

In Silico Evaluation of Selective HDAC6 Inhibitors J27820 and J22352 Against Zika Virus Proteins: Molecular Docking and Dynamics Insights

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Zika Virüsü Proteinlerine Karşı Seçici HDAC6 İnhibitörleri J27820 ve J22352'n In Silico Değerlendirmesi: Moleküler Yerleştirme ve Dinamikler Hakkında Bilgiler

SUMMARY

The Zika virus (ZIKV) is classified as a type of the Flavivirus family, which includes various other significant viruses characterized by positive-sense, single-stranded RNA genomes. ZIKV is primarily transmitted to humans via mosquito vectors. While ZIKV infections are often asymptomatic, they can also cause mild flu-like symptoms or severe complications, posing a significant threat to human health. Several studies have demonstrated that histone deacetylase 6 (HDAC6) inhibitors exhibit antiviral activity against the Zika virus. The current study employs computational chemistry and various *in silico* techniques, including molecular docking, ADMET predictions, and molecular dynamics simulations. Initially, the pharmacokinetic and physicochemical properties of J27820 were assessed using ADMET analysis. The therapeutic potential of compounds J22352 and J27820 against three Zika virus (ZIKV) proteins (5H4I, 5TFR, and 6THV) was evaluated using molecular docking simulations. These simulations indicated that the studied compounds exhibited the highest binding affinities and strong interactions with the target proteins. To further assess the stability of the complexes and their interactions over time, 100 ns molecular dynamics simulations were performed. The results of this study highlight the significant advantages of J27820 and J22352, emphasizing their potential for targeted inhibition and the promise of developing effective antiviral therapies against the Zika virus.

Keywords: Histone deacetylase; Zika virus; antiviral; molecular dynamics.

ÖZ

Zika virüsü (ZIKV), pozitif polariteli, tek zincirli RNA genomlarıyla karakterize edilen çeşitli diğer önemli virüsleri içeren Flavivirüs ailesinin bir türü olarak sınıflandırılır. ZIKV, insanlara öncelikle sivrisinek vektörleri aracılığıyla bulaşır. ZIKV enfeksiyonları genellikle asemptomatik olmakla birlikte, hafif grip benzeri semptomlara veya ciddi komplikasyonlara da yol açarak insan sağlığı için önemli bir tehdit oluşturabilir. Çeşitli çalışmalar, histon deasetilaz 6 (HDAC6) inhibitörlerinin Zika virüsüne karşı antiviral aktivite gösterdiğini göstermiştir. Mevcut çalışma, hesaplamalı kimya ve moleküler yerleştirme, ADMET öngörülleri ve moleküler dinamik simülasyonları gibi çeşitli *in silico* tekniklerini kullanmaktadır. Başlangıçta, J27820'nin farmakokinetik ve fizikokimyasal özellikleri ADMET analizi kullanılarak değerlendirilmiştir. J22352 ve J27820 bileşiklerinin üç Zika virüsü (ZIKV) proteinine (5H4I, 5TFR ve 6THV) karşı terapötik potansiyeli, moleküler yerleştirme simülasyonları kullanılarak değerlendirilmiştir. Bu simülasyonlar, incelenen bileşiklerin hedef proteinlerle en yüksek bağlanma afinitelerini ve güçlü etkileşimleri sergilediğini göstermiştir. Komplekslerin stabilitesini ve zaman içindeki etkileşimlerini daha ayrıntılı olarak değerlendirmek için 100 ns moleküler dinamik simülasyonları gerçekleştirilmiştir. Bu çalışmanın sonuçları, J27820 ve J22352'nin önemli avantajlarını vurgulayarak, hedefli inhibisyon potansiyellerini ve Zika virüsüne karşı etkili antiviral tedaviler geliştirmek için umut verici fırsatlar sunmaktadır.

Anahtar Kelimeler: Histon deasetilaz; Zika virüsü; antiviral; moleküler dinamikler.

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INTRODUCTION

The emergence of pathogenic viruses has become a significant problem for modern medicine and the global economy, posing a threat to human health. Most of these viruses originate from animals, meaning they were transmitted to humans after emerging from specific animal hosts (Rohr et al., 2019). Because they can transmit between people, emerging viruses can cause isolated cases, leading to local spread or, in worst-case scenarios, a global pandemic (Piret & Boivin, 2021). The mutation and evolution of viruses, influenced by environmental, social, and economic factors, have made managing viral infections increasingly challenging. Globalization and climate change also exacerbate the situation, further complicating efforts to control these diseases (Grubaugh et al., 2019). These factors have contributed to the emergence of various viruses, including the dengue virus, influenza viruses responsible for swine flu and avian flu, as well as newly identified viruses such as Zika, Ebola, and SARS-CoV-2 (Al-Tawfiq, Barry, & Memish, 2022; Reperant & Osterhaus, 2017). Certain viruses exhibit significant rates of mutation and/or genome reconfiguration, allowing them to elude the host's immune response, resist antiviral drugs, and alter antigens to reduce the effectiveness of immunizations (Shao, Li, Goraya, Wang, & Chen, 2017; Van de Sandt, Kreijtz, & Rimmelzwaan, 2012). When a virus spreads and raises concern, a coordinated global response must be implemented, including media outreach, social distancing, personal protection, quarantine, and the development of antiviral drugs and vaccines (Lu et al., 2018; Yamey et al., 2017). Large-scale drug development is expected to target a variety of viruses, despite the time required for vaccine development (Adalja & Inglesby, 2019; Hoffmann et al., 2020; Zelikin & Stelacci, 2021). The Zika virus is one of these viruses; it belongs to the genus *Flavivirus* and family *Flaviviridae*. This positive-sense, single-stranded RNA virus has a genome approximately 11 kilobases in size (Giraldo, Gonzalez-Orozco, & Rajsbaum, 2023). Viral

proteases and cellular enzymes transform the single polyprotein encoded by the single open reading frame that makes up the viral genome into 10 proteins. These viral proteins, which include the envelope (E), membrane (M), and capsid (C), combine to form the seven nonstructural (NS) proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5) as well as the viral particle, which is essential for processing, replication, and virus assembly (Sirohi et al., 2016). In 1947, the Zika virus was first identified in a sentinel rhesus monkey from Uganda (Gubler, Vasilakis, & Musso, 2017). Nigeria reported the first case of human isolation in 1954 (Duong, Dussart, & Buchy, 2017). Since 1964 and 2007, some isolated human instances have been recorded in Africa and Asia; these cases had no significant negative effects on health (Chu, Nguyen, & Son, 2021; Honein et al., 2017; Karkhah et al., 2018). However, the first recognized outbreak of ZIKV-related illness was reported in Micronesia in 2007. An outbreak that spread to other Pacific islands was later reported in French Polynesia in 2013 (Duong et al., 2017). Brazil reported cases of the Zika virus in 2015, sparking serious concerns about its spread (Escosteguy et al., 2020). Most South and Central American nations are now affected by this epidemic. In over 87 nations, ZIKV continues to circulate in tropical and sub-tropical areas (Escosteguy et al., 2020; Musso & Gubler, 2016). Growing urban populations, increased international travel and trade, and climate change have contributed to a rise in ZIKV infections over the past few decades. Humans contract the Zika virus primarily through two efficient mosquito vectors, *Aedes aegypti* and *Aedes albopictus* (Musso et al., 2017). The World Health Organization declared ZIKV a public health emergency of global significance in February 2016 (Imperato, 2016). The *Aedes* mosquito transmits the Zika virus. In addition, *Aedes luteocephalus*, *Aedes albopictus*, *Aedes africanus*, and *Aedes aegypti* (Ayres, 2016). Additionally, ZIKV can spread directly from person to person through sexual contact or from mother to fetus (Carod-Artal, 2018). Pregnant women are particularly vulnerable to viral infections in the

first and second trimesters of pregnancy when the fetus is more likely to suffer congenital damage. ZIKV can infect neural precursors and placental cells in the fetus; infections in pregnant women can cause intra-uterine growth restriction, spontaneous miscarriage, and microcephaly in the fetus (Blázquez & Saiz, 2016; Smoots, 2020). Five to fifteen percent of children born to pregnant mothers infected with the Zika virus may have congenital disabilities due to Congenital Zika Syndrome (CZS), a disorder associated with ZIKV-related issues. Fetal abnormalities, including cortical atrophy with microcephaly and functional deficits such as dysphagia and epilepsy, can result from both symptomatic and asymptomatic infections. Currently, no specific vaccine or medication is available to treat Zika virus infection. However, some vaccines are undergoing clinical trials. The present study aims to develop a vaccine against the Zika virus by combining multiple B-cell and T-cell epitopes. Conjunctivitis, arthralgia, rash, and low-grade fever are moderate indications of a ZIKV infection (Kazmi, Ali, Bibi, & Nouroz, 2020; Musso et al., 2015). All physiological fluids, including blood, urine, and saliva, can contain the Zika virus; therefore, it is relatively easy to clinically diagnose the infection (Li, Tian, & Zhu, 2020). Therefore, the creation of anti-flaviviral medications is essential to combating these serious and deadly illnesses. Over the past few decades, histone deacetylases (HDACs) have been considered reasonable targets for the creation of new antiviral therapies (Milazzo et al., 2020). A class of enzymes known as histone deacetylases (HDACs) is involved in protein transport, stability, chromatin remodeling, and gene expression, but most clinically used HDAC inhibitors are non-selective (Slingerland, Guchelaar, & Gelderblom, 2014). In humans, 18 HDACs play different roles in cellular balance. They can be classified into two main functional groups based on the nature of the enzymatic cofactor to which they are bound. Zinc-dependent HDACs are thus separated from NAD⁺-dependent HDACs (Lu et al., 2018). The HDAC enzyme family is classified into four classes for this purpose:

class I includes HDAC1, HDAC2, HDAC3, and HDAC8; class IIa includes HDAC4, HDAC5, HDAC7, and HDAC9; class IIb includes HDAC6 and HDAC10; class III includes SIRT1, SIRT2, SIRT3, SIRT4, SIRT5, SIRT6, and SIRT7; and class IV includes HDAC11. Unlike other HDAC subtypes, HDAC6 possesses two active catalytic domains and is primarily cytosolic, targeting a variety of non-histone substrates. Such as cortactin (Kaluza et al., 2011), α -tubulin (Li, Jiang, Chang, Xie, & Hu, 2011), and HSP90 (Kovacs et al., 2005). According to research, both catalytic domains of HDAC6 were essential for complete tubulin deacetylation activity (TDAC). However, in other research, TDAC activity has been associated with the second domain (Sinatra et al., 2022). However, it exhibits particular resistance to potent HDAC inhibitors such as trapoxin-B and sodium butyrate. These treatments have been used to demonstrate that HDAC6 acts as an α -tubulin deacetylase both *in vivo* and *in vitro* (Su, Gong, & Liu, 2021). Furthermore, several studies indicate that specific HDAC6 inhibitors have anti-flavivirus activity. For example, treatment with tubastatin A reduced the Hsp90-NS5 interaction and decreased viral protein and antisense RNA levels in infected cells (Wan, Song, Li, & He, 2020). Another example is tubastatin A (TBSA), a selective HDAC6 inhibitor, which reduced viral RNA concentration in hepatocytes infected with the hepatitis C virus (HCV) replicon (Lu et al., 2017). Compounds J22352 and I27820 are selective HDAC6 inhibitors. They are being investigated to assess their antiviral effects against the Zika virus, which shows therapeutic potential (Baz & Boivin, 2019). In this context, we focus on the structural activity relationships of selective HDAC6 inhibitors against the Zika virus (Shih et al., 2023). In this context, we are focusing on a computational study to investigate the structure-activity relationships of selective HDAC6 inhibitors against the Zika virus. These small molecules of the selective HDAC6 inhibitors (J22352 and I27820), as illustrated in Figure 1, exhibit superior therapeutic efficacy compared to treatment with the drug Tubastatin (A), leading to a

decrease in the Hsp90-NS5 association, as well as a reduction in the number of viral proteins and anti-sense RNA in infected cells (Zheng Jiang, He, Kitazato, & Wang, 2017). Various computational methods, including molecular docking, ADMET, and molecular dynamics, are used to evaluate the efficacy of these compounds. Furthermore, Lipinski's criteria are applied to compounds to ensure oral bioavailability.

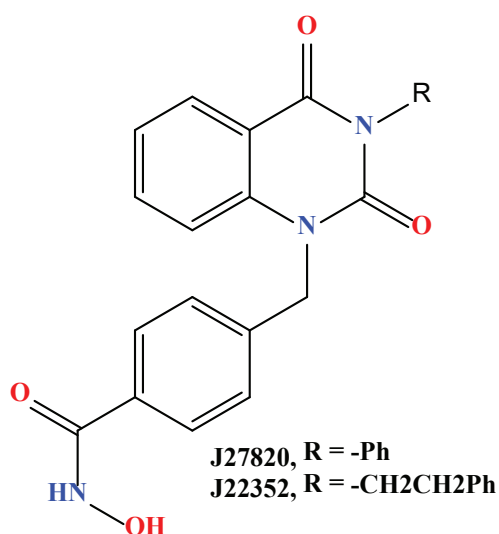


Figure 1. Chemical structures of J22352 and J27820

MATERIALS AND METHODS

Molecular docking simulation

Molecular docking methodology aims to improve understanding of binding modalities and make informed assumptions about the interaction between a ligand and a receptor (Mane & Yadav, 2024). Afterwards, we realized that the molecular calibration method (Figure 5.) by re-anchoring is only effective when the RMSD is less than or equal to 2 Å, including several measurements, such as interaction energy and root mean square deviation (RMSD) values. We have employed two programs to perform molecular docking: AutoDock Vina and AutoDock Tools (version 1.5.6) (Belghalia et al., 2024). According to the literature, we have used three receptors (PDB: 5H4I, PDB: 5TFR, and PDB: 6THV). For 5H4I's choice: The unbound NS2B-NS3 protease of the Zika virus (PDB: ID 5H4I) is a free enzyme bound to a reverse-orient-

ed peptide at the active site. The unbound NS2B-NS3 protease adopts a closed conformation in which NS2B engages with NS3 to form an empty substrate-binding site. A second protease in the same crystal binds to residues K14K15G16E17 of the neighbouring NS3 in a reverse orientation, resistant to proteolysis. These characteristics of the ZIKV NS2B-NS3 protease could accelerate the discovery of structure-based antiviral drugs against ZIKV and related pathogenic flaviviruses. In 5TFR, the nonstructural protein 5 of the Zika virus (NS5) plays an essential role in Zika virus replication through 5'-RNA capping and RNA polymerase activities; its N-terminal methyltransferase (MTase) domain mediates 5'-RNA capping, and the C-terminal RNA-dependent RNA polymerase (RdRp) domain mediates RNA polymerase activity. The structure of the NS5 protein suggests possibilities for structure-based drug design targeting either its MTase domain or its RdRp domain. For 6THV, the protein associated with PDB code ID 6THV is histone deacetylase 6 (HDAC6). Recent studies show that HDAC6 is involved in ZIKV infection. One study shows that the interaction between the ZnF-UBP domain of HDAC6 (zinc finger ubiquitin-binding domain) and ubiquitin is necessary for ZIKV infection: blocking this interaction reduces the virus's infectivity. Another study indicates that the nonstructural protein NS5 of ZIKV interacts with HDAC6: NS5 alters the cytoskeleton (microtubules), the autophagy pathway, and the function of HDAC6. HDAC6 appears to act as an anti-ZIKV factor by promoting NS5 degradation via autophagy, depending on the BUZ domain. Before molecular docking, the ligands were prepared according to a standard protocol. The chemical structures were first optimized by minimizing energy to obtain a stable conformation using GaussView 5.0.8. This step was followed by assigning polar hydrogens only and calculating Gasteiger-type partial charges. The prepared ligands were then saved in PDBQT format for molecular docking using AutoDock Tools 1.5.7. The Protein Data Bank provided these structures. The three receptors of interest were

prepared by removing all non-protein components and water molecules prior to molecular docking. The three receptors involved were prepared by removing all non-protein components and water molecules before beginning molecular docking. Next, the 5H4I, 5TFR, and 6THV receptors were added to the polar hydrogen atoms. Next, the computed Gausseiger charges were added and recorded in PDBQT format. The active region of the proteins was defined using a grid box size of 40x40x40 Å, centered at coordinates (-7.597, 4.233, -18.003) for 5H4I, a grid box size of 38x38x38 Å, centered at coordinates (25.174, -36.876, -34.198) for 5TFR, and a grid box size of 36x36x36 Å, centered at coordinates (-2.010, 18.523, -20.440) for 6THV. PyMOL tools were used to assess the resulting findings (Elbouhi et al., 2025), and the Discovery Studio program was used to visualize and analyze the results (Hajji et al., 2022).

ADME-Tox prediction

The relative properties of molecules' Absorption, Distribution, Metabolism, Excretion, and Toxicity (ADME-Tox) are commonly predicted using cheminformatics. In this regard, the search for new drugs. It helps to improve the molecule's pharmacokinetic properties by removing those that would not be good drug candidates (Abdessadak et al., 2023) they can frequently disrupt microtubule/tubulin dynamics by binding to the α -tubulin receptor. To this end, we have developed compounds against α -tubulin receptor using several tools of computational chemistry: 3D-QSAR, Molecular Docking, Molecular Dynamics Simulation, and ADMET prediction. The significant findings incorporated two reliable models: CoMFA ($Q^2=0.75$; $R^2=0.89$). Molecules were converted to SMILES, and the pkCSM web server provided ADMET information for each molecule. The Swiss-ADME server was utilized to calculate Lipinski's rules, which stipulate that a drug must possess additional qualities besides being bioavailable and efficacious, which are available on the website (<http://www.swissadme.ch>) (Ouabane et al., 2023).

Molecular dynamic simulation

The molecular dynamics simulation was employed to confirm ideal stable docking positions. Schrodinger LLC (Boutalaka et al., 2024; Zaki et al., 2024), based on the OPLS3 force field with Desmond. The ligand-protein complex was stabilized in an orthorhombic periodic box, with a minimum of 10 Å between the protein atoms and the box edges, and the box was soaked in solvent. A single-point charge (SPC) water model was employed to construct the solvent. After introducing Na^+ and Cl^- counterions to neutralize the system's charge, the physiological system's 0.15 M NaCl salt concentration was set using the Desmond System Builder panel. After using the default Desmond protocol, OPLS3e force field parameters were used to relax and reduce the created solvated system. The temperature and pressure of the isothermal-isobaric ensemble (normal pressure and temperature/NPT) were set to 300 K and 1.0315 bar, respectively, using the Nose-Hoover chain thermostat and the Martyna-Tobias-Klein barostat (Bai et al., 2023). For 100 ns, the simulation recorded trajectory snapshots, which can be used to confirm or refine a docking position.

RESULTS AND DISCUSSION

Molecular docking results

The process of inserting a ligand into a target protein's active site in three dimensions (3D) is known as molecular docking. Two crucial factors are predicting the exact location of the ligand in the protein's active site and estimating the affinity of [ligand-protein] complexes. Affinity prediction is linked to the different ligands in the collection, some more suitable than others. Position prediction refers to the same ligand molecule in different orientations. Three proteins were chosen for this investigation to determine which receptor had the highest affinity for the substances under investigation. Comparing the newly developed small molecules J22352 and J27820 to Tubastatin (A), the ligands were chosen. The co-crystallized ligand highlighted the links between the three target receptors.

Additionally, this link will be used to confirm the anchoring method. The ideal location was chosen based on the ligand's binding energy in the protein's active site. According to the results, the three receptors, 5TFR, 6THV, and 5H4I, exhibited significant affinity for three ligands, albeit to varying degrees. In the case of the 5TFR receptor (Figure 2.), compound J22352 formed four conventional hydrogen bonds with the residues THR -104, SER-56, TRP-87, and CYS-82. These hydrogen bonds form between the amine hydrogens and the ketone carbonyl groups.

Additionally, two pi-alkyl interactions involve ILE-147 and VAL-132 with the aromatic ring, and pi-cation LYS-105. These amino acids, involved in all established interactions, are key residues located in the 5TFR protein and are directly in contact with the ligand, thereby enhancing stability. This interaction contributes to a binding energy of -9.9 kcal/mol. For compound J27820, which interacts with the 5TFR receptor, two conventional hydrogen bonds are formed with residues ARG-160 and LYS-105, as well as two pi-alkyl bonds and carbon-hydrogen bonds with residue HIS-110. The latter are those established in the 5TFR protein with its co-crystallized ligand, resulting in a higher binding energy of -10.3 kcal/mol. In contrast, Tubastatin (A) does not form hydrogen bonds with the 5TFR receptor; instead, it forms only pi-alkyl

interactions via the VAL-132 residues, resulting in a lower binding energy than compounds J22352 and J27820.

6THV is a zinc-dependent protein consisting of three parts: a zinc-binding domain (ZBD), which binds to the catalytic zinc ion inside the catalytic pocket; a capping group, which interacts with residues near the entrance to the pocket and is essential for the potency and selectivity of the subtypes; and a linker, which connects the ZBD and the capping group. Its role in stabilising the active site coordinates several conserved residues to ensure the stability of complexes (Kong et al., 2023).

Receptor 6THV (Figure 3.) establishes conventional hydrogen bonds with compound J22352, with the most active amino acids ASN-530, LYS -577, and ASP-578, with a binding energy of (-8.4 Kcal/mol). Compound J27820 has four conventional hydrogen bonds with residues SER-531, TYR-745, HIS-574, and GLY-582, with a binding energy of (-10.0 Kcal/mol). Whereas with the drug Tubastatin (A), receptor 6 THV established three conventional hydrogen bonds with residues HIS-574, ASP-612, and ASP-705, which are key amino acids in direct contact with the ligand. It is accompanied by an equal binding energy (-9.1 Kcal mol⁻¹).

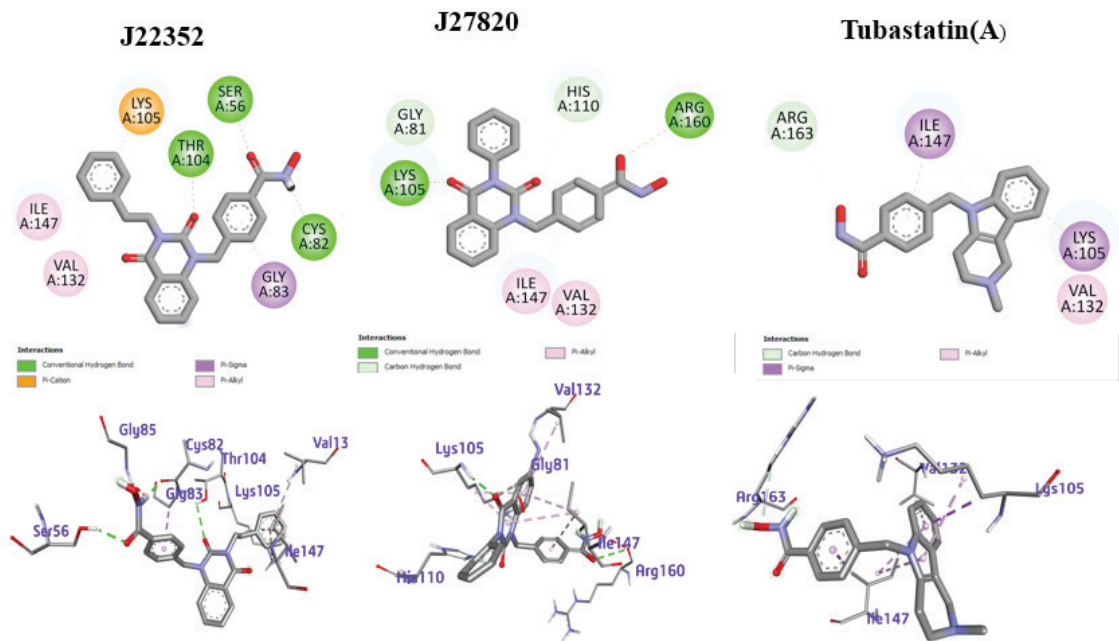


Figure 2. 2D and 3D visualization showing interaction of the receptor 5TFR with ligand J22352, J27820 and Tubastatin(A)

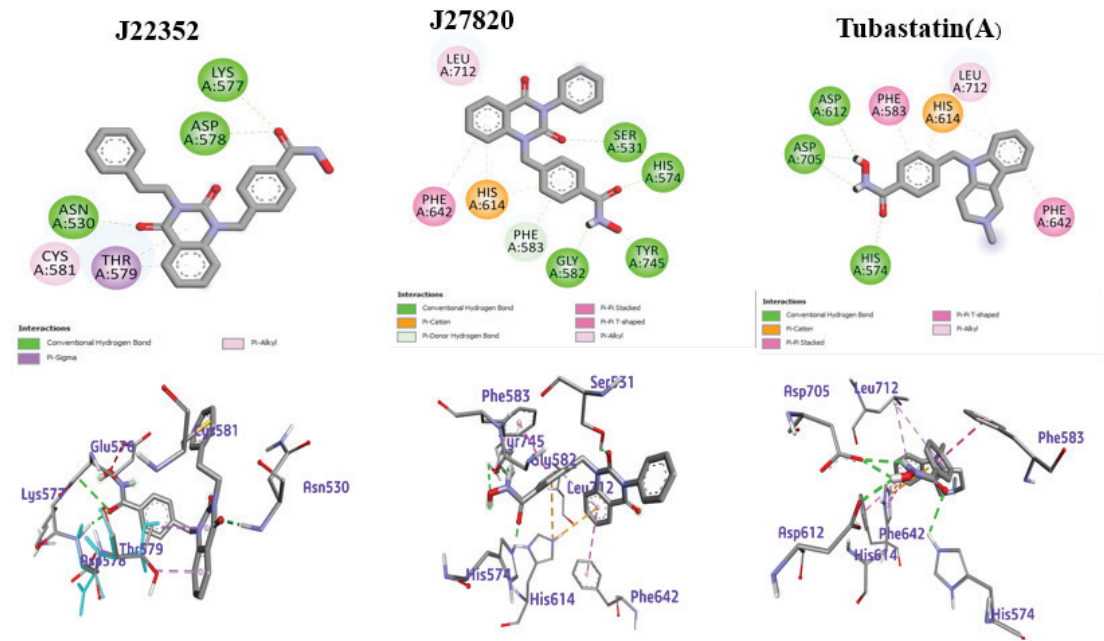


Figure 3. 2D and 3D visualization showing interaction of the receptor 6THV with ligand J22352, J27820 and Tubastatin(A)

For the 5H4I receptor (Figure 4.), the compound J22352 formed a single conventional hydrogen bond with the residue GLN-167 and two pi-alkyl bonds with ILE-123 and ALA-164 with a binding energy of (-9.0 Kcal/mol) for Tubastatin (A) forms a single conventional hydrogen bond with the TRP-89 residue, and

carbon-hydrogen bonds with the THR-166 and ILE-123 residues with a bond energy of (-7.7 kcal/mol). In contrast, compound J27820 forms two conventional hydrogen bonds with amino acids TRP-89 and ILE-147, as well as two pi-sigma bonds with ILE-123 and GLN-167, resulting in a bond energy of -8.2 kcal/mol.

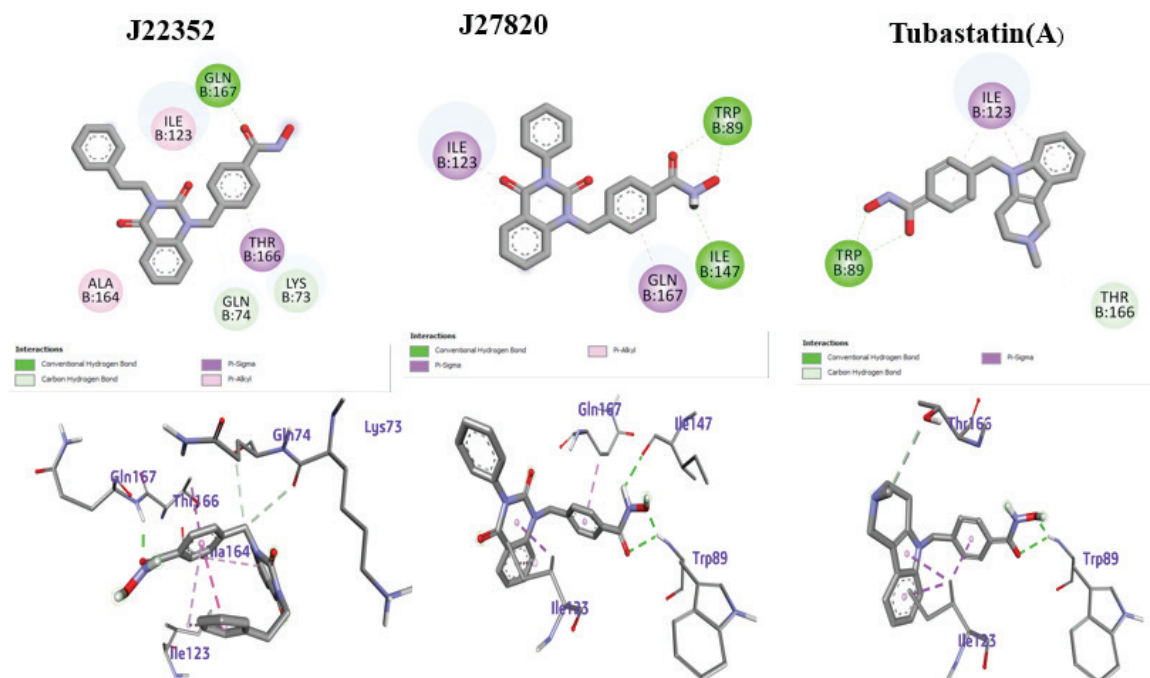


Figure 4. 2D and 3D visualization showing interaction of the receptor 5H4I with ligand J22352, J27820 and Tubastatin(A)

Re-docking results

The evaluation of the 5TFR, 6THV, and 5H4I receptors shows a very good match between the native

and redocked ligands, with respective RMSD values of 0.450 Å, 0.446 Å, and 0.654 Å. These results indicate a precise superimposition of the ligands and confirm the effectiveness of the method used.

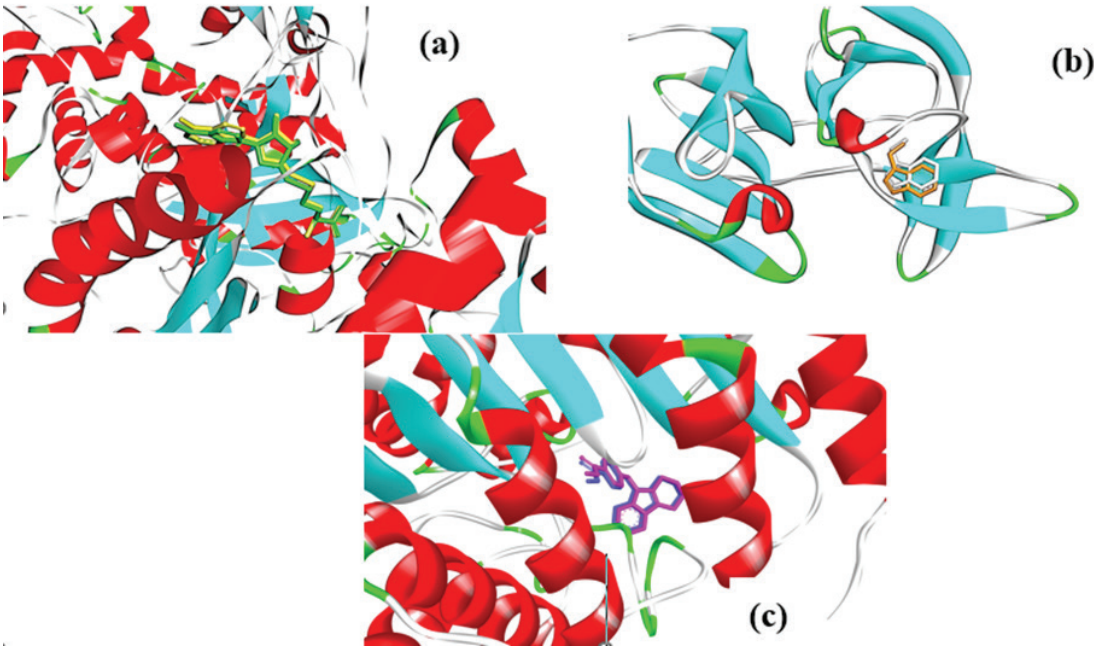


Figure 5. Re-docking pose inside active sites of (a) 5TFR receptor (b) 5H4I receptor (c) 6THV receptor

Table 1 summarizes the interactions between ligands and proteins; the values obtained for these characteristics indicate the stability and conformational changes that occur during these interactions, as well

as the flexibility with which ligands bind to proteins. The degree of protein structural variation during ligand binding is indicated by the RMSD values for all proteins less than two.

Table 1. The affinity of the ligand-protein with RMSD values

PDB Code	Ligand code	Interaction energy (Kcal/mol)	RMSD(Å)
5TRF	J22352	-9.9	0.450
	J27820	-10.3	
	Tubastatin (A)	-9.0	
6THV	J22352	-8.4	0.446
	J27820	-10.0	
	Tubastatin (A)	-9.1	
5H4I	J22352	-9.0	0.654
	J27820	-8.2	
	Tubastatin (A)	-7.7	

ADME-Tox results

Despite the drug’s biological action, as indicated in Table 2, and regardless of the significance of the protein’s active site affinity. The results are insufficient if the bioavailability and physiological action of these substances are not examined. All three compounds

showed high intestinal absorption, with 86.65% for J22352, 87.88% for J27820, and 93.33% for Tubastatin (A), suggesting high oral bioavailability. The theoretical volume to which a drug’s entire dose should be distributed to maintain a uniform concentration in blood plasma is the volume of distribution at steady state

(VDss). A larger VDss suggests that more medication is distributed to tissues than to plasma. The VDss was higher for Tubastatin (A) (0.74 l/kg) than for J22352 (-0.56 l/kg) and J27820 (-0.67 l/kg), suggesting better tissue penetration for Tubastatin (A). The molecules studied were CYP3A4 substrates but did not inhibit CYP2D6. while the inhibitory cytochromes CYP3A4

and CYP2C9 do not appear to inhibit molecules J22352 and J27820, except for Tubastatin(A). However, all three were inhibited by the CYP2D6 enzyme. One of the most important pharmacokinetic (PK) parameters in drug discovery and clinical practice is total clearance (TC). It assesses the ability of a living being or a particular organ to eliminate a drug.

Table 2. ADME-Toxic parameters of the three compounds

Compounds			J22352	J27820	Tubastatin(A)
Absorption	Water solubility (log mol/l)		-4.64	-3.51	-3.91
	Intestinal absorption (%)		86.65	87,88	93.33
Distribution	VDss humain(l/kg)		-0,56	-0,67	0.74
	CNS permeability		-2.55	-2,54	-2.17
Metabolism	CYP Substrate	2D6	No	No	No
		3A4	Yes	Yes	Yes
	CYP Inhibitor	2D6	No	No	No
		3A4	Yes	Yes	Yes
		2C9	YES	Yes	No
Excretion	Total Clearance(log ml/min/kg)		0,87	0,90	0.94
Toxicity	Tolerated human		0.61	0.61	0.23

Lipinski rules

Lipinski's rule, also known as the rule of five, is a rule of thumb in medicinal chemistry for predicting a compound's oral bioavailability from its chemical structure. The rule was formulated by Christopher A.

Lipinski in 1997. According to this rule, a molecule is orally bioavailable. We applied this rule to three ligands, J22352, J27820, and Tubastatin (A), which satisfy this rule. The results are shown in the (Table 3.) below.

Table 3. Lipinski Rules parameters of three compound

Compound	Lipinski Rules				
	HBD	HBA	MW	LogP	RB
J22352	2	4	415.44	2.57	7
J27820	2	4	387.39	2.31	5
Tubastatin(A)	2	3	335.40	2.31	4
Reference ligand	≤10	≤5	≤ 500	- 0,7 to + 5	≤9

MW: Molecular Weight, LogP: logarithm of partition coefficient of compound between n-octanol and water
HBA: number of hydrogen bond acceptors, HBD: number of hydrogen bond donors, RB: rotatable bonds.

Simulation molecular dynamic

The use of molecular simulation is an effective way of checking the robustness of the ligand in the active center and the contribution of the essential amino acids in the interaction between the ligand and the protein, to obtain the best and most stable configurations, and additionally to support the molecular docking results. The three compounds J22352, J27820, and Tubastatin (A) were studied via an MD simulation. This simulation, which simulated typical ambient temperature levels, ran for 100 ns. Based on trajectory visualization and post-simulation analysis. Several computations were performed to evaluate the stability of each three-component structure, including measurements of RMSD, RMSF, and the radius of gyration (Rg). The ligand's conformational stability for the protein and its binding pocket is usually confirmed throughout the simulation using the RMSD (Root Mean Square Deviation) measurements. Based on suggesting an initial adjustment phase where the structures begin to stabilize. For the initial structures comprising all trajectories of the simulated system, the protein's RMSD value is computed as a function of all Ca atoms in the backbone. For the drug Tubastatin (A), the RMSD values are very high at the start (0-20 ns) for both the protein and the ligand, suggesting an initial adjustment phase.

The variation in the RMSD of the protein is highest between 20 and 80 sec, while that of the ligand is less marked.

The values stabilize after 80 sec, suggesting that the protein-ligand complex conformations may be stabilizing.

In contrast, compound J22352 uses the RMSD of the protein's Ca atoms. Values fluctuate between approximately 1 and 4 Å, with several peaks over time, suggesting significant protein flexibility and conformational changes. At the beginning of the simulation, the RMSD values for both entities exhibit notable peaks, the ligand, the RMSD values fluctuate between 2.0 and 5.0 Å, indicating significant movement about the protein. This is further evidenced by the plot in J22352, which shows that the protein's RMSD increases between 20 and 80 ns slightly. At the same time, that of the ligand shows more pronounced variations, suggesting dynamic adjustments and possibly various interactions. After 80 ns, the two curves have reached stability, although variations persist.

For the compound J27820, we observed significant peaks in the RMSD values in both datasets. This suggests an initial conformational adjustment, with the protein's RMSD values fluctuating between approximately 0.5 and 4 Å, indicating changes in its conformation over time. The ligand's RMSD values range from 4 to 8 Å, suggesting considerable movement during the simulation. Notably, between 20 and 80 ns, the RMSD of the protein is slightly higher, while the RMSD of the ligand shows even greater values, indicating dynamic interactions between the two. Additionally, the RMSD of the ligand is compared with that of the protein, and the range of 4 to 8 Å further highlights the ligand's significant movement throughout the simulation. After 80 ns, the RMSD values stabilize; however, variations persist, particularly for the ligand (Figure 6.).

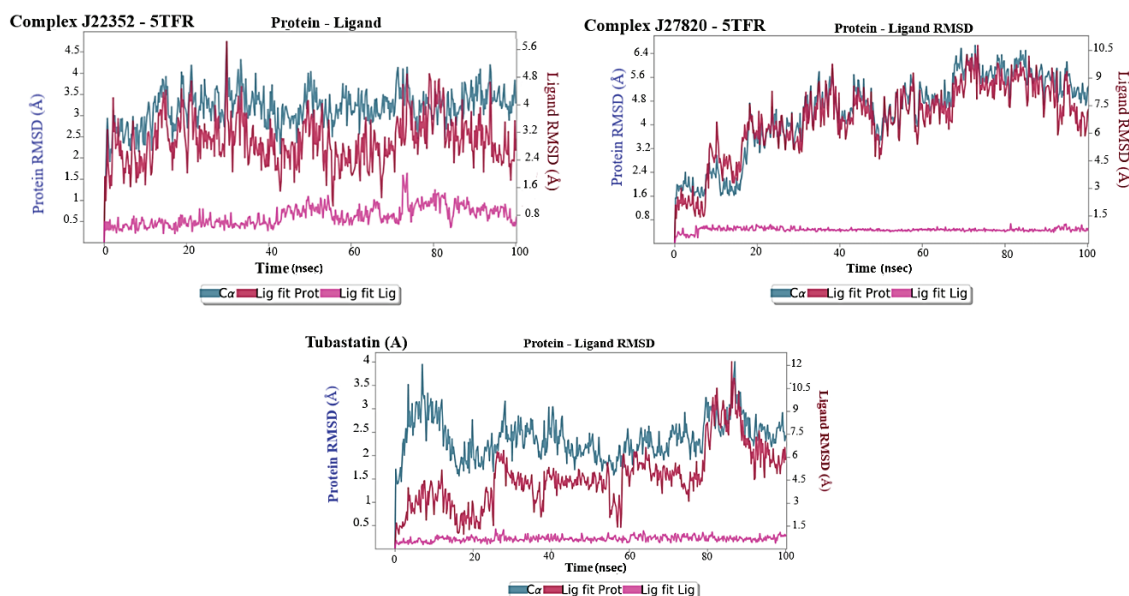


Figure 6. RMSD of the compounds Tubastatin (A), J22352, and J27820 during a 100 ns simulation

One crucial element that conveys the ability and form of intricate protein complexes during the simulation is the radius of gyration (Rg). As demonstrated by the radius of the gyration Rg graph (Figure 7.), it is thus an additional measure of ligand stability. The variation of the radius of gyration over time for Tubastatin (A) shows fluctuations around an average of about 1.2 Å, with significant variations. This indicates flexibility or dynamic movements within the molecule. In the J22352 plot, the gyration radius values fluctuate around an average of about 1.8 Å, with visible variations. These variations indicate changes in the compound's structure during the simulation. For compound J27820, the graph shows that most of the

gyration radius values are around 4.3 Å during the simulation, suggesting that the structure remains relatively stable over time compared to others, as shown in Figure 7.

As illustrated in Figure 8, the solvent-accessible surface area (SASA) was investigated to evaluate differences in hydrophilic and hydrophobic residues for a more thorough examination. The 5TFR protein exhibited increased stability with the J27820 ligand starting at 40 ns, with no discernible change in surface area until the simulation's conclusion. However, the J22352 and Tubastatin (A) compounds fluctuated after 40 ns throughout the simulation, making both SASA values unstable.

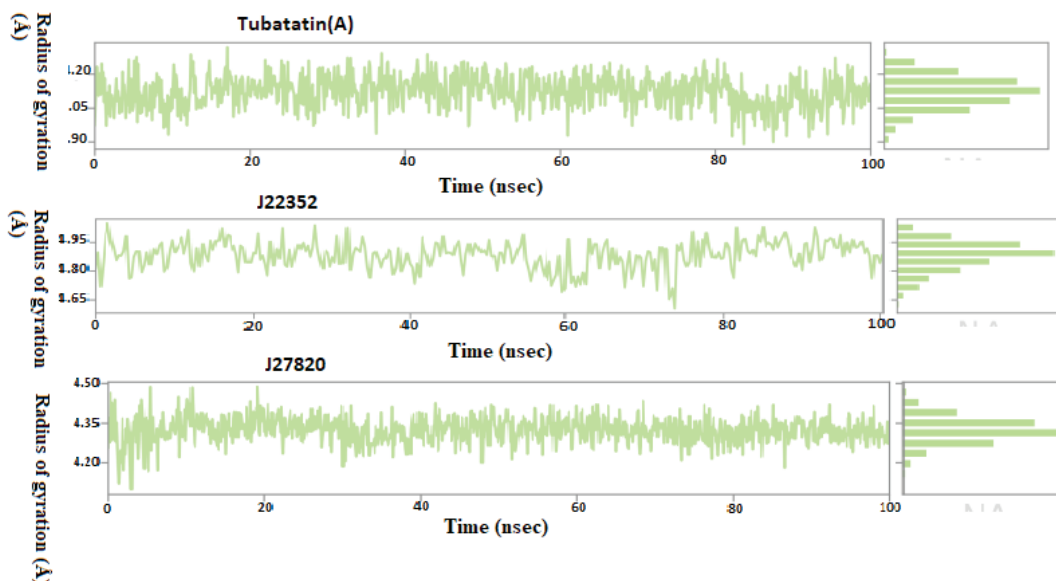


Figure 7. Radius of gyration of Tubastatin (A), J22352, and J27820 with 5TFR protein complex during 100 ns simulation

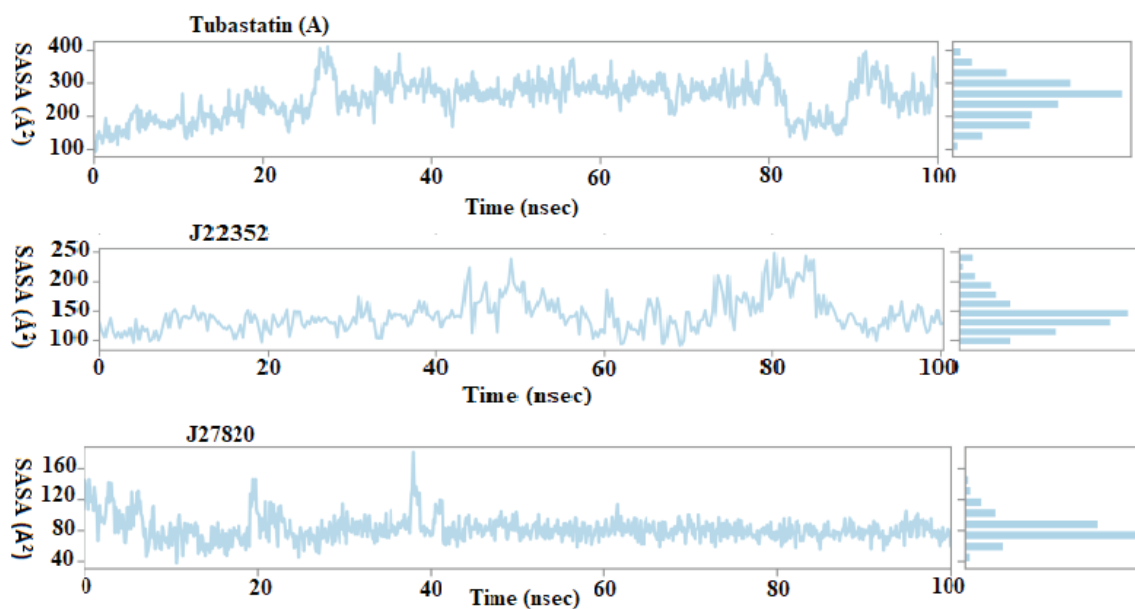


Figure 8. Surfaces of tubastatin (A), J22352, and J27820, which are accessible to SASA solvent, respectively

It is possible to track the interactions between the proteins and the ligand throughout the simulation. These interactions can be classified by type, as shown in the graph below. There are four types of protein-ligand interaction: hydrogen bonds, hydrophobic bonds, ionic bonds, and water bridges. Each type of

interaction plays a specific role, which can be explored in the Simulation Interactions Diagram panel; these stacked bar graphs are normalized along the trajectory. From values greater than 1.0, certain protein residues can establish several contacts of the same subtype as the ligand.

Figure 9 compares two compounds, J22352 and J27820, with the drug Tubastatin (A). The results show that hydrogen bonds and hydrophobic interactions account for most of the important ligand-protein interactions identified by MD. To confirm the stability of these complexes at the dynamic simulation level in relation to the results obtained in molecular docking, it can be seen that compound J22352 retains the same residues that result from the SER-56 hydrogen bond interaction, TRP-87, THR-104, CYS-82, pi-cation LYS-105, pi-alkyl ILE-147, VAL-132, pi-sigma GLY-83, and carbon-hydrogen bond GLY-58. This further reinforces the compound's stability during dy-

namic simulation and confirms the molecular docking results. Compound J27820 is characterised by the number of bonds that reinforce its stability with the protein, which is evident in the presence of amino acids obtained in molecular docking that remain after dynamic simulation, such as pi-cation interactions with residues LYS-105, ARG-160, pi-alkyl VAL-132, and ILE-147, which confirms the previous molecular docking results. On the other hand, for tubastatin (A), the dynamic simulation results show no interactions, unlike those observed in molecular docking, except for pi-sigma interactions with LYS-105, due to instability of the complexes.

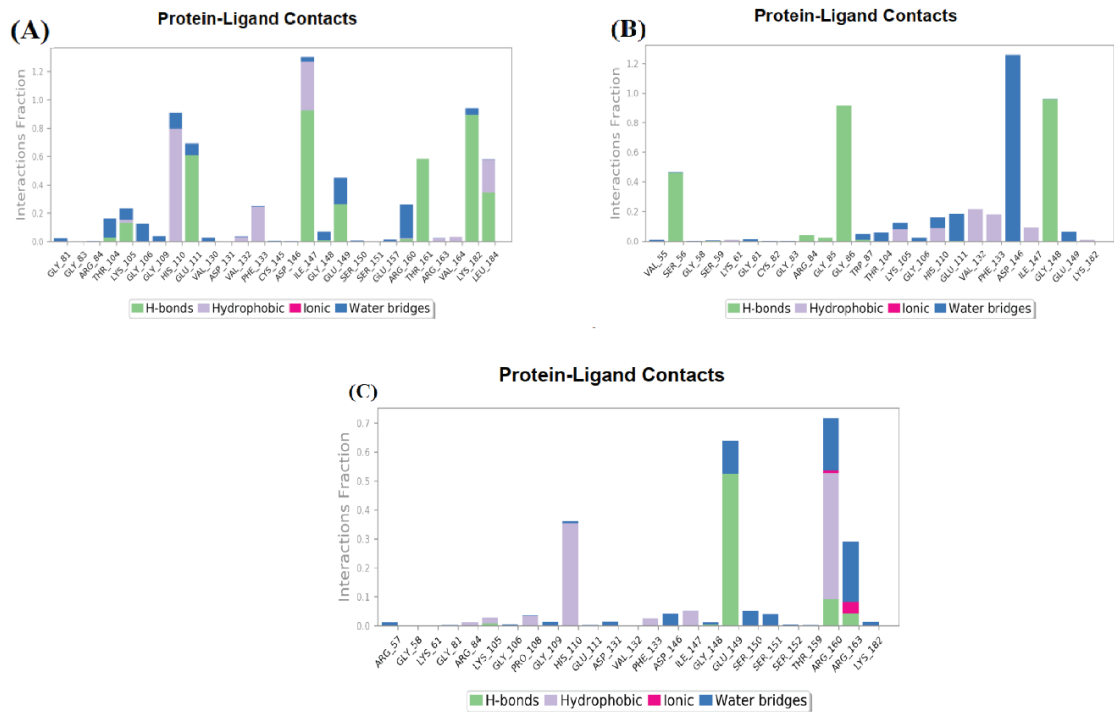


Figure 9. Histogram graphs and percentage of interactions using dynamic simulations of (a) compound J27820, (b) compound J22352, and (c) compound Tubastatin (A)

CONCLUSION

In this study, we examined two small molecules, the selective HDAC6 inhibitors J22352 and J27820, using a range of computational chemistry techniques, including molecular docking, ADMET predictions, and molecular dynamics simulations. The therapeutic potential of these compounds, J22352 and J27820, with Zika virus proteins

(5H4I, 5TFR, and 6THV), was demonstrated by their strong interactions with these targets. In order to validate the stability of the complexes, we performed molecular dynamics simulations. In addition, the physicochemical and pharmacokinetic ADMET properties of these compounds demonstrated significant advantages and antiviral therapeutic potential against the Zika virus.

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AUTHOR CONTRIBUTION STATEMENT

F.E.: Concept, Design, Writing, Analysis. M.B.: Supervision, Analysis. M.C.: Resources. T.L. and M.A.: Reviewing the text, Critical Reviews, literature search. E.B. and M.E.: Collection and/or Processing, Materials. A.S. and M.A.A: Analysis and/or Interpretation.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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