

MOLECULAR MODELING AND COMPUTATIONAL SCREENING OF URIDINE DERIVATIVES FOR ANTIVIRAL POTENTIAL AGAINST CHIKUNGUNYA VIRUS

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Uridine and its derivatives are significant macromolecules with substantial therapeutic potential due to their various biological actions, such as their antiviral, antibacterial, and anticancer qualities. This study used computational techniques to examine recently synthesized uridine derivatives. DFT was used to optimize molecular geometries in order to assess their electrostatic, frontier orbital, and thermodynamic characteristics. Electronic and Gibbs free energies became more negative with increasing substitution; higher stability and polarizability were indicated by HOMO–LUMO gaps ranging from 0.1838–0.3363 eV, dipole moments from 3.29–7.42 D, and polarizabilities from 120.78–469.75 a.u. Possible locations for hydrogen bonding and nonbonding interactions were identified by MEP and NBO analysis. Through interactions with ARG168, ILE200, ARG208, and HIS206, derivative 7 demonstrated the greatest score (–7.9 kcal·mol^{–1}) when docked with the chikungunya virus (CHIKV) glycoprotein (3N40), which displayed binding affinities ranging from –6.3 to –7.9 kcal·mol^{–1}. While ADMET predicted intestinal absorption and BBB permeability and class III acute toxicity (LD₅₀ 500–5000 mg·kg^{–1}), PASS predicted antiviral Pa up to 0.858. The most promising contender turned out to be Derivative 7.

Keywords: Uridine; DFT; molecular docking; chikungunya virus; ADMET.

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1. Introduction

Nucleosides are structurally diverse biomolecules composed of a nitrogenous base linked to a pentose sugar, and their variations and modifiable sites make their analysis complex [1]. They are crucial to the development of treatments and disease mechanisms because they play critical roles in the transfer of genetic information and the regulation of enzymes [2]. Their capacity to take on many conformations and substitution patterns results in a variety of physiologically active compounds with enhanced solubility, selectivity, and binding affinity, all important

characteristics in drug design [3]. Nucleosides are significant pharmacophores because they have higher chemical stability and biological recognition than free bases [4]. Uridine (Figure 1), in particular, is widely used due to its similarity to natural ribonucleotides and its roles in health and disease. Its acylated derivatives have recently gained significant attention as nucleoside-based drug candidates due to their notable enzyme-inhibitory, antibacterial, and anticancer properties [5].

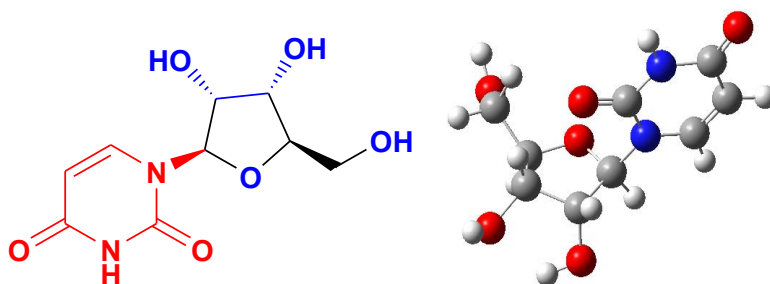


Figure 1. 2D and 3D structures of uridine (1).

Some popular marketed drugs containing cytidine moieties are shown in Figure 2.

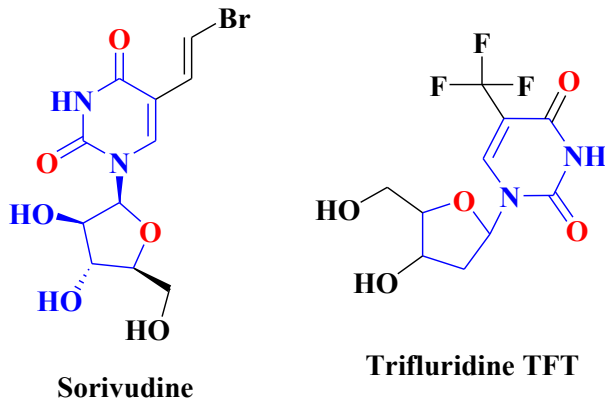


Figure 2. Marketed uridine-based drugs.

Numerous studies have shown that uridine, cytidine, and their analogs possess broad-spectrum biological activities-including antifungal, antibacterial, anticancer, and antiviral effects-particularly through interactions with nucleic-acid-processing proteins [6,7]. Because their synthesis and analysis can be challenging, nucleoside derivatives are often prioritized for computational evaluation using modern in silico tools. Several nucleoside-based antiviral and anticancer drugs have

been approved since the early 2000s [8]. Antiviral compounds that have been previously reported against chikungunya virus (CHIKV), such as nucleoside analogs, including ribavirin, and other small-molecule inhibitors discovered using molecular docking and structure-based drug design methods, have shown promising activity against viral proteins. The compounds are useful as reference standards in determining the binding affinity and pharmacokinetic characteristics of newly developed uridine derivatives. Computational parameters such as Lipinski rules, ADME, toxicity, and molecular docking are widely used to assess their drug potential [9,10]. Modified nucleosides show diverse biological functions across organisms, with hydroxyl-substituted derivatives demonstrating strong antiviral and antibacterial activity. In the case of CHIKV, the envelope glycoproteins E1 and E2—well characterized through structural studies such as PDB 3N40—play central roles in host-cell entry and are key antiviral targets [11]. As no highly effective treatments exist, computational strategies like docking, simulations, and ADME/T predictions can accelerate drug discovery. Computational strategies have been important in identifying potential inhibitors of the chikungunya virus (CHIKV). The viral envelope glycoprotein complex (E1–E2), whose structure is illustrated in the PDB ID: 3N40) is an essential target protein because it is involved in viral attachment and in membrane fusion. Structural analyses have demonstrated that receptor binding occurs through the E2 protein, whereas E1, which causes membrane fusion, is the protein involved in the formation of this complex, making it a crucial component in the development of antiviral drugs. Possible binding pockets and key residues (e.g., Gly91 and His230) of this glycoprotein complex that are involved in ligand interaction have been identified in previous molecular docking and virtual screening studies. Moreover, structure-based drug design activities have shown that small molecules, such as synthetic analogs and natural products, are capable of binding to CHIKV glycoproteins and preventing viral entry. [12] These data underscore the relevance of computational approaches in finding new antiviral drugs and offer a solid foundation to consider modified nucleoside analogs, including uridine analogs, as potential inhibitors against viral surface proteins. The PASS and ADMET profiles of the majority of the investigated drugs in this investigation were encouraging, indicating their potential for further medicinal development. In general, structural enhancements in uridine derivatives for efficient CHIKV suppression are found through DFT, physicochemical, and pharmacokinetic investigations [13,14]. Thermal and electrical stability, comprising characteristics like free energy, enthalpy, entropy, dipole moment,

HOMO–LUMO gap, and electrostatic potential mapping, were evaluated using quantum mechanical methods. All things considered, this work combines computational methods to find uridine derivatives as possible Chikungunya virus inhibitors. Over the past few years, *in silico* methods have been extensively used in the identification of possible antiviral agents against CHIKV. Molecular docking, virtual screening, structure-based drug design, and other techniques have made possible the identification of small molecules binding to key viral proteins, including the envelope glycoprotein complex (E1–E2) that is involved in viral attachment and membrane fusion. These computational methods offer a fast and inexpensive system for initial antiviral drug discovery.

The recent developments in computational drug discovery have played a major role in identifying possible inhibitors against CHIKV. Molecular docking and virtual screening methods have been extensively applied to study binding pockets and to determine small molecules that interact with important viral proteins, such as the envelope glycoprotein complex (E12) exemplified by the crystal structure (3N40), a protein that is crucial to the viral attachment and membrane fusion process. The importance of the CHIKV glycoprotein as a therapeutic target has been reported in previous studies that have identified potential inhibitors interacting with key residues on this protein using docking-based techniques. Moreover, coordinated computational methods involving molecular docking, QSAR and ADMET studies have been utilized to enhance the accuracy and pharmacokinetic characterization of potential antiviral agents. Moreover, these *in silico* methods have been used to investigate both natural and synthetic compounds that exhibit promising antiviral effects against CHIKV. All these studies underline the significance of computational methodologies in the discovery of antiviral drugs and offer a powerful paradigm to assess modified nucleoside derivatives, including the uridine analogs that are studied in the current research.

2. Computational details

Computer-aided drug design heavily uses quantum mechanical methods to compute electrostatic and molecular orbital properties as well as thermal properties [15]. The geometry optimization of all uridine derivatives in this study was performed using the Gaussian software [16], followed by DFT calculations to obtain the correct electronic parameters, as presented in our previous work [17]. The molecular electrostatic potential (MEP) was obtained based on DFT-optimized geometries (B3LYP/6-31G) to predict the location of electrophilic and nucleophilic

reactions in the uridine derivatives. The resulting contour maps reflect the distribution of charges, the shape of the molecules themselves, and other possible regions of hydrogen bonding and biomolecular interactions [18,19]. HOMO-LUMO and natural bond orbital (NBO) analyses were also done. Molecular docking was performed in order to determine the interactions between the uridine derivatives and the CHIKV glycoprotein (PDB ID: 3N40) (Figure S1). Docking was performed after the removal of water molecules and nonprotein ligands using AutoDock Vina. Discovery Studio [20] was used to visualize binding poses and record binding affinities, and hydrogen bonding, hydrophobic, and other noncovalent interactions were analyzed to identify the most stable compounds [21,22]. The admetSAR platform was used to analyze the derivatives by predicting the toxicity, metabolism, excretion, distribution, and absorption profiles of the derivatives. Such parameters as acute oral toxicity, cytochrome P450 and hERG inhibition, blood-brain barrier permeability, and intestinal absorption were taken into consideration. The probabilities (Pa values) of antiviral and antibacterial activities were estimated through the prediction of activity spectra of substances (PASS), which illuminated the potential biological activities as presented in the study workflow. (Figure S2). All quantum chemical calculations were done with density functional theory (DFT) as done in [software name, e.g., Gaussian 09/16]. The uridine derivatives [functional, e.g., B3LYP] level was fully optimized using the [basis set, e.g., 6-31G(d,p)]. The frequency calculations were done on the same level to ensure there were no imaginary frequencies and also that the optimized structures were actually minima. To analyze the electronic properties and chemical reactivity of the compounds, the frontier molecular orbitals (HOMO and LUMO) were studied. Molecular electrostatic potential (MEP) surfaces were also produced to determine the electrophilic and nucleophilic regions of the molecules, which would help in understanding the possible points of interaction. Molecular docking studies were conducted [software, e.g., AutoDock Vina]. The Protein Data Bank was searched, and the crystal structure of chikungunya virus glycoprotein (PDB ID: 3N40) was obtained, and the water molecules were removed and replaced with hydrogen atoms. Docking was preceded by optimization of the ligand structures. A grid box was specified to encompass the region of active /binding site; default docking parameters were applied unless stated otherwise. Docking scores were used to determine binding affinities, and interactions between proteins and ligands were analyzed with [software, e.g., Discovery Studio Visualizer]. Prediction of ADMET properties of the designed compounds was carried out using [tool name, e.g., SwissADME / pkCSM] with parameters of absorption, distribution, metabolism, excretion, and toxicity. A PASS (Prediction of Activity Spectra of Substances) analysis was performed to determine the likely biological activity of the compounds, especially their antiviral activity.

3. Results and Discussion

3.1 Analysis of thermodynamics

Structural changes have a significant effect on the thermal and molecular orbital properties. Free energy and enthalpy refer to the spontaneity of a reaction and the stability of a product [23]. Six uridine derivatives were chosen and optimized by a quantum mechanical method, as presented in Table S1. Table 1 represents the quantum chemical properties of the optimized uridine derivatives, such as electronic energy, enthalpy, dipole moment, Gibbs free energy, and polarizability.

Table 1. Thermodynamic properties of Uridine derivatives.

Entry	Stoichiometry	Electronic energy	Enthalpy	Gibbs free energy	Dipole moment	Polarizability
1	C ₉ H ₁₂ N ₂ O ₆	-910.726	-910.483	-910.544	3.292	120.782
2	C ₁₇ H ₁₈ N ₂ O ₇	-1294.354	-1293.983	-1294.062	5.150	206.428
3	C ₂₆ H ₃₄ N ₂ O ₈	-2149.820	-2148.945	-2149.091	5.278	403.316
4	C ₃₇ H ₅₄ N ₂ O ₉	-2228.428	-2227.494	-2227.643	5.129	425.692
5	C ₂₇ H ₃₄ N ₂ O ₉	-2307.036	-2306.041	-2306.201	5.100	448.018
6	C ₄₁ H ₆₂ N ₂ O ₉	-2385.644	-2384.589	-2384.755	5.109	469.749
7	C ₁₇ H ₁₈ N ₂ O ₇	-1835.400	-1834.767	-1834.882	7.415	316.189

The larger the size of the molecules in acylated uridine derivatives, the more negative the electronic and Gibbs free energies and the greater the thermodynamic stability. The dipole moments were 3.29-7.41 D, with compound **7** having the highest value, which may result in increased solubility and hydrogen bonding. The larger the size, the higher the polarizability, which is an indication of increased deformability of the electron cloud and enhanced molecular interactions [24]. The range of free energies for uridine is between -0.2057 Hartrees and -2384.76 Hartrees with compound **6**. Altogether, acylation stabilizes uridine energetically and enhances electronic and physicochemical properties, which could increase biological activity. Overall, these results confirm that structural modification of uridine by acylation not only energetically stabilizes the molecules but also enhances their electronic and physicochemical properties, which may influence their biological activity [25].

3.2 Frontier molecular orbital analysis

Frontier molecular orbitals, the HOMO and LUMO, are key indicators of a molecule's chemical reactivity and kinetic stability [26]. Table 2 presents their energy values along with global chemical descriptors, softness, and hardness, calculated for each compound.

Table 2. Analog energy (eV) of the HOMO, LUMO, energy gap, hardness and softness.

Entry	^s HOMO	^s LUMO	Gap	Hardness	Softness
1	-0.35550	-0.01916	0.33634	0.16817	5.9463
2	-0.25634	-0.06285	0.19349	0.09675	10.336
3	-0.25922	-0.06408	0.19514	0.09757	10.249
4	-0.25807	-0.06300	0.19507	0.09754	10.253
5	-0.25791	-0.06286	0.19505	0.09753	10.254
6	-0.25767	-0.06282	0.19485	0.09743	10.265
7	-0.24227	-0.05850	0.18377	0.09189	10.888

Compound **7** exhibited the highest softness, lowest hardness, and smallest HOMO–LUMO gap, indicating greater reactivity than the other derivatives. For compound **6**, the LUMO is localized on the uridine ring, while the HOMO is concentrated on the acylation group [27] (Figure S3).

This density of states (DOS) diagram can give a detailed view of the distribution of electronic states in the system as a function of energy, as shown in Figure S4. It can be used to locate the position of the frontier orbitals (such as the HOMO and LUMO) and to indicate the number of states that can be accessed at each energy level. In the evaluation of the electronic structure, band gap, and reactivity of the compounds under study, DOS analysis, especially, is useful in obtaining valuable information regarding their chemical stability and potential biological activity.

3.3 Molecular electrostatic potential

The maps of molecular electrostatic potential (MEP) indicate the most probable locations of electrophilic and nucleophilic attacks, and they are used to understand hydrogen bonding and biological recognition.

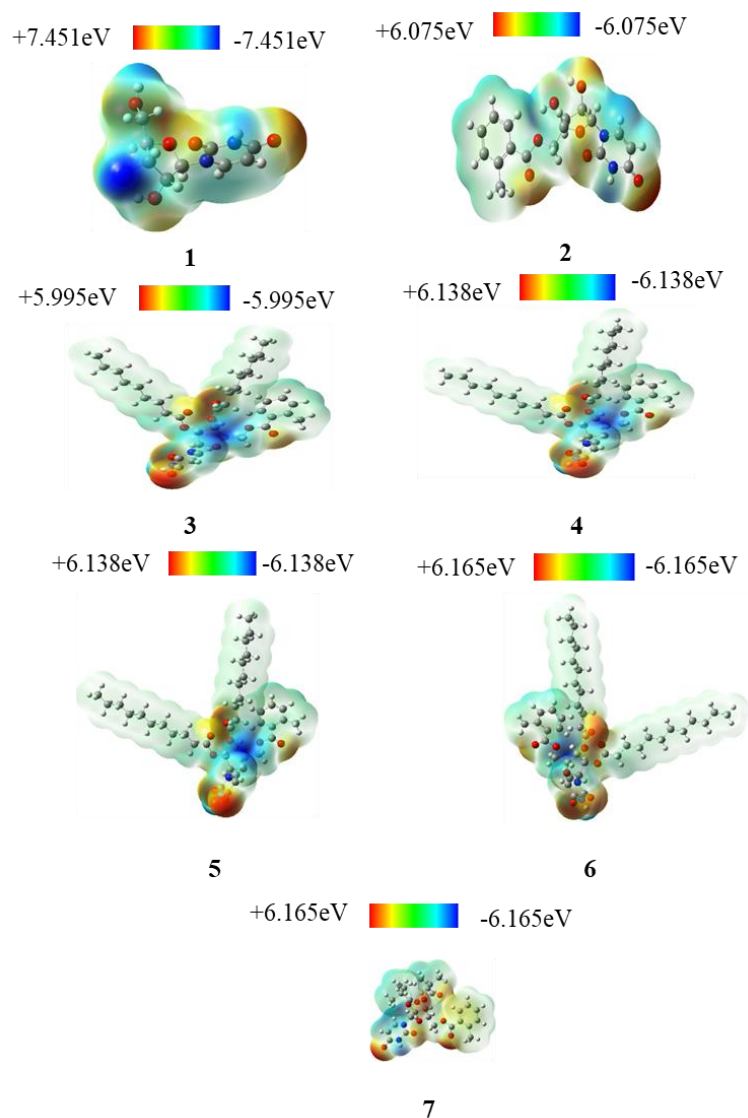


Figure 3. Molecular orbitals of uridine derivatives (1-7).

The uridine analogs (2-7) of PM6-optimized geometries demonstrate the molecular size, shape, and area of positive, negative, and neutral electrostatic potential (Figure 3) that give information about the reactive sites.

In MEP maps, red to blue is used to indicate increasing potential: red to electrophilic sites, green to zero potential, and blue to nucleophilic sites. Electron-rich and electron-deficient regions can be deduced from atomic partial charges; natural bond orbital analysis aids in understanding molecular reactivity and intermolecular interactions [28] (Figure 3).

Red < orange < yellow < green < blue is an indication of potential increases. Green represents the zero potential area, and blue represents the maximum positive area that is favorable to nucleophilic attack, and red represents the maximum negative area that indicates an unwanted site for nucleophilic attack [29]. The electronic distribution in the molecule presented in Fig. 3 is explained by the atomic partial charges obtained after the analysis with natural bond orbital (NBO). These values show the distribution of electron density between atoms, indicating areas of electron-rich and electron-deficient character. Molecular reactivity, intermolecular interactions, and overall electronic nature of the system [30]. The results of natural bond orbital (NBO) analysis of uridine derivatives **2**, **6**, and **7** are shown below in Figure S5.

3.4 Molecular docking analysis

To increase the scientific quality of the current study, we have compared our findings with other previous studies done on the inhibitors of the chikungunya virus (CHIKV). The viral envelope glycoprotein (E1-E2) complex, represented by the crystal structure (3N40), is key to viral entry and fusion, and has been identified as a potential target for antiviral therapy. Inhibitory effects on CHIKV via interaction with the viral glycoprotein and preventing viral entry have been reported with a number of small molecules and natural products. Conversely, the uridine analogs developed in the present study had good binding affinity to the active/binding site of the glycoprotein, which implies their ability to disrupt viral fusion or host cell recognition. Although it is known that nucleoside analogs bind to viral polymerases, recent reports show that modified nucleoside analogs can also bind to non-polymerase viral proteins via hydrogen bonding and other polar interactions. In this regard, the binding interactions observed between uridine analogs and key amino acid residues of the CHIKV glycoprotein, primarily hydrogen bonding and hydrophobic interactions, suggest their potential as a polypharmacological agent. Furthermore, the reported binding energies of the uridine derivatives are comparable to or even better than, previously reported binding energies of CHIKV inhibitors, which indicates a high probability that the uridine derivatives will become useful lead compounds. This research offers a different view on the potential use of nucleoside-based scaffolds for targeting not only polymerases [31]. The crystal structure of the chikungunya virus (CHIKV) envelope glycoprotein complex (E1–E2) (3N40) was chosen in the present study as it is highly resolved in structure and has a well-characterized conformation used in viral attachment and membrane fusion. This structure offers a complete and consistent display of the glycoprotein interface, which is essential to study ligand binding and interaction. Though there are other CHIKV structures (3N42 and 3N44) they are analogous conformations or partial structural variations of the

glycoprotein complex. Hence, 3N40 was selected as a representative and trustworthy model to achieve uniformity and clarity in the docking analysis. Molecular docking is widely used to examine ligand–receptor interactions and determine the preferred ligand orientation [32]. This study focused on the crystal structure of the chikungunya virus (CHIKV) envelope glycoprotein complex (E12) (PDB ID: 3N40) because it has a high resolution (~ 2.65 Å) and the structural features of interest to viral attachment and membrane fusion are well-resolved. This geometry gives a stable and full representation of the glycoprotein interface, allowing the identification of ligand-binding interactions to be made reliably. Other CHIKV glycoprotein structures exist, including 3N42 and 3N44, but they are very similar conformations with small structural differences. As such, 3N40 was selected as a representative model so that there is uniformity and conciseness in the docking analysis [33].

The CHIKV receptor (3N40) was prepared by removing water and nonprotein components. Water molecules and all nonprotein components were removed from the three involved receptors to prepare them for the molecular docking computations [34]. Uridine (**1**) showed a binding affinity of -6.1 kcal/mol, while its derivatives (**1-7**) ranged from -6.3 to -7.9 kcal/mol (Table 3). These results were compared with standard antifungal drugs fluconazole and voriconazole.

Table 3. Binding affinities (kcal/mol) of uridine and its derivatives.

Entry	Chikungunya virus receptor 3N40			
	Binding affinity	No. of hydrogen bond	No. of hydrophobic bond	Interaction type
1	-6.3	5	1	H, PS
2	-7.6	6	3	C, H, PS, A, PA
3	-7.0	4	10	H, C, A, PA
4	-6.6	6	8	C, H, PC, PS, PPT, A
5	-6.4	6	10	C, H, A, PA
6	-7.0	6	7	C, H, A, PA, PSu
7	-7.9	8	5	C, H, A, PC, PSu, PPT, PA

PS = Pi-sigma; PSu = Pi-sulfur; PPT = Pi-Pi T-shaped; H = conventional hydrogen bond; C = carbon–hydrogen bond; A = alkyl; PA = Pi–alkyl; PC = Pi cation; PPS = Pi–Pi stacked

In addition to interacting with the HIS405, UNKO, and ASN533 proteins, the parent molecule uridine also demonstrated strong hydrogen bonding at a relatively close bond distance (3.00517) (Table S2).

Compound **7** showed the highest binding affinity for the main protease 3N40, likely due to its strong electron-withdrawing pivaloyl group. Compounds **2** and **6** contain methyl benzoyl and decanoyl groups, which also enhanced binding. Modifications of the $-OH$ group with long aliphatic chains or aromatic rings, as well as halogenated aromatics, generally increased binding affinity. CH/O interactions were the most prominent nonbonding interactions, along with CH/ π ,

NH/ π , OH/ π , and CH/N interactions. The parent uridine also formed strong hydrogen bonds with HIS405, UNKO, and ASN533 at a short bond distance of 3.005 Å.

It was found that derivative **7** had the highest binding affinity for the main protease 3N40, attributed to its pivaloyl group, which enhanced electron density and binding. Compounds **2** and **6** contain methyl benzoyl and decanoyl groups. Binding affinity was further influenced by hetero groups (Cl/F), long aliphatic chains, aromatic rings, and –OH modifications, with halogenated aromatics generally increasing affinity. Nonbonding interactions, especially CH/O, were key in predicting molecular behavior, alongside CH/ π , NH/ π , OH/ π , and CH/N interactions (Figure 4). The parent uridine formed strong hydrogen bonds with HIS405, UNKO, and ASN533 at a short bond distance of 3.005 Å (Figure 5).

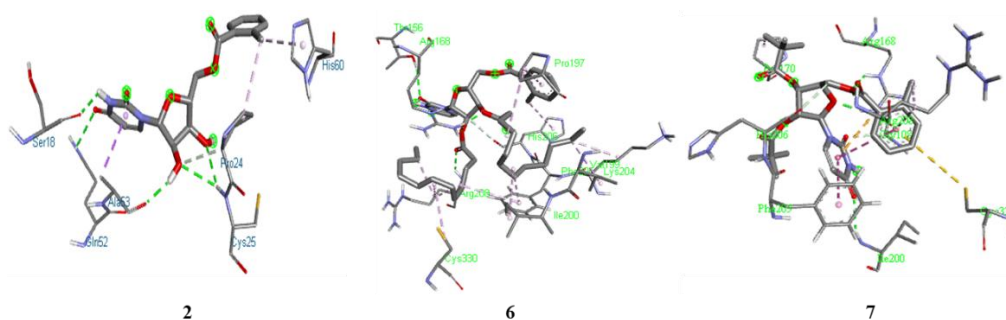


Figure 4. Discovery Studio's nonbonding interactions between molecules (**2**, **6**, and **7**) and the 3N40 active site.

Blind docking studies suggest that all compounds have potential as antifungal agents [35,36].

The molecular docking results were carefully analyzed, and it was found that the binding affinities of the uridine derivatives to the chikungunya virus glycoprotein are heavily dependent on discrete active site residues and intermolecular interactions. Interestingly, the residues including Arg168, Arg208, Ile200, Phe205, and Cys330 are at the focus of the ligand stabilization process due to a complex of hydrogen bonding and hydrophobic interactions. Compound **7** demonstrated the highest binding affinity (-7.9 kcal/mol), and it is possible to suggest that this compound demonstrated the strongest hydrogen bonds with the key residues, such as Arg168, Ile200, and Arg208 (bond distances are around 1.8-2.6 Å), as well as a significant number of hydrophobic interactions between Phe205 and Cys likewise, compounds **4-6** were also found to bind favorably after repeated interactions with Arg168 indicating that this residue is a critical hotspot on the binding region.

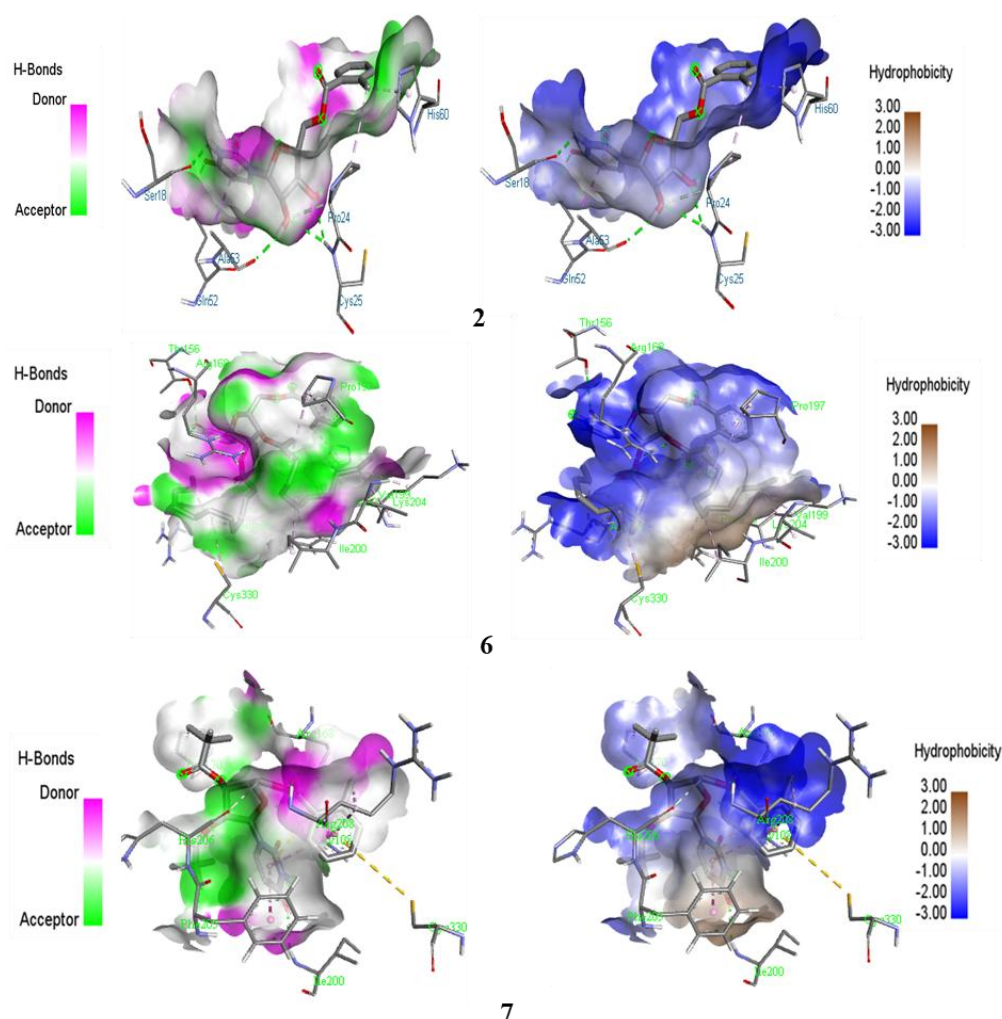


Figure 5. Hydrogen bonds and hydrophobicity of compounds no. **2**, **6**, and **7** with 3N40.

Conversely, less potent binding compounds, like compounds **1**, had fewer interactions with these crucial residues and fewer hydrophobic contacts, leading to less stable interactions. The structure-activity relationship shows that the existence of functional groups that can establish several hydrogen bonds and π -type interactions has a significant positive impact on binding affinity. Also, polar (hydrogen bonding) and non-polar (hydrophobic/ π -alkyl) interactions, which may co-occur, seem to play a crucial role in the best ligand accommodation by the glycoprotein binding site. On the whole, these results show the significance of certain amino acid residues, especially Arg168 and Phe205, in the regulation of the interaction with the ligands, and indicate that the structural alterations leading to the increase in the variety of interactions can greatly increase the antiviral properties of uridine derivatives.

Compound **7** appears to be the most effective, with the lowest binding free energy of -7.9 kcal/mol, indicating the strongest inhibition (Figure 6).

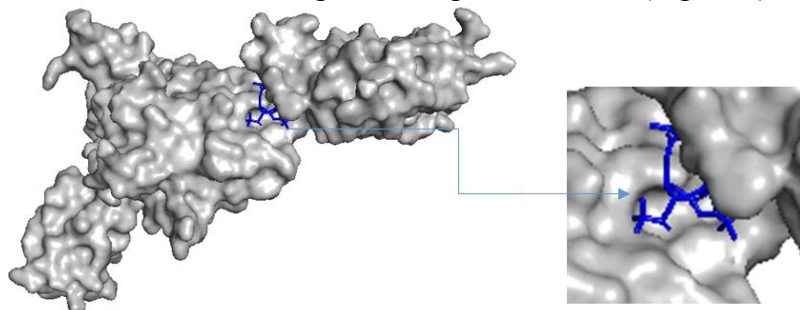


Figure 6. Docked pose of compound no. **7** with 3N40.

3.5 ADMET analysis

The admetSAR server was used to evaluate the toxicity and pharmacokinetic profiles of the modified compounds [37]. The analyses of ADMET and PASS are important in understanding the pharmacological potential of the designed uridine derivatives in addition to their binding affinity. The ADMET parameters are used to give insight into drug-likeness because they measure the important characteristics of the drug, namely, absorption, bioavailability, toxicity, and metabolic stability, which are crucial for predicting performance in vivo. In the current study, the majority of the compounds had high human intestinal absorption and reasonable toxicity (class III), which shows good pharmacokinetic characteristics. These findings are further complemented by PASS analysis, which predicts the most likely biological activity of the compounds, such as antiviral activity based on their structural characteristics.

Table 4. Selected pharmacokinetic parameters of uridine and its designed analogs.

Entry	BBB	Human intestinal absorption	CaCO ₂ permeability	Human Ether -a-go-go-Related Gene	Carcinogenicity (Three-class)	Acute oral toxicity	Aqueous solubility LogS	Rat acute toxicity LD50 mol/kg
1	+0.7679	0.8393	+0.9175	0.9648	0.4917	III(0.6185)	-1.4249	1.6859
2	-0.619	0.7604	0.535	0.9765	0.5008	III(0.6749)	-2.6786	1.7911
3	+0.8559	0.9920	0.5871	0.9259	0.6096	III(0.6772)	-4.3842	2.3804
4	+0.8599	0.9920	0.5871	0.9259	0.6096	III(0.6772)	-4.3842	2.3804
5	+0.8599	0.9920	0.5871	0.9259	0.6096	III(0.6772)	-4.3842	2.3804
6	+0.8599	0.9920	0.5871	0.9259	0.6096	III(0.6772)	-4.3842	2.3804
7	+0.7388	0.9761	-0.6908	0.9896	0.5414	III(0.6362)	-3.8102	2.0164

The results of docking were correlated with ADMET profiles, with compounds having higher binding affinities, especially Drug **7**, showing balanced pharmacokinetic behaviors, indicating their potential to be antiviral candidates. The

designed uridine analogs have similar binding affinities and satisfactory ADMET properties compared to the earlier reported antiviral agents as well as nucleoside analogs, including ribavirin and other CHIKV inhibitors identified through computational studies. These findings suggest that docking and ADMET analysis can be used in combination to create a complete model to identify potential antiviral compounds that have good target interaction and good drug-like behavior. Parameters included acute oral and rat toxicity, cytochrome 3N40 inhibition, human intestinal absorption, blood–brain barrier permeability, and hERG inhibition. A summary of the results is provided in Table 4.

Compounds with an LD₅₀ between 500 and 5000 mg/kg fall into Category III (+). All compounds showed positive blood–brain barrier permeability and human intestinal absorption, indicating good bioavailability, and modifications produced P-glycoprotein non-inhibitors. Compounds **3–6** showed lower hERG inhibition, suggesting safer profiles. In acute rat toxicity tests, all compounds were comparable, with **3–6** being the least toxic relative to parent uridine. As hERG inhibition can cause long QT syndrome, further studies are warranted.

3.6 PASS prediction

PASS (Prediction of Activity Spectra for Substances) is a software tool used to assess the potential biological activities of organic drug-like molecules. Based on compound structures, PASS predicts a wide range of activities before experimental testing (Table 5). The probability of being active (Pa) indicates the likelihood of a compound belonging to an active class, while the probability of being inactive (Pi) indicates the likelihood of belonging to an inactive class. Predictions were performed using the Way2Drug online server, with the invariant error of prediction (IEP) representing the average prediction error from cross-validation [38].

Table 5. Prediction of the antiviral, antimicrobial and anticarcinogenic activities of uridine derivatives.

Entry	Antiviral		Antimicrobial		Anti carcinogenic	
	Pa	Pi	Pa	Pi	Pa	Pi
1	0.858	0.005	0.087	0.004	0.785	0.006
2	0.698	0.006	0.261	0.0003	0.0722	0.008
3	0.486	0.008	0.473	0.013	0.0402	0.016
4	0.474	0.008	0.118	0.066	0.403	0.131
5	0.475	0.0008	0.334	0.048	0.165	0.016
6	0.607	0.014	0.437	0.023	0.699	0.010
7	0.608	0.014	0.437	0.023	0.689	0.060

These findings indicate that these compounds are relatively effective against microbial, viral, and cancer pathogens.

4. Conclusions

This study shows that uridine derivatives are promising scaffolds for developing antiviral drugs against CHIKV. DFT calculations showed the increased stability and reactivity of the compounds in comparison with parent uridine, and FMO and MEP analyses indicated that the compounds have favorable electronic properties for intermolecular interactions. Molecular docking revealed that the highest binding affinities were observed with the CHIKV glycoprotein (PDB: 3N40), in which compound 7 scored the highest (-7.9 kcal/mol) due to a number of nonbonding and hydrogen-bond interactions. The acyl modifications resulted in the optimization of ligand-receptor complementarity and biological activity. Good pharmacokinetic profiles, non-toxicity, and blood-brain barrier permeability were confirmed by ADMET analysis, and PASS predictions suggested the presence of antiviral, antibacterial, and anticancer potential. On the whole, this in silico study that has combined DFT, MEP, FMO, ADMET, PASS, and docking has justified uridine modification to enhance pharmacological characteristics, with compound 7 being the best candidate to be subjected to experimental testing. A combination of synthetic and computational methods can provide an effective approach to creating nucleoside-based antivirals.

Supplementary Materials

Additional experimental data are provided in Figure S1-S5 and Table S1-S2 in the Supplementary Materials.

Author Contributions

Conceptualization, S.M.A.K.; methodology, S.M.A.K. and T.E.; software, T.E.; formal analysis, T.E.; investigation, S.M.A.K.; data curation, S.M.A.K.; writing—original draft preparation, T.E.; writing—review and editing, S.M.A.K.; supervision, S.M.A.K.; project administration, S.M.A.K.; funding acquisition, S.M.A.K. All authors have read and agreed to the published version of the manuscript.

Data Availability Statement

Data supporting the findings of this study are available upon reasonable request from the corresponding author.

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Conflicts of Interest

The authors declare no conflict of interest.

Artificial Intelligence Disclosure

No artificial intelligence-based or generative tools were used in the preparation of this manuscript.

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REFERENCES

- [1] Bzowska, A.; Kulikowska, E.; Shugar, D. Purine nucleoside phosphorylases: Properties, functions, and clinical aspects. *Pharmacol. Ther.* **2000**, *88*, 349–425. DOI: 10.1016/S0163-7258(00)00097-8.
- [2] Crain, P.F. Preparation and enzymatic hydrolysis of DNA and RNA for mass spectrometry. *Methods Enzymol.* **1990**, *193*, 782–790. DOI: 10.1016/0076-6879(90)93450-Y.
- [3] Jordheim, L.P.; Durantel, D.; Zoulim, F.; Dumontet, C. Advances in the development of nucleoside and nucleotide analogues for cancer and viral diseases. *Nat. Rev. Drug Discov.* **2013**, *12*, 447–464. DOI: 10.1038/nrd4010.
- [4] Song, C.; Liu, Z.-J.; Xu, B.; Zou, R.; Hu, W. The role of uridine in health and disease. *J. Inflamm. Res.* **2025**, *18*, 10163–10179. DOI: 10.2147/JIR.S506308.
- [5] Basri, R.; Ullah, S.; Khan, A.; Mali, S.N.; Abchir, O.; Chtita, S.; El-Gokha, A.; Taslimi, P.; Binsaleh, A.Y.; El-Kott, A.F.; Al-Harrasi, A.; Shafiq, Z. Synthesis, biological evaluation and molecular modelling of 3-formyl-6-isopropylchromone derived thiosemicarbazones as α -glucosidase inhibitors. *Bioorg. Chem.* **2023**, *139*, 106739. DOI: 10.1016/j.bioorg.2023.106739.
- [6] Kabir, A.K.M.S.; Kawsar, S.M.A.; Bhuiyan, M.M.R.; Islam, M.R.; Rahman, M.S. Biological evaluation of some mannopyranoside derivatives. *Bull. Pure Appl. Sci.* **2004**, *23*, 83–91.
- [7] Groaz, E.; De Jonghe, S. Overview of biologically active nucleoside phosphonates. *Front. Chem.* **2021**, *8*, 616863. DOI: 10.3389/fchem.2020.616863.
- [8] Rhabori, S.E.; Alaqarbeh, M.; Aissouq, A.E.; Bouachrine, M.; Chtita, S.; Khalil, F. Design, 3D-QSAR, molecular docking, ADMET, molecular dynamics and MM-PBSA simulations for new anti-breast cancer agents. *Chem. Phys. Impact* **2024**, *8*, 100455. DOI: 10.1016/j.chphi.2023.100455.
- [9] De Clercq, E. Historical perspectives in the development of antiviral agents against poxviruses. *Viruses* **2010**, *2*, 1322–1339. DOI: 10.3390/v2061322.
- [10] Munia, N.S.; Alanazi, M.M.; Bakri, Y.E.; Alanazi, A.S.; Mukhrish, Y.E.; Hasan, I.; Kawsar, S.M.A. Uridine derivatives: Synthesis, biological evaluation, and in silico studies as antimicrobial and anticancer agents. *Medicina* **2023**, *59*, 1107. DOI: 10.3390/medicina59061107.
- [11] Vardanyan, R.; Hruby, V. Antiviral drugs. In *Synthesis of Best-Seller Drugs*; Elsevier, **2016**, pp. 687–736. DOI: 10.1016/B978-0-12-411492-0.00034-1.

- [12] Khedraoui, M.; Abchir, O.; Nour, H.; Yamari, I.; Errougui, A.; Samadi, A.; Chtita, S. An in silico study based on QSAR and molecular docking and molecular dynamics simulation for the discovery of novel potent inhibitor against AChE. *Pharmaceuticals* **2024**, *17*, 830. DOI: 10.3390/ph17070830.
- [13] Voss, J.E.; Vaney, M.-C.; Duquerroy, S.; Vonnrhein, C.; Girard-Blanc, C.; Crublet, E.; Thompson, A.; Bricogne, G.; Rey, F.A. Glycoprotein organization of Chikungunya virus particles revealed by X-ray crystallography. *Nature* **2010**, *468*, 709–712. DOI: 10.1038/nature09555
- [14] Hossain, M.A.; Sultana, S.; Alanazi, M.M.; Hadni, H.; Bhat, A.R.; Hasan, I.; Kawsar, S.M.A. In vitro antimicrobial, anticancer evaluation, and in silico studies of mannopyranoside analogs against bacterial and fungal proteins: Acylation leads to improved antimicrobial activity. *Saudi Pharm. J.* **2024**, *32*, 102093. DOI: 10.1016/j.jsps.2024.102093.
- [15] Akter, N.; Bourougaa, L.; Ouassaf, M.; Bhowmic, R.C.; Uddin, K.M.; Bhat, A.R.; Ahmed, S.; Kawsar, S.M.A. Molecular docking, ADME-Tox, DFT and molecular dynamics simulation of butyroyl glucopyranoside derivatives against DNA gyrase inhibitors as antimicrobial agents. *J. Mol. Struct.* **2024**, *1307*, 137930. DOI: 10.1016/j.molstruc.2024.137930.
- [16] Frisch, M.J.; Trucks, G.W.; Schlegel, H.B.; Scuseria, G.E.; Robb, M.A.; Cheeseman, J.R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G.A.; et al. *Gaussian 09, Revision B.01*; Gaussian, Inc.: Wallingford, CT, USA, **2010**.
- [17] Kawsar, S.M.A.; Hossain, M.A.; Saha, S.; Abdallah, E.M.; Bhat, A.R.; Ahmed, S.; Jamalis, J.; Ozeki, Y. Nucleoside-based drug target with general antimicrobial screening and specific computational studies against SARS-CoV-2 main protease. *ChemistrySelect* **2024**, *9*, e202304774. DOI: 10.1002/slct.202304774.
- [18] Hehre, W.J.; Ditchfield, R.; Pople, J.A. Self-consistent molecular orbital methods. XII. Further extensions of Gaussian-type basis sets for use in molecular orbital studies of organic molecules. *J. Chem. Phys.* **1972**, *56*, 2257–2261. DOI: 10.1063/1.1677527.
- [19] Peters, G.J.; van Groenigen, C.J. Clinical relevance of biochemical modulation of 5-fluorouracil. *Ann. Oncol.* **1991**, *2*, 469–480. DOI: 10.1093/oxfordjournals.annonc.a057994.
- [20] Hariharan, P.C.; Pople, J.A. Accuracy of AH_n equilibrium geometries by single determinant molecular orbital theory. *Theor. Chim. Acta* **1974**, *27*, 209–214. DOI: 10.1007/BF00521967.
- [21] Lagunin, A.; Stepanchikova, A.; Filimonov, D.; Poroikov, V. PASS: Prediction of biological activity spectra for biologically active substances. *Bioinformatics* **2000**, *16*, 747–748. DOI: 10.1093/bioinformatics/16.8.747.
- [22] Islam, M.M.; Arifuzzaman, M.; Rahman, M.M.; Rahman, M.A.; Kawsar, S.M.A. Novel methyl 4,6-O-benzylidene- α -D-glucopyranoside derivatives: Synthesis, structural characterization and evaluation of antibacterial activities. *Hacettepe J. Biol. Chem.* **2019**, *47*, 153–164. DOI: 10.15671/hjbc.622038.
- [23] Arifuzzaman, M.; Islam, M.M.; Rahman, M.M.; Rahman, M.A.; Kawsar, S.M.A. An efficient approach to the synthesis of thymidine derivatives containing various acyl groups: Characterization and antibacterial activities. *Acta Pharm. Sci.* **2018**, *56*, 7–22. DOI: 10.23893/1307-2080.APS.05622.
- [24] Yasmin, F.; Amin, M.R.; Hosen, M.A.; Bulbul, M.Z.H.; Dey, S.; Kawsar, S.M.A. Monosaccharide derivatives: Synthesis, antimicrobial, PASS, antiviral and molecular docking studies against SARS-CoV-2 Mpro inhibitors. *Cellulose Chem. Technol.* **2021**, *55*, 477–499. DOI: 10.35812/CelluloseChemTechnol.2021.55.44.
- [25] Kawsar, S.M.A.; Faruk, M.O.; Rahman, M.S.; Fujii, Y.; Ozeki, Y. Regioselective synthesis, characterization and antimicrobial activities of some new monosaccharide derivatives. *Sci. Pharm.* **2014**, *82*, 1–20. DOI: 10.3797/scipharm.1308-03.
- [26] Aussedat, J. Effect of uridine supply on glycogen resynthesis after ischaemia in the isolated perfused rat heart. *Cardiovasc. Res.* **1983**, *17*, 145–151. DOI: 10.1093/cvr/17.3.145.

- [27] Stewart, J.J.P. Optimization of parameters for semiempirical methods V: Modification of NDDO approximations and application to 70 elements. *J. Mol. Model.* **2007**, *13*, 1173–1213. DOI: 10.1007/s00894-007-0233-4.
- [28] Murray, J.S.; Politzer, P. The electrostatic potential: An overview. *WIREs Comput. Mol. Sci.* **2011**, *1*, 153–163. DOI: 10.1002/wcms.19.
- [29] Ahmed, S.; Bhat, A.R.; Rahiman, A.K.; Dongre, R.S.; Hasan, A.H.; Niranjana, V.; Lavanya, C.; Sheikh, S.A.; Jamalis, J.; Berredjem, M.; Kawsar, S.M.A. Green synthesis, antibacterial and antifungal evaluation of new thiazolidine-2,4-dione derivatives: Molecular dynamic simulation, POM study and identification of antitumor pharmacophore sites. *J. Biomol. Struct. Dyn.* **2024**, *42*, 10635–10651. DOI: 10.1080/07391102.2023.2258404.
- [30] Urasaki, Y.; Pizzorno, G.; Le, T.T. Uridine affects liver protein glycosylation, insulin signaling, and heme biosynthesis. *PLoS ONE* **2014**, *9*, e99728. DOI: 10.1371/journal.pone.0099728.
- [31] Daoui, O.; Elkhatabi, S.; Chtita, S. Rational identification of small molecules derived from 9,10-dihydrophenanthrene as potential inhibitors of 3CLpro enzyme for COVID-19 therapy: A computer-aided drug design approach. *Struct. Chem.* **2022**, *33*, 1667–1690. DOI: 10.1007/s11224-022-02004-z.
- [32] Yamari, I.; Abchir, O.; Nour, H.; Kouali, M.E.; Chtita, S. Identification of new dihydrophenanthrene derivatives as promising anti-SARS-CoV-2 drugs through in silico investigations. *Main Group Chem.* **2023**, *22*, 469–484. DOI: 10.3233/MGC-220127.
- [33] Kawsar, S.M.A.; Huq, E.; Nahar, N. Cytotoxicity assessment of the aerial parts of *Macrotyloma uniflorum* Linn. *Int. J. Pharmacol.* **2008**, *4*, 297–300. DOI: 10.3923/ijp.2008.297.300.
- [34] Niedzwicki, J.G.; Chu, S.H.; El Kouni, M.H.; Rowe, E.; Cha, S. 5-Benzylacetyluridine and 5-benzoyloxybenzylacetyluridine, potent inhibitors of uridine phosphorylase. *Biochem. Pharmacol.* **1982**, *31*, 1857–1861. DOI: 10.1016/0006-2952(82)90488-9.
- [35] Lafriidi, H.; Almalki, F.A.; Hadda, T.B.; Berredjem, M.; Kawsar, S.M.A.; Alqahtani, A.M.; Esharkawy, E.R.; Lakhrissi, B.; Zgou, H. In silico evaluation of molecular interactions between macrocyclic inhibitors with the HCV NS3 protease: Docking and identification of antiviral pharmacophore site. *J. Biomol. Struct. Dyn.* **2023**, *41*, 2260–2273. DOI: 10.1080/07391102.2022.2029571.
- [36] Hossain, M.A.; Sultana, S.; Islam, M.M.; Akhter, S.; Nur, F.; Majabin, F.; Islam, K.; Hossain, K.J.; Ozeki, Y.; Kawsar, S.M.A. DFT-based chemical reactivity descriptors, pharmacokinetics and molecular docking studies of thymidine derivatives. *Comput. Chem.* **2023**, *11*, 81–103. DOI: 10.4236/cc.2023.114006.
- [37] Meng, X.-Y.; Zhang, H.-X.; Mezei, M.; Cui, M. Molecular docking: A powerful approach for structure-based drug discovery. *Curr. Comput.-Aided Drug Des.* **2011**, *7*, 146–157. DOI: 10.2174/157340911795677602.
- [38] Stepanchikova, A.V.; Lagunin, A.A.; Filimonov, D.A.; Poroikov, V.V. Prediction of biological activity spectra for substances: Evaluation on the diverse sets of drug-like structures. *Curr. Med. Chem.* **2003**, *10*, 225–233. DOI: 10.2174/0929867033368510.

Supplementary Materials



Figure S1. Crystal structure of the Chikungunya virus (PDB 3N40).

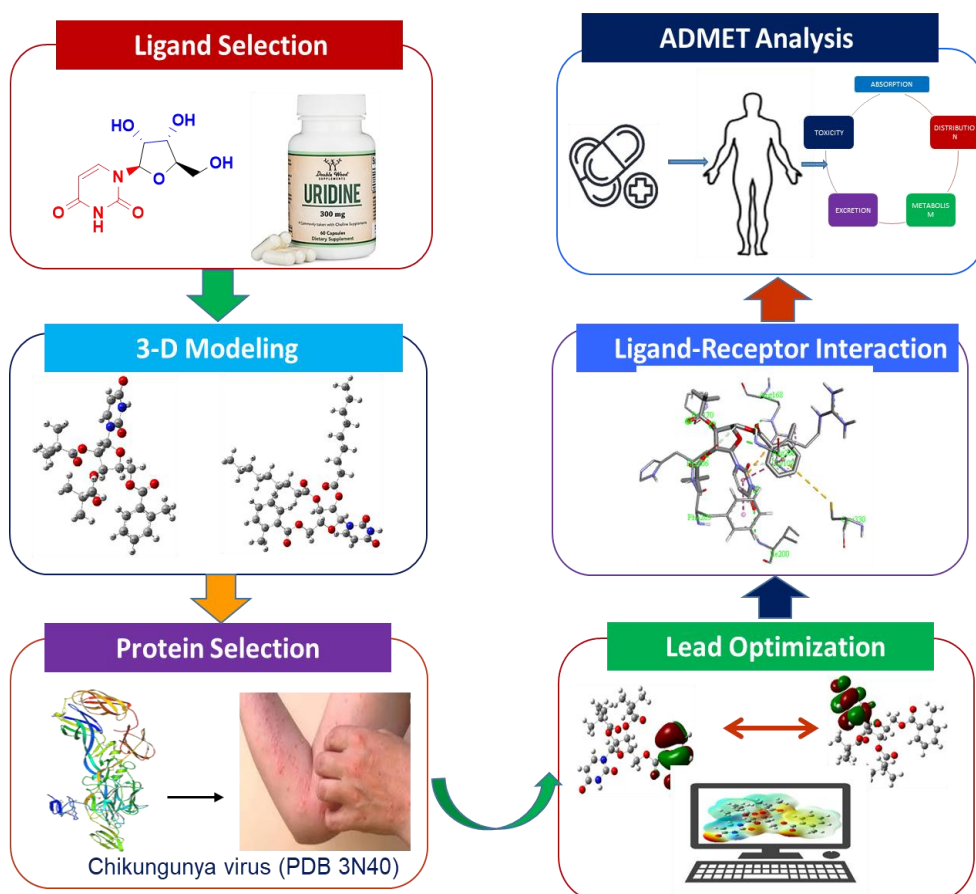


Figure S2. Workflow of the current research.

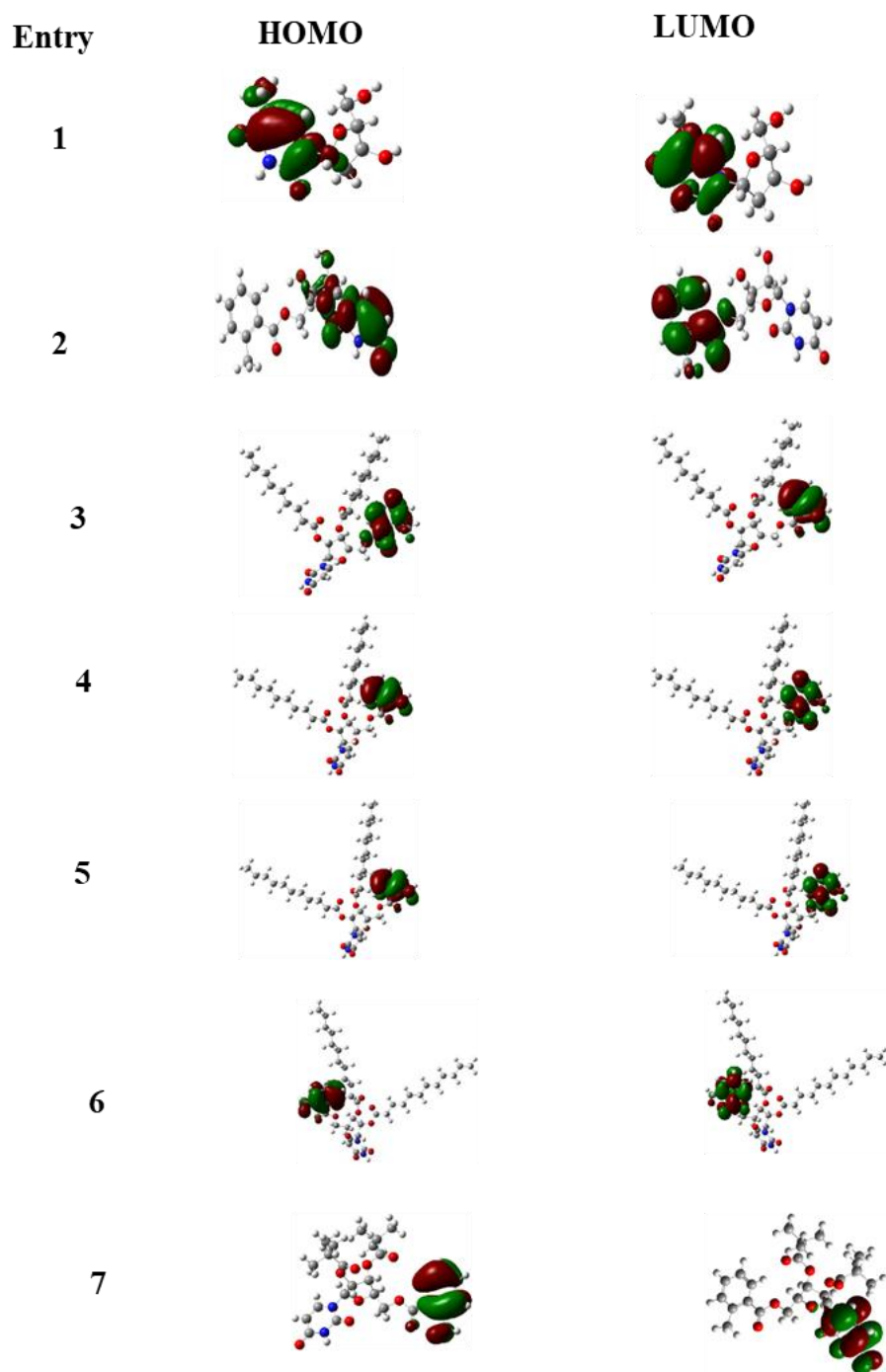


Figure S3. HOMO and LUMO plots of the parent uridine (1) and the uridine derivative (2-7).

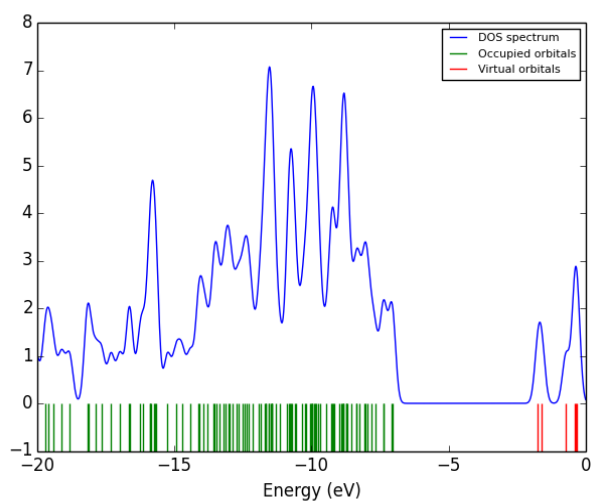
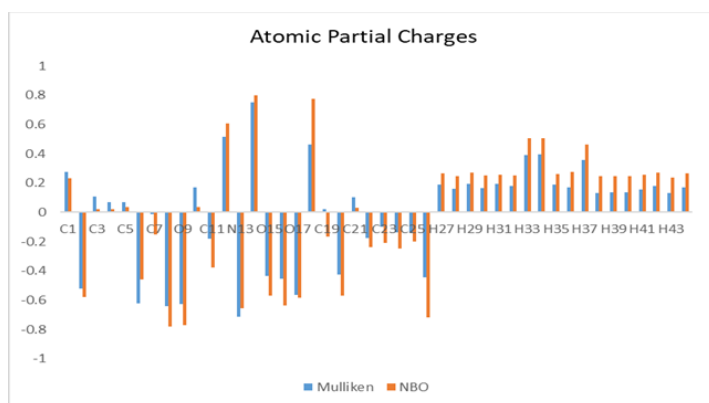
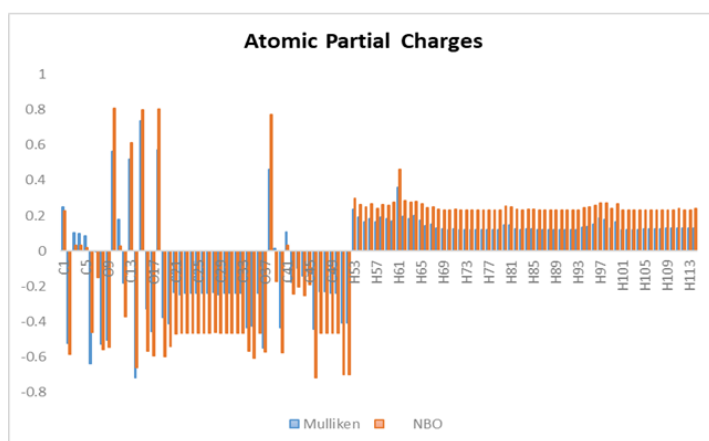


Figure S4. DOS diagram of uridine derivative 7.



2



6

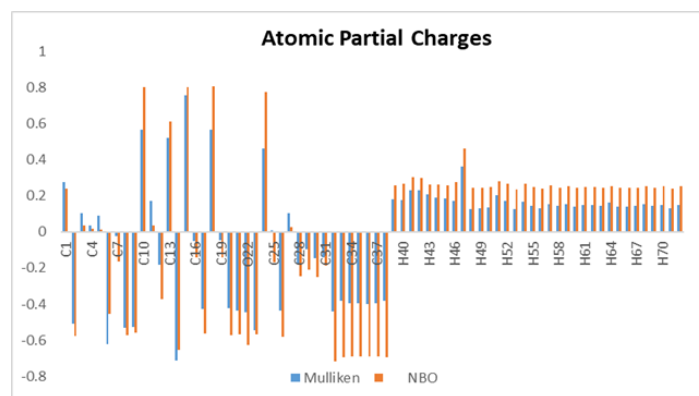
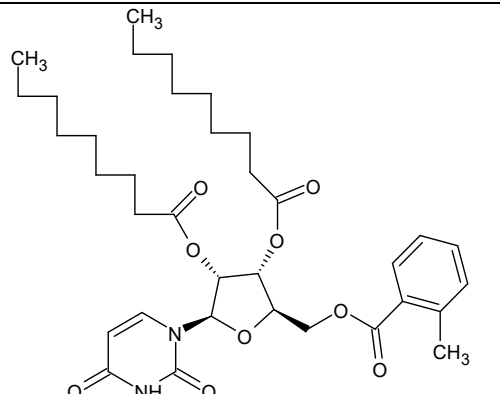
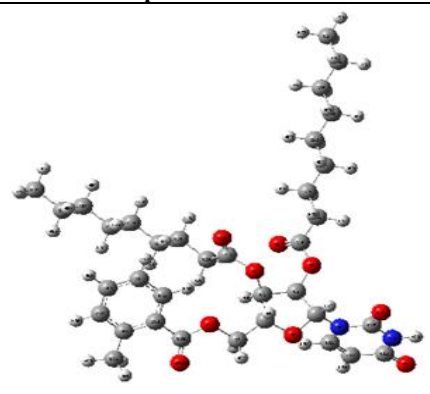
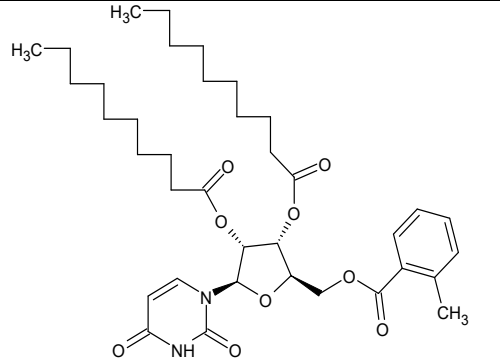
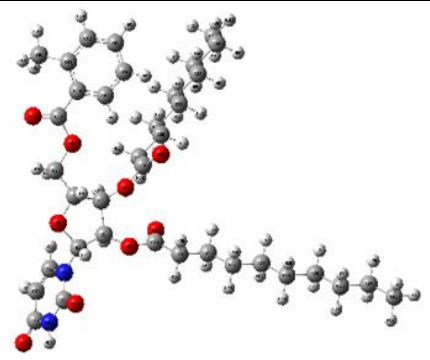
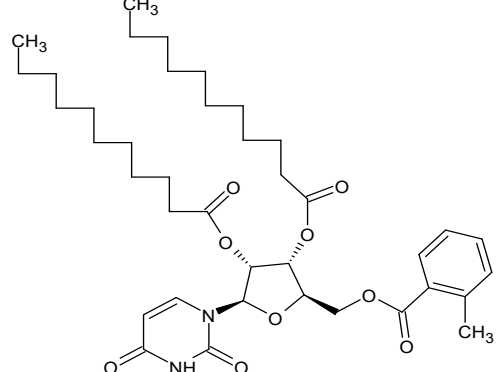
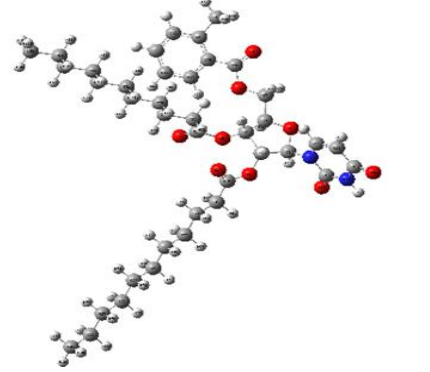


Figure S5. Natural bond orbital (NBO) analysis of compounds **2**, **6** and **7**.

Table S1. Optimization of uridine derivatives (1-7).		
Entry	Structure	Optimized structure
1		
2		

Entry	Structure	Optimized structure
3		
4		
5		

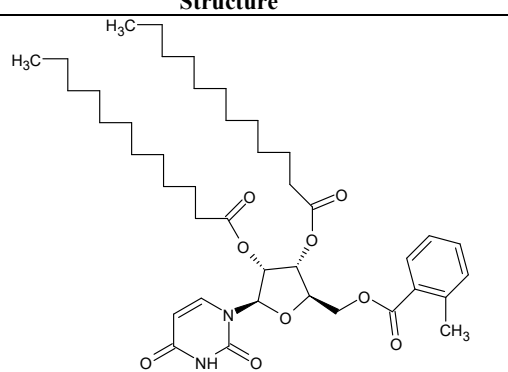
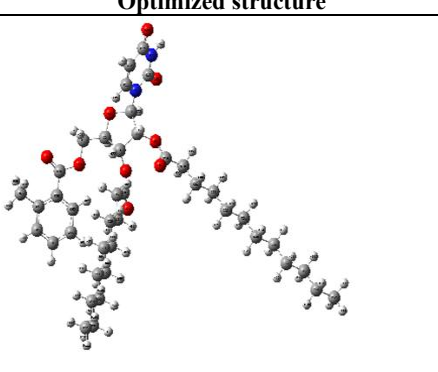
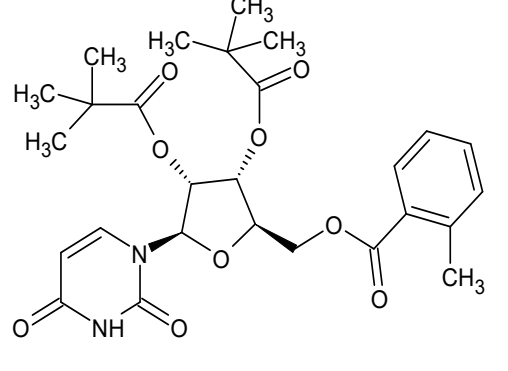
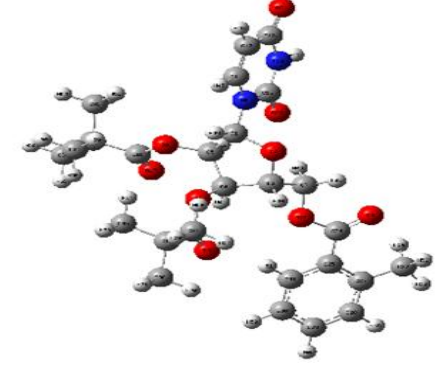
Entry	Structure	Optimized structure
6		
7		

Table S2. Selected binding affinities (kcal/mol) and nonbonding interactions of uridine and its derivatives.

Chikungunya virus receptor 3N40				
Drug	Hydrogen bond		Hydrophobic bond	
	Residues	Distance (Å)	Residues	Distance (Å)
1	HIS405	2.13157	PRO235	5.25286
	UNKO	3.00517	PRO537	5.35415
	ASN533	2.51117		
2	CYS25	2.66669	ALA53	3.67364
	CYS25	2.76733	UNKO	4.27439
	GLN52	3.02369	HIS60	3.63395
	UNKO	2.50981	-	-
	UNKO	2.07958	-	-
	PRO24	3.57497	-	-
3	THR156	2.74389	VAL199	4.5368
	ARG168	2.59528	LYS204	4.48559
	ARG168	3.02153	UNKO	5.01728
	PRO170	3.17472	UNKO	4.54593
			PHE205	5.41281
			PHE205	4.46615
			HIS206	4.92145
			UNKO	4.85445
			UNKO	5.21957
			UNKO	4.75094
4	ARG168	2.27246	UNKO	3.98163
	ARG168	1.84151	PHE205	5.03128
	ARG168	2.68309	UNKO	5.3066
	ILE200	1.85318	UNKO	4.33961
	ARG208	2.57393	UNKO	4.09878
	UNKO	3.30231	UNKO	4.08771
	-	-	UNKO	4.08919
	-	-	UNKO	3.83304
5	ARG168	2.54409	CYS330	4.17952
	ARG168	2.29308	PRO170	5.33788
	ARG331	2.34818	PRO197	4.37828
	CYS330	3.38006	VAL199	4.9513
	UNKO	3.47777	LYS204	4.48051
	ARG168	2.7214	PHE205	4.85098
	-		UNKO	4.33144
	-		UNKO	4.04012
6	THR156	3.0343	PRO197	4.75932
	ARG168	1.9674	ARG208	4.04996
	ARG168	2.45909	ARG208	5.20604
	ARG208	2.45757	CYS330	4.39523
	ARG168	3.53105	UNKO	4.98937
	UNKO	3.4302	UNKO	4.38022
		-	UNKO	3.8144
	-	-	UNKO	4.08995
	-	-	PHE205	4.37035
			PHE205	4.98434

Chikungunya virus receptor 3N40				
Drug	Hydrogen bond		Hydrophobic bond	
	Residues	Distance (Å)	Residues	Distance (Å)
7	ARG168	2.4967	ARG168	3.67824
	ARG168	1.83739	ARG168	3.89206
	ARG168	2.64441	CYS330	5.93485
	ILE200	2.34387	PHE205	5.59727
	ARG208	2.42739	UNKO	4.95854
	GLY108	3.68549	UNKO	4.053
	HIS206	3.56986	UNKO	3.50533
	UNKO	3.1016	UNKO	4.04604