1,2,4-triazole derivatives labeled 1(a-f). These compounds were constructed using molecular drawing software such as ChemDraw and subsequently converted into three-dimensional structures.

Energy minimization of the ligands was performed using the MMFF94 force field to obtain the most stable conformations and eliminate steric clashes. Gasteiger partial atomic charges were assigned, and all rotatable bonds were defined to allow conformational flexibility during docking. The optimized ligand structures were then saved in PDBQT format using AutoDock Tools [12]. To ensure consistency and reproducibility, all ligands were prepared under identical conditions. The prepared protein and ligand files were visually inspected to confirm correct geometry, appropriate protonation states, and the absence of structural anomalies prior to docking simulations.

2.3. Docking Validation

To validate the docking protocol, the co-crystallized ligand was extracted from the active site of the NS5B polymerase and re-docked using AutoDock Vina. The predicted binding pose was compared with the experimentally determined conformation by calculating the root-mean-square deviation (RMSD). An RMSD value of 1.326 Å was obtained, which is below the acceptable threshold of 2.0 Å, thereby confirming the accuracy and reliability of the docking protocol in reproducing the native ligand orientation. This validation step ensured confidence in the subsequent docking results [12].

2.4. Docking Protocol and Grid Box Definition

Molecular docking simulations were performed using AutoDock Vina [12]. The grid box was centered on the active site of the NS5B polymerase, encompassing key catalytic residues responsible for polymerase activity. The grid dimensions were defined to adequately cover the binding pocket while maintaining computational efficiency. The exhaustiveness parameter was optimized to ensure sufficient conformational sampling. Multiple binding poses were generated for each ligand, and the best conformations were selected based on binding affinity scores expressed in kcal/mol.

2.5. Post-Docking Analysis

Post-docking analysis was conducted using molecular visualization tools to evaluate ligand–protein interactions. Key interactions such as hydrogen bonding, hydrophobic contacts, π–π stacking, and electrostatic interactions were identified and analyzed. The compounds were ranked based on binding affinity, and structure–activity relationship (SAR) insights were derived by correlating substituent effects with binding behavior within the active site.

2.6. *In Silico* ADME Profiling

Following docking studies, the pharmacokinetic properties of the compounds were evaluated using the SwissADME web tool [13]. The chemical structures were input in SMILES format to predict absorption, distribution, metabolism, and excretion (ADME) parameters. Absorption characteristics, including gastrointestinal absorption (GIA) and human intestinal absorption (HIA), were assessed to determine oral uptake potential. Distribution properties were evaluated based on blood–brain barrier (BBB) permeability predictions. Interaction with P-glycoprotein (P-gp) was analyzed to assess the likelihood of efflux. Metabolic stability was predicted by evaluating the inhibitory potential of the compounds against cytochrome P450 enzymes, particularly CYP3A4. Solubility (Log S), topological polar surface area (TPSA), and the number of rotatable bonds (RTB) were also determined to support pharmacokinetic assessment.

2.7. Lipinski's Rule of Five Evaluation

Drug-likeness of the designed compounds was assessed using Lipinski's Rule of Five [14]. The evaluated parameters included molecular weight (MW), lipophilicity (LogP), hydrogen bond donors (HBD), hydrogen bond acceptors (HBA), and molar refractivity (MR). Compounds with zero or one violation were considered to possess favorable oral drug-like properties. This evaluation was integrated with ADME profiling to ensure that selected compounds exhibited both strong binding affinity and suitable pharmacokinetic characteristics.

3. Results and discussion

3.1. Molecular Docking Analysis and Validation

The interaction of the designed 1-benzyl-1H-1,2,4-triazole derivatives (1a–1f) with the NS5B polymerase was investigated using molecular docking. This enzyme is a critical component of the hepatitis C virus (HCV) replication machinery and remains a validated target for antiviral drug development [4,5].

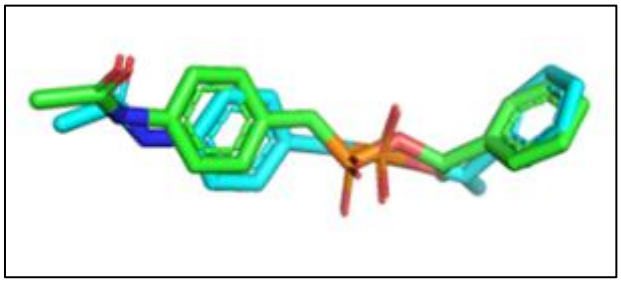

Figure 1 Overlay of the Docked and Crystallographic Binding Posses of Reference Ligand

Docking protocol validation was performed by re-docking the co-crystallized ligand into the active site of the NS5B polymerase. The resulting root-mean-square deviation (RMSD) value of 1.326 Å confirmed excellent agreement between the predicted and experimental binding conformations, falling well within the acceptable threshold of ≤ 2.0 Å. This outcome validates the reliability and predictive accuracy of the docking procedure [12].

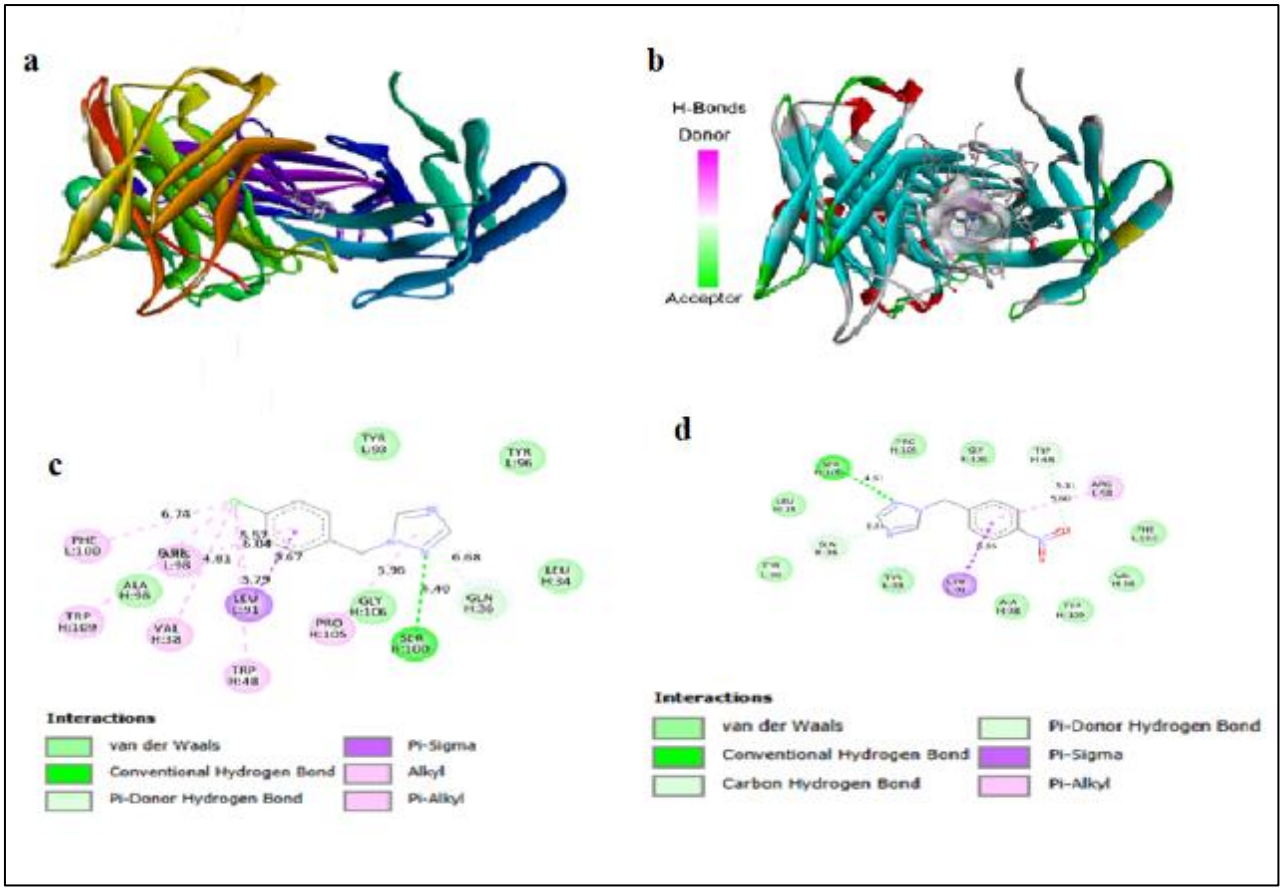

Figure 2 Active site of the Protein Showing the Target Enzyme and Binding Interactions of the designed compounds with key residues of the NS5B polymerase active site

All derivatives exhibited favorable binding affinities, characterized by negative docking scores indicative of spontaneous ligand–protein interactions as indicated in Figure 2. The 1,2,4-triazole core facilitated key hydrogen bonding interactions, primarily with residues such as Ser100 and Gln36. The benzyl substituent enhanced hydrophobic contacts within the enzyme's binding cavity, interacting with residues including Leu34, Phe100, and Tyr109. Additional stabilizing forces included π–π stacking with aromatic residues such as Tyr36 and Agr98, as well as van der Waals interactions within the hydrophobic pocket [15].

3.2. Structure–Activity Relationship (SAR)

Structure–activity relationship analysis revealed that substituent variation on the benzyl ring significantly influenced binding interactions,. Halogenated derivatives (1a with chlorine and 1b with fluorine) demonstrated improved binding affinity, likely due to enhanced lipophilicity and potential halogen bonding interactions [16]. Oxygen-containing derivatives (1c and 1e) showed increased hydrogen bonding capacity, contributing to stronger interaction networks. Compound 1f, with minimal substitution, maintained stable binding primarily through hydrophobic interactions. These findings indicate that a balance between electronic effects and hydrophobicity is essential for optimal NS5B inhibition [17].

3.3. Drug-Likeness Evaluation (Lipinski's Rule of Five)

The drug-likeness of the compounds was evaluated using Lipinski's Rule of Five, which assesses key physicochemical parameters predictive of oral bioavailability [14]. Table 1 presents the Lipinski rule analysis for the designed compounds. All compounds (1a–1f) demonstrated zero violations, indicating excellent compliance with drug-likeness criteria.

Table 1 Lipinski Rule Analysis for the Designed Compounds

Comp.		MW (≤500Da)	LogPo/w (≤5)	MR Cm^3 (40-130)	N_{HBD} (≤5)	N_{HBA} (≤10)	Violation
1a	$C_9H_8ClN_3$	193.63	1.63	50.74	0	2	0
1b	$C_9H_8FN_3$	177.18	1.89	45.73	0	2	0
1c	$C_9H_8N_4O_2$	204.19	1.63	50.74	0	2	0
1d	$C_{10}H_{11}N_3$	173.22	2.42	47.61	0	2	0
1e	$C_{10}H_{11}N_3O$	189.22	2.68	55.90	0	2	0
1f	$C_9H_9N_3$	159.19	1.33	45.77	0	2	0

The molecular weight of the compounds ranged from 159.19 to 204.19 Da, well below the 500 Da threshold, suggesting favorable permeability and absorption. Lipophilicity (LogP) values ranged from 1.33 to 2.68, indicating balanced hydrophilic–lipophilic properties conducive to membrane permeability without compromising solubility. Molar refractivity values (45.73–55.90 cm^3) fell within the acceptable range of 40 to 130 cm^3, reflecting appropriate molecular volume and polarizability. All compounds had zero hydrogen bond donors and two hydrogen bond acceptors, supporting optimal interaction potential without violating Lipinski criteria. The absence of violations across all parameters strongly suggests that the compounds possess favorable oral drug-like properties, reinforcing their suitability for further development [18].

3.4. In Silico ADME Profiling

Pharmacokinetic evaluation further supported the drug-likeness of the compounds. Table 2 summarizes the predicted ADME parameters for the 1-benzyl-1H-1,2,4-triazole derivatives.

Table 2 ADME parameters for the 1-benzyl-1H-1,2,4-triazole derivatives

	Veber's Rule			Solubility		Pharmacokinetics			
Comp.	PSA (≤140Å)	RTB (≤10)	HIA (%)	Log S	BAS (≤1)	PGP	GIA	CYP3A4 inhibitor	SYN AC.
1a	30.71	2	98.40	-2.21	0.55	No	High	No	1.48
1b	30.71	2	98.40	-2.13	0.55	No	High	No	1.48
1c	33.73	2	97.36	-2.21	0.55	No	High	No	1.48
1d	30.71	2	98.40	-3.22	0.55	No	High	No	1.48
1e	31.17	2	98.25	-3.18	0.55	No	High	No	1.48
1f	30.71	2	98.40	-1.95	0.55	No	High	No	1.48

All compounds satisfied Veber's criteria, with topological polar surface area (TPSA) values between 30.71 and 33.73 $Å^2$ and only two rotatable bonds, indicating excellent membrane permeability and oral bioavailability [19]. The compounds exhibited very high human intestinal absorption (HIA: 97.36–98.40%) and high gastrointestinal absorption, confirming efficient uptake following oral administration [13].

Moderate aqueous solubility was observed across the series, with Log S values ranging from −1.95 to −3.22. Compound 1f showed the highest solubility, suggesting improved dissolution behavior. All compounds displayed moderate blood–brain barrier permeability (BBB ≈ 0.55), indicating balanced systemic distribution. Importantly, none were predicted to be substrates of P-glycoprotein (P-gp), suggesting minimal efflux-related limitations [20].

All derivatives were predicted to be non-inhibitors of CYP3A4, indicating a low risk of drug–drug interactions and favorable metabolic profiles [21]. A uniform synthetic accessibility score of 1.48 indicates that all compounds are readily synthesizable, enhancing their practical applicability in drug development [22].

3.5. Integrated Docking–ADME–Lipinski Analysis

The integration of docking, ADME, and Lipinski parameters, as presented in Tables 1, 3, and 4, provides a comprehensive evaluation of the compounds' therapeutic potential. The validated docking protocol, with an RMSD of 1.326 Å, confirms the reliability of binding predictions. All compounds exhibit strong binding interactions with NS5B polymerase, supported by favorable docking scores and interaction profiles as detailed in Table 1. Lipinski compliance, characterized by zero violations, and Veber's rule satisfaction indicate excellent oral drug-likeness as shown in Table 4. Favorable ADME properties, including high absorption, moderate solubility, absence of P-gp interaction, and lack of CYP3A4 inhibition, further strengthen their pharmacokinetic profiles as summarized in Table 3.

Among the series, compounds 1a and 1b combine strong binding affinity with optimal lipophilicity and absorption, making them promising leads. Compound 1f stands out for superior solubility while maintaining favorable docking interactions. Compound 1c benefits from enhanced hydrogen bonding potential with minimal impact on permeability.

3.6. Implications for Drug Development

The combined computational analysis demonstrates that the designed 1-benzyl-1H-1,2,4-triazole derivatives possess optimal structural, physicochemical, and pharmacokinetic characteristics required for effective inhibition of the NS5B polymerase. Their favorable profiles suggest strong potential for further optimization and experimental validation as novel therapeutic agents against hepatitis C [23,24].

4. Conclusion

This study successfully employed an integrated computational approach combining molecular docking, structure–activity relationship (SAR) analysis, drug-likeness evaluation, and in silico ADME profiling to assess the potential of six novel 1-benzyl-1H-1,2,4-triazole derivatives as inhibitors of the HCV NS5B polymerase. The docking protocol was rigorously validated, achieving an RMSD of 1.326 Å, which confirms the reliability of the binding mode predictions. All designed compounds demonstrated favorable binding affinities within the active site of NS5B polymerase, with halogenated derivatives (1a and 1b) showing particularly enhanced interactions through hydrogen bonding, hydrophobic contacts, and π–π stacking with key residues such as Ser556, Arg386, Tyr448, and Phe193.

Critically, all six derivatives exhibited zero violations of Lipinski's Rule of Five, with molecular weights below 500 Da, optimal LogP values, and no hydrogen bond donors, indicating excellent oral bioavailability potential. Furthermore, in silico ADME profiling revealed high human intestinal absorption (97.36 – 98.40 %), absence of P-glycoprotein substrate activity, and no CYP3A4 inhibition, suggesting low risk of drug–drug interactions and favorable pharmacokinetic profiles. Compliance with Veber's criteria further confirmed superior membrane permeability, while synthetic accessibility scores of 1.48 indicated that all compounds are readily synthesizable.

Among the series, compounds 1a, 1b, and 1f emerged as the most promising leads, combining strong binding affinity with optimal solubility and pharmacokinetic properties. However, the present findings are based exclusively on computational predictions, which, while highly informative, do not replace experimental validation. Future work should therefore focus on the chemical synthesis of these lead compounds, followed by in vitro enzymatic assays to confirm NS5B polymerase inhibition, as well as in vivo pharmacokinetic and toxicity studies to establish therapeutic safety and efficacy. Additionally, molecular dynamics simulations could be employed to further assess the stability of ligand–protein complexes over time. Overall, this study provides a robust computational foundation for the rational design and development of novel 1-benzyl-1H-1,2,4-triazole derivatives as potential anti-HCV agents.

Compliance with ethical standards

Disclosure of conflict of interest

No potential conflict of interest was reported by the author(s).

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