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UNVEILING THE POTENTIAL OF OXADIAZOLE TRIAZINE NUCLEOSIDE DERIVATIVE AS AN INHIBITOR OF SARS COV-2: A COMPUTATIONAL BREAKTHROUGH

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ABSTRACT

SARS-CoV-2 created havoc worldwide in 2019 and was responsible for many deaths. No antiviral drugs have been developed to combat this virus. Oxadiazoles have multiple biological functions, such as anti-inflammatory, anti-tussive, anticancer, analgesic, cough suppressant, anti-oxidant, vasodilator, and more. Many drugs with oxadiazole nuclei have been repurposed to combat COVID-19. To identify a potent oxadiazole derivative against SARS-CoV-2, this article screened 45 substituted oxadiazole triazine nucleoside analogs to counter the three key targets of the SARS-CoV-2 life cycle: spike protein, main proteases, and RNA-dependent RNA-polymerase. The geometry of 45 substituted oxadiazole triazine nucleoside analogs was optimized by density functional theory (DFT) with the B3LYp method. Drug-likeness criteria, ADMET prediction, and docking were carried out for screening. Further analysis of ligand-protein interactions was performed by molecular dynamics simulation at 50 ns. Compounds 1a (-8.5 kcal) and 1m (-8.5 kcal) showed an excellent binding affinity with main proteases (6LU7) and -7.8Kcal, -7.6Kcal, respectively, for RdRp (6M71), while compound 1a and 1m exhibited -8.0 kcal, -8.2 kcal binding affinity respectively for spike protein (6LZG). The MD simulation of the protein-ligand complex with compounds 1a and 1m exhibited good compactness and stability, further validating the docking results. This study proposes these two compounds would be robust inhibitors of SARS CoV-2.

Keywords: SARS Cov-2; Oxadiazole Derivatives; ADMET Analysis; Spike Protein; Main Proteases; RDRP.

1. INTRODUCTION

In 2019, China faced a viral threat caused by SARS-CoV-2 that contributed to a pandemic worldwide(Calisher et al., 2020; Ciotti et al., 2020; Hasnain et al., 2020). WHO named it as COVID-19(Organization, 2020). COVID-19 has caused a large number of deaths across the world. Symptoms of coronavirus disease (COVID-19) incorporate respiratory problems, fever, dry cough, fatigue, and sneezing(Abebe et al., 2020; Ali & Alharbi, 2020; Jamil et al., 2020), etc., while many patients were found asymptomatic(Kronbichler et al., 2020; Wells et al., 2020). SARS CoV-2 transmits mainly through

aerosol(Eslami & Jalili, 2020; Tang et al., 2020) formed by coughing, talking, sneezing, etc. The mortality rate was found to be higher in the patients with comorbidities.

Coronaviruses belong to the Coronaviridae family of the order Nidovirales and are characterized by a spike protein (crown) on their outer surface. Furthermore, their sub-family is split into four genera: alpha, beta, gamma, and delta, out of which beta coronaviruses are severe acute respiratory syndrome coronavirus (SARS), Middle East respiratory syndrome coronavirus (MERS), and severe acute respiratory syndrome coronavirus-2 (SARS CoV-2), etc. A pandemic was created by SARS in 2003 in which nearly 8,000 people got contaminated, and almost 900 people had to lose their lives, while MERS was responsible for nearly 2500 cases and more than 800 deaths worldwide in 2012. In 2019, a new pandemic caused by SARS-CoV-2, because of which approximately 770 million people got infected, and more than 6.9 million lives were lost worldwide as of December 2023(*WHO Coronavirus (COVID-19) Dashboard*, n.d.).

SARS CoV-2 consists of 29903 nucleotides wrapped in nucleocapsid with a single-stranded positive sense R.N.A and has 16 non-structural (nsp) and 4 structural proteins(Jakhmola et al., 2021; R. Yadav et al., 2021). The entry of the virus into the host cell machinery occurs with the help of the angiotensin-converting enzyme (hACE-2) of a host cell(Lan et al., 2020; Letko et al., 2020). Spike protein (S) is a glycoprotein trimer with two domains, S1 and S2. The S1 domain comprises two subdomains: one N-terminal subdomain, where the receptor binding domain (RBD) resides, and another C-terminal subdomain, which has a membrane fusion peptide; both of which facilitate the connection and fusion of the virus with the host cell(Duan et al., 2020; Nguyen et al., 2021). The transmembrane protease serine2 (TMPRSS2) protein further promotes the entrance of SARS-CoV-2 in human cells(Rais et al., 2021). nsp1 of the SARS CoV-2 downregulates the host's inherent immune response against viral infection by hampering its gene expression (Min et al., 2020; Schubert et al., 2020). The main protease (Mpro, also known as 3CLpro) is nsp5, which cleaves peptides, takes an integral part in viral protein processing, and helps in viral replication(Hu et al., 2022). This is a promising target to hamper the SARS-CoV-2 infection. RNA-dependent RNA polymerase (nsp12) is an essential protein for transcription and translation and is accountable for virus replication(Y. Wang et al., 2021). RdRp is a crucial target of SARS-CoV-2. SARS-CoV-2 infected almost every country and evolved many variants due to mutations, many of which were more potent in infecting and harmful to human beings. The reoccurrence of infection of SARS CoV-2 has also been noted in vaccinated health workers(Keehner et al., 2021), possibly due to mutations in different variants. The vaccine is ineffective in immunocompromised patients and those who undergo organ transplantation. Hence, there is a need to identify robust drug candidates to counter SARS-CoV-2.

The three critical targets of SARS CoV-2, Spike protein (6LZG), Mpro (6LU7), and RdRp (6M71), were targeted by oxadiazole triazine nucleosides. Heterocyclic compounds are known for their therapeutic value. Oxadiazoles are also a class of heterocycles (Fig.1), having two N atoms, two C atoms, and a single O atom with an isomeric five-membered ring.

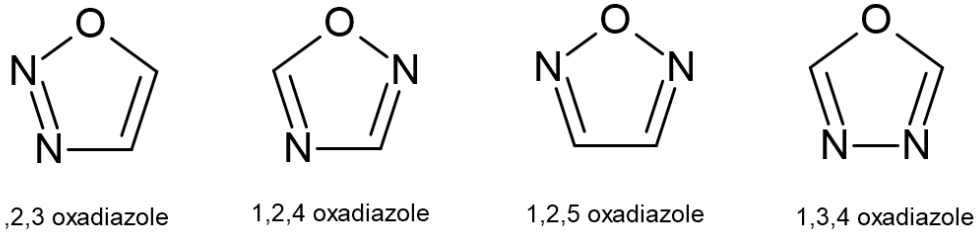
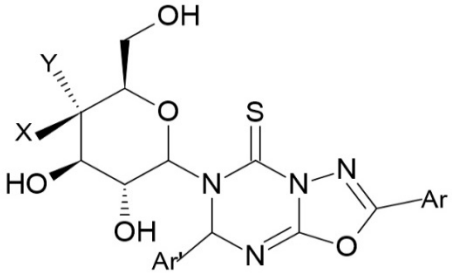


Fig. 1. Isomers of oxadiazole

Oxadiazoles exhibit anticancer(Altıntop et al., 2018; Rashid et al., 2012), anti-inflammatory(Gobec et al., 2015; Jayashankar et al., 2009), antibacterial(Othman et al., 2019; Peng et al., 2021), anticonvulsant(Almasirad et al., 2004; S. Wang et al., 2020), antifungal(Rodrigues-Vendramini et al., 2019; Yao et al., 2022), and antiviral(Gan et al., 2017; Li et al., 2011; Tan et al., 2006; Wu et al., 2015) properties. Drug repurposing is also an excellent approach for reassessing existing drugs against a particular disease; many drugs with oxadiazole nuclei have been repurposed for SARS CoV-2, such as 2-[(4- chlorophenyl) disulfanyl] -1,3,4-oxadiazole(He et al., 2020; L. Wang et al., 2017), N-[(E)-(2-hydroxyphenyl)methylideneamino]-4-[[[4-[[(E)-(2-hydroxyphenyl) methylideneamino]carbamimidoyl]-1,2,5-oxadiazol-3-yl]amino]methylamino]-1,2,5-oxadiazole-3-carboximidamide(Elseginy et al., 2021; Hamdy et al., 2021), 4-[5-(5-fluoro-1H-indol-2-yl)-1,3,4-oxadiazol-2-yl]phenol(Elseginy et al., 2021), Taroxaz(Rabie, 2021a, 2021c), CoVitris 2020(Rabie, 2021b) etc.

Danveer Singh Yadav et al. synthesized derivatives of oxadiazole triazine nucleosides (Xa-f)(D. S. Yadav, 1993), which were found to be active against Cornvirus, Beanvirus, and Cucumber mosaic virus, as shown in Fig. 2.



a, Ar=Ar'=Ph, X=H, Y=OH
b, Ar=Ar'=Ph, x=OH, Y=H
c, Ar=Ph, Ar'=*p*-OMeC_6H_4, X=OH, Y=H
d, Ar=*p*-Cl.C_6H_4, Ar'=Ph, X=H, Y=OH
e, Ar=*p*-Cl.C_6H_4, Ar'=Ph, X=OH, Y=H
f, Ar=Ar'=*p*-Cl.C_6H_4, X=OH, Y=H

Xa-f

Fig. 2. Derivatives of oxadiazole triazine nucleoside

This study used a computational perspective: molecular modeling, docking, ADMET property screening, and molecular dynamics simulation. The 45 oxadiazole triazine nucleoside analogs (Table S1) of the above oxadiazole derivatives were prepared using Gauss view 6.0.16, and energy calculations were performed using the DFT method given in Table S1. Molecular docking was done by Auto Dock 4.2, further accompanied by molecular dynamics simulations.

2. MATERIALS AND METHODS

2.1. LIGAND AND TARGET PREPARATION

The 3D structure of the ligand was created using Gauss Vies 6.0.16 software. The energy of ligands was minimized through the DFT method employing- the B3LYP method and a basic set of 6-31G; the memory limit -was specified at 10GB with four shared processors. After energy calculation, the log file was generated and changed into a mol file. This mol file was further changed to pdb through the aid of Open Babel 3.1.1 software. The 3D structures of the spike protein (6LZG), Mpro (6LU7), and RdRp (6M71) of SARS CoV-2 were collected by the Protein Data Bank (pdb format). Both the pdb files of the ligand and protein were changed to the pdbqt format using AutoDock 4.2.

2.2. MOLECULAR DOCKING

Molecular docking of analogs of oxadiazole triazine nucleosides was performed using AutoDock 4.2. The rigid docking was achieved by fixing the protein position while the ligands were flexible. An intensive literature survey revealed the active sites of target proteins 6LZG, 6LU7, and 6M71. Discovery Studio visualizer visualized the best binding sites of the target protein with the ligand after molecular docking.

2.3. MOLECULAR DYNAMICS SIMULATION

The MD simulation was done by GROMACS. The applied force field was CHARMM 36. The protein-ligand system was solvated in a cubic water box utilizing TIP3P water model. All parameters were taken the same way as in the gromacs tutorial, and the simulation was done at 50ns.

2.4. DRUG-LIKENESS PROPERTIES

We have used Lipinski's rule of five for the criteria of drug-likeness characteristics for ligands by the website (http://www.swissadme.ch/).

2.5. ADMET properties

Adsorption, distribution, metabolism, excretion, and toxicity (ADMET) properties were studied using the website (http://lmmd.ecust.edu.cn/admetsar2).

3. RESULTS AND DISCUSSION

3.1. DRUG-LIKENESS CRITERIA FOR OXADIAZOLE TRIAZINE NUCLEOSIDE ANALOGS

Lipinski's rule was a significant criterion for determining the drug-likeness characteristics of the oxadiazole triazine nucleoside analogs After analyzing the 45 oxadiazole derivatives, 13 derivatives (1a, 1b, 1d, 1e, 1f, 1g, 1h, 1m, 1o, 2a, 2b, 3a, and 3b) followed Lipinski's rule, as shown in Table S2. Most analogs showed good synthetic accessibility and bioavailability.

3.2. ADMET prediction

The 13 oxadiazole triazine nucleoside analogs that followed Lipinkski's rule were further analyzed for their ADMET properties. All analogs of oxadiazole triazine nucleoside exhibited intestinal absorption, no carcinogenic activity, and no AMES toxicity (Table 1).

Table 1. Selected ADMET properties of the oxadiazole triazine nucleoside analogs.

S.N	Compound	BBB	Human intestinal absorption	Caco-2 Permeability	Pgp substrate	CYP2C9-inhibitor	CYP2C9-substrate	CYP2D6-inhibitor	CYP2D6-substrate	Carcinogens	AMES toxicity
1	1a	0.754	0.875	0.638	0.757	0.733	0.749	0.862	0.814	0.689	0.50
2	1b	0.799	0.861	0.631	0.752	0.731	0.786	0.848	0.816	0.687	0.51
3	1d	0.508	0.594	0.645	0.691	0.779	0.641	0.861	0.818	0.791	0.56
4	1e	0.734	0.694	0.655	0.790	0.815	0.705	0.880	0.816	0.750	0.542
5	1f	0.573	0.732	0.650	0.664	0.770	0.676	0.871	0.812	0.732	0.572
6	1g	0.835	0.883	0.668	0.745	0.855	0.803	0.912	0.818	0.726	0.557
7	1h	0.658	0.905	0.632	0.581	0.803	0.714	0.891	0.806	0.741	0.553
8	1m	0.600	0.932	0.658	0.674	0.813	0.648	0.916	0.823	0.712	0.531
9	1o	0.749	0.889	0.661	0.743	0.833	0.727	0.921	0.821	0.729	0.528
10	2a	0.754	0.875	0.638	0.757	0.733	0.749	0.862	0.814	0.690	0.500
11	2b	0.799	0.861	0.631	0.752	0.730	0.786	0.849	0.816	0.687	0.510
12	3a	0.782	0.912	0.650	0.736	0.761	0.812	0.863	0.816	0.687	0.539
13	3b	0.826	0.903	0.647	0.730	0.754	0.842	0.850	0.817	0.682	0.547

3.3. MOLECULAR DOCKING

Thirteen analogs of oxadiazole triazine were further docked to counter the active sites of the three selected targets of SARS-CoV-2 for this study. Docking was done by AUTODOCK 4.2, and active sites of the target were determined through the extensive literature survey. Compounds 1a and 1m exhibited more promising binding affinity, as given in Table 2.

Table 2. The binding affinity of oxadiazole analogs with three key proteins of SARS-CoV-2.

S.N.	Compound	Binding affinity with 6LU7(In kcal)	Binding affinity with 6LZG (In kcal)	Binding affinity with 6M71 (In kcal)
1	1a	-8.5	-8.0	-7.8
2	1b	-7.8	-7.9	-7.4
3	1d	-7.9	-7.9	-7.4
4	1e	-7.7	-7.8	-7.6
5	1f	-8.4	-7.9	-7.6
6	1g	-7.6	-7.9	-7.6
7	1h	-8.3	-7.7	-7.6
8	1m	-8.5	-8.2	-7.7
9	1o	-8.0	-7.5	-7.2
10	2a	-7.7	-7.6	-7.2
11	2b	-7.2	-7.4	-7.6
12	3a	-7.3	-7.3	-7.5
13	3b	-6.8	-7.0	-7.2

3.3.1. MOLECULAR DOCKING OF SCREENED OXADIAZOLE DERIVATIVE WITH MAIN PROTEASES (6LU7)

The thirteen screened oxadiazole analogs (Table S3) were docked with the main proteases (6LU7), out of which compound 1a and compound 1m exhibited the most binding affinity with the identical value of -8.5 kcal/mol. Compound 1a showed hydrogen bonding with CYS145, HIS163, PHE140, GLU166, LEU141 and van der Waals interaction with MET49, ASN142, GLY143, ASP187, MET165, HIS172, SER144, GLN189, ARG188, while Pi-Alkyl interaction with HIS41 and halogen interaction with HIS164 was seen.

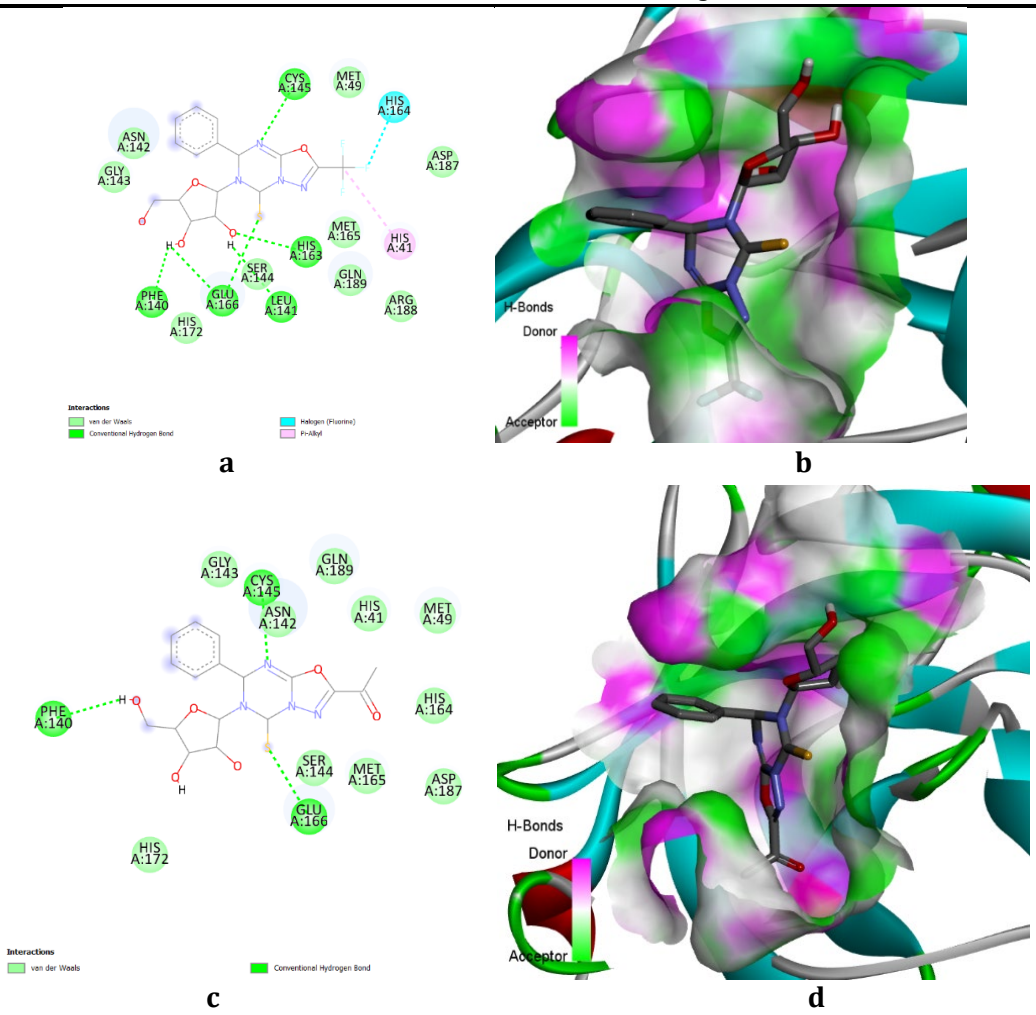


Fig. 3. Interactions of compound 1a (a - b) and 1m (c - d) with the main protease.

Compound1m exhibited hydrogen bonding with CYS145, PHE140, GLU166, and van der Waals interactions with GLY143, GLN189, ASN142, HIS41, MET49, HIS164, SER144, MET165, ASP187, and HIS172. The interaction profiles of the docked complexes in 2D and 3D are shown in Fig. 3.

3.3.2. MOLECULAR DOCKING OF SCREENED OXADIAZOLE DERIVATIVE WITH SPIKE PROTEIN (6LZG)

The best 13 oxadiazole analogs (Table S4) were furthermore docked with the 6LZG. Compound 1m revealed the maximum binding affinity of -8.2 kcal/mol. In the compound 1m-spike protein docked complex, the amino acid residues ASN394, TYR385, and ARG393 were engaged in hydrogen bonding formation, ALA348, THR347, HIS401, GLY395, ASP350, SRE44, SER43, and SER47 residues exhibited van der Waals interactions whereas TRP349 and PHE 40 established pi-pi T-shaped and pi-sulfur interactions respectively.

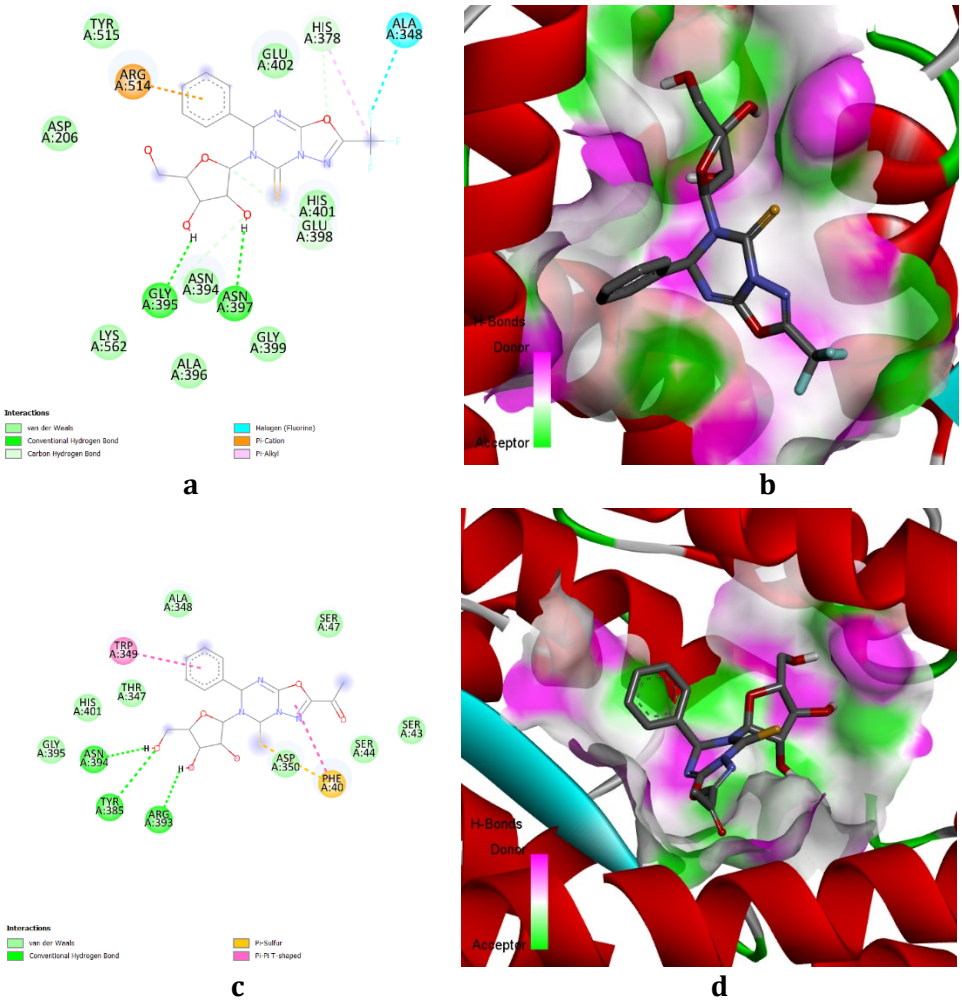
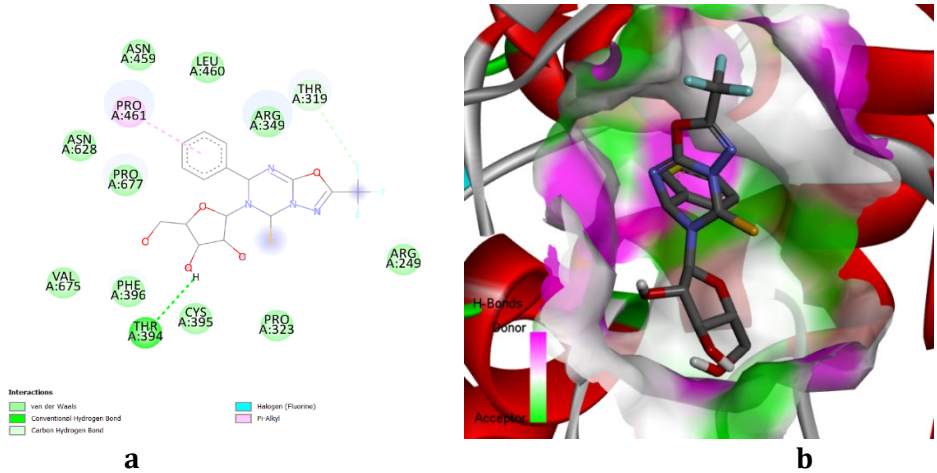


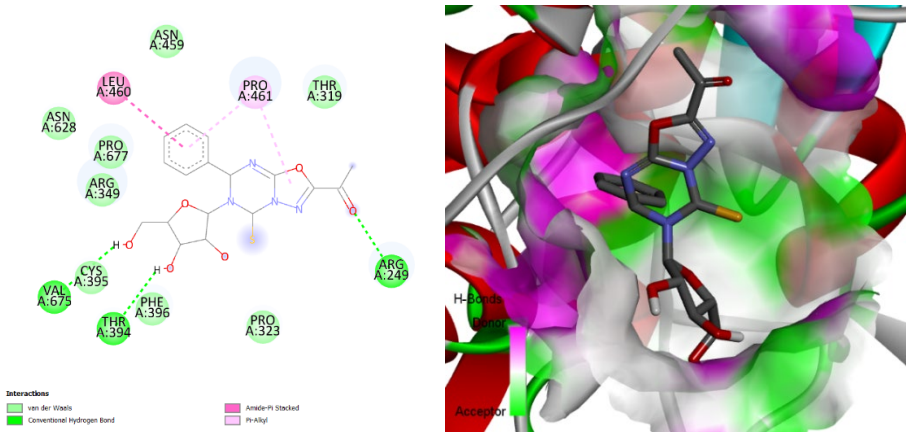
Fig. 4. Interactions of compound 1a (a - b) and compound 1m (c - d) with the spike protein.

Compound 1a exhibited a binding affinity of -8.0 kcal/mol. It showed hydrogen bond interactions with GLY395 and ASN397, whereas TYR515, ASP206, LYS562, ALA396, ASN394, GLU402, GLY399, and HIS 401 residues were involved in van der Waals interactions. Compound 1a also showed halogen interactions with ALA348, pi-alkyl interactions with HIS378, pi-cation interaction with ARG514, and carbon-hydrogen interaction with GLU398, as shown in Fig. 4.

3.3.3 MOLECULAR DOCKING OF SCREENED OXADIAZOLE DERIVATIVE WITH RDRP (6M71)

The 13 leading oxadiazole analogs (Table S5) were also docked with RNA-dependent RNA polymerases (RdRp). Again, compound 1a displayed the most binding energy, -7.8 kcal/mol.





c d

Fig. 5. Interactions of compounds 1a (a - b) and 1m (c - d) with RdRp.

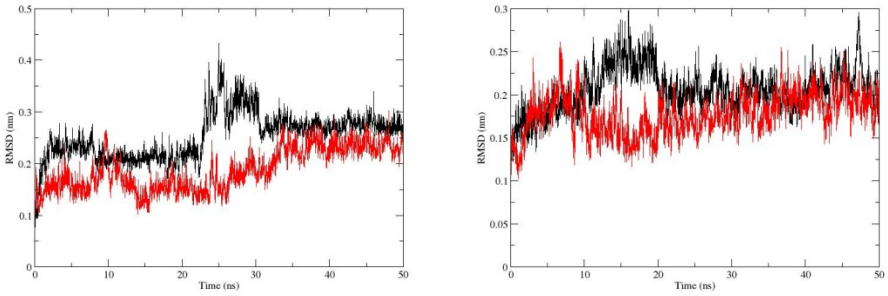
Compound 1a-RdRp docked complex involved hydrogen bonding with THR394, and additional interactions such as van der Walls (ARG349, LEU460, ASN459, ASN628, PRO677, VAL675, PHE396, CYS395, PRO323, and ARG249 residues), pi-alkyl with PRO461, and halogen with THR319. Compound 1m exhibited a binding affinity of -7.7 kcal/mol. Compound 1m-RdRp docked complex exhibited hydrogen bonding (VAL675, THR394, and ARG249 residues), van der Waals interaction (THR319, ASN459, ASN628, PRO677, ARG349, CYS395, PHE396, and PRO323 residues), amide-pi with LEU460 and pi-alkyl interaction with PRO461 (Fig. 5).

3.4. MOLECULAR DYNAMICS SIMULATION ANALYSIS

MD simulation is essential for recognizing the conformation and firmness of the protein-ligand docked complex. The interaction in molecular docking of the chosen key protein targets with oxadiazole triazine nucleoside analogs was corroborated by MD simulation.

3.4.1. RMSD AND RMSF ANALYSIS

The RMSD analysis is an inevitable query about the stability of the protein-ligand docked complex. The RMSD of each protein-ligand docked complex (Fig. 6) was recorded up to 50ns. The average deviation for the docked complex found between .1 nm and .3 nm indicates that the protein complex sustains its stability over time. The RMSF data of all protein ligand-docked complexes (Figure 6) justify the RMSD trajectory of these complexes.



a **b**

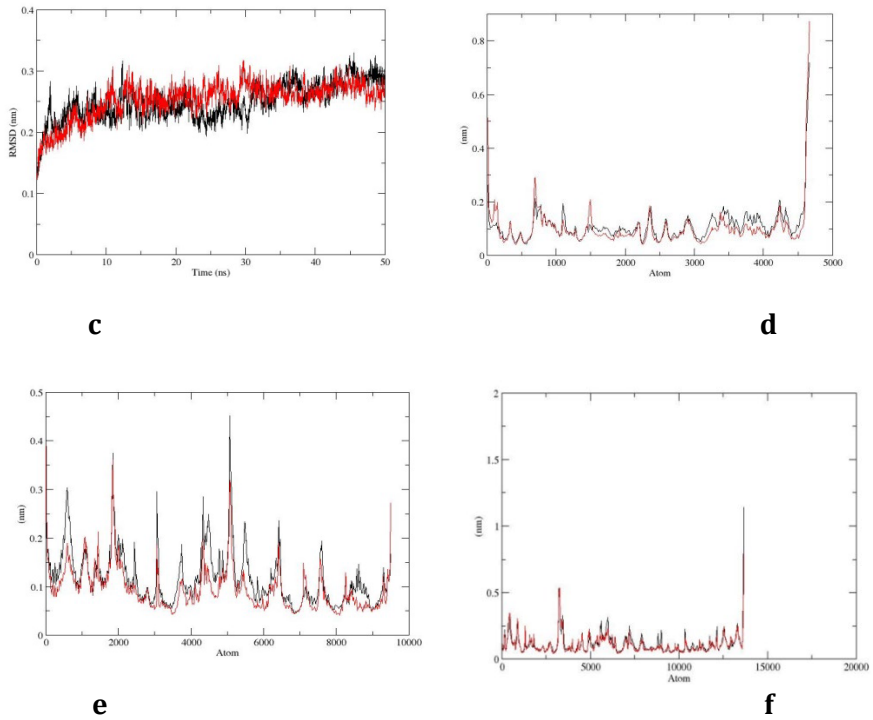
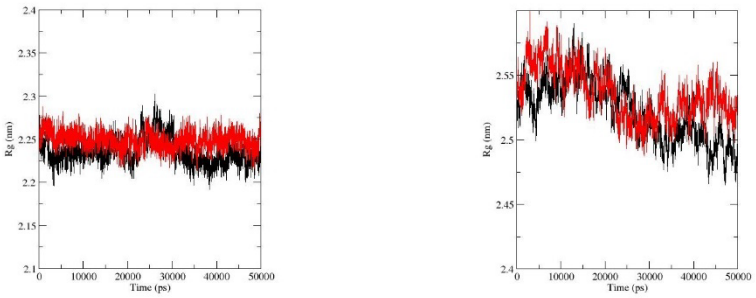
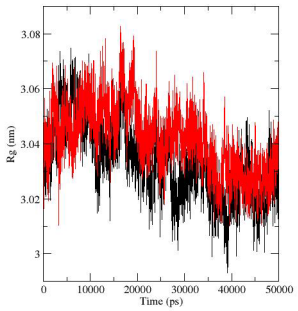


Fig. 6. RMSD plot for complexes of compound 1a (back), 1m (red) with 6lu7 (a), 6lzg (b), 6m71 (c), and RMSF plot for complexes of compound 1a (back), 1m (red) with 6lu7 (d), 6lzg (e), 6m71 (f).

3.4.2. RADIUS OF GYRATION (R_G)

The R_g value reveals the compactness and placement of the protein complex. The average R_g value (Fig. 7) of the protein ligand-docked complex of compound 1a with 6lu7, 6lzg, and 6m71 was found 2.24 nm, 2.52 nm, and 3.04 nm, respectively, and of compound 1m with 6lu7, 6lzg, and 6m71 was found 2.24 nm, 2.54 nm, and 3.05 nm, respectively, which indicates the excellent compactness that leads to the stability of system.



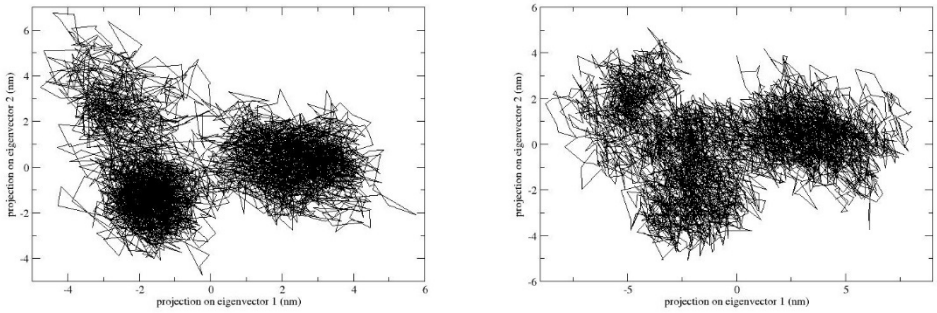


c

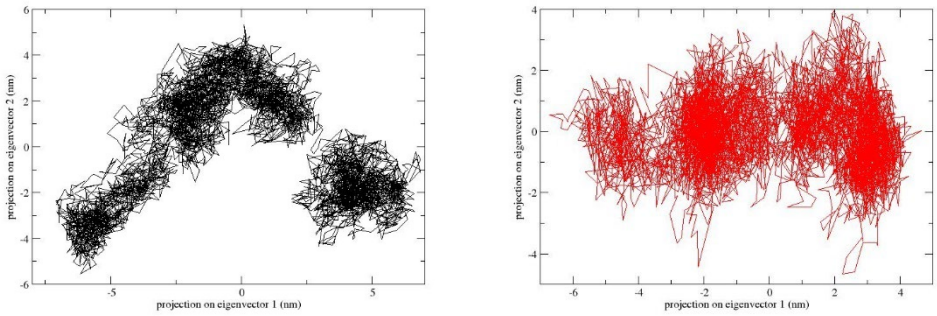
Fig. 7. Radius of gyration for complexes of compound 1a (back), 1m (red) with 6lu7 (a), 6lzg (b), 6m71 (c).

3.4.3. PCA

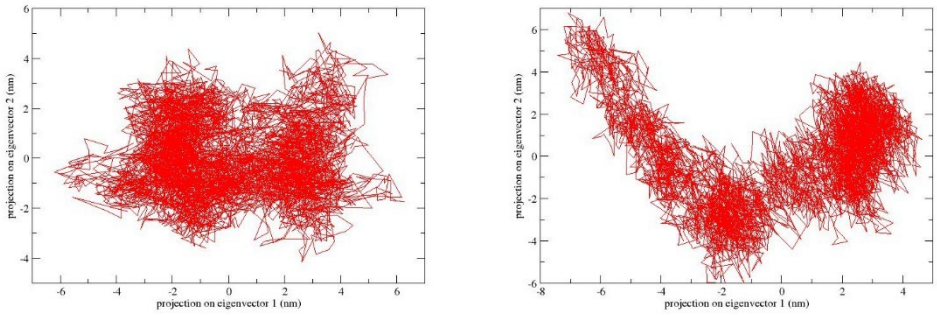
Principal component analysis (PCA) (Fig. 8) was executed to examine the conformational change in target proteins, viz 6lu7, 6lzg, and 6m71, due to binding with compounds 1a and 1m. This analysis revealed no remarkable conformational and structural changes in the target protein after binding, confirming the stability of the docked-protein complex.



a **b**



c **d**

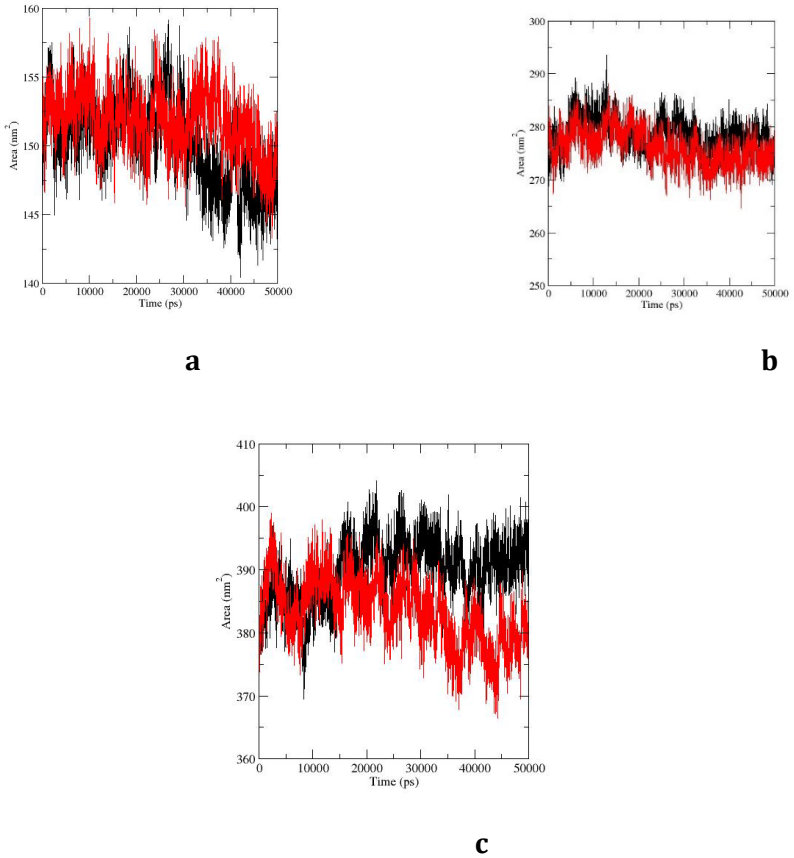


e **f**

Fig. 8. Trajectories on eigenvectors exhibited projection of 6lu7, 6lzg, 6m71 in compound1a-6lu7 (a), compound 1a-6lzg (b), compound 1a-6m71 (c) and of 6lu7, 6lzg, 6m71 in compound 1m- 6m71 (d), compound 1m-6lu7 (e), compound 1m-6m71 (f).

3.4.4. SOLVENT ACCESSIBLE SURFACE AREA (SASA)

The portion of the protein accessible by the solvent is calculated by the SASA value and plays an imperative role in protein folding and stability. The average SASA values of docked complexes (Fig. 9) of compound 1a with 6lu7, 6lzg, and 6m71 were 150 nm^2, 279 nm^2, and 390 nm^2, whereas the values of the docked complex of compound 1m with 6lu7, 6lzg, and 6m71 were 148 nm^2, 275 nm^2, and 380 nm^2 respectively, indicates the stability of the docked complexes.



a **b**

c

Fig. 9. Solvent accessible surface area for complexes of compound 1a (back), 1m (red) with 6lu7 (a), 6lzg (b), 6m71 (c).

4. CONCLUSION

The current study aimed to identify a robust drug candidate against SARS-CoV-2. Heterocyclic compounds, especially oxadiazoles, are renowned for their anti-inflammatory, anticancer, antiviral, and other therapeutic properties. Molecular docking, MD simulation, ADMET screening, and virtual screening of different 45 oxadiazole triazine nucleoside analogs were done against SARS CoV-2 by targeting its three key proteins, including the main protease (6LU7), RdRp (6M71),

and spike protein (6LZG). The two oxadiazole triazine nucleoside analogs, compound 1a and compound 1m, exhibited the most promising binding affinity with the selected targets.

The deviations in molecular dynamics simulation were found mainly in the favorable range, confirming the stability of the protein-docked complex. The drug-likeness characteristics, ADMET criteria, binding affinity, protein-ligand interaction profile, and molecular dynamics simulation trajectory findings suggest that the two oxadiazole triazine nucleoside analog compounds 1a and 1m could be potent drug candidates against SARS CoV-2. Thus, these two oxadiazole triazine nucleoside analogs may pave the way for novel therapeutics against SARS-CoV-2.

USE AI TOOL

The authors declare they have not used Artificial Intelligence (AI) tools in the creation of this article

CONFLICT OF INTERESTS

None.

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