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MOLECULAR DOCKING STUDY OF SULPHONYL HYDRAZIDE AS AN INHIBITOR OF VIRAL PROTEIN (VP40) OF MARBURG VIRUS

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Abstract

*Conventional pharmacotherapy is employed to counteract the effects of Marburg virus (VP40) and their associated pathologie for example Ibuprofen, naproxen, aspirin, ketorolac, celeocoxib, rofecoxib, etoricoxib, lumiracoxib etc. but these drugs are not more efficient because of some side effects like cardiovascular, gastrointestinal, insomnia, and diarrhea. Owing to these side effects we have selected some of synthetic supramolecular compounds containing sulphones and hydrazide, **SM (1-5).** All selected **SM (1-5)** compound were optimized by using Avogadro, gaussian09 software, using B3LYP theory and 6-31g basis sets through density functional theory. The title target enzymes were obtained from protein data bank, the optimized supra-molecular compounds were theoretically docked in an active pocket of target enzymes Marburg virus (VP40) by using MGL tools, Auto Dock vina. For each compound ten conformers were generated in which top ranked conformations with lowest binding energy of each compound was selected for further analysis. The inhibitors-protein interaction was visualized after docking in Pymol, BIOVIA discovery studio and ligplot which help in visualization of ligand-receptor hydrogen bonding, π…π interaction, aromatic interactions and hydrophobic interactions. The tested compounds show better inhibitory activity against Marburg virus (VP40). Their strong binding energies suggest that these inhibitor compounds have the ability to effectively modulate the activity of Marburg virus (VP40) enzymes, making them valuable candidates for the development of novel therapies addressing inflammation, pain, and other related conditions. Further exploration and evaluation of these compounds may lead to the discovery of potent Marburg virus (VP40) inhibitors with enhanced efficacy and fewer side effects.*

INTRODUCTION

The Marburg virus (MARV), a member of the *Filoviridae* family, is an enveloped, non-segmented, negative-sense RNA virus known for causing severe hemorrhagic fever with high mortality rates. [1] One

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of its essential structural and functional components is the viral matrix protein VP40, which plays a crucial role in the virus's life cycle, particularly in virion assembly, budding, and pathogenesis. [2, 3] VP40 is a multifunctional protein that mediates viral egress by interacting with the host cellular machinery, facilitating the formation of filamentous virions characteristic of *Filoviridae* viruses. [4, 5] Structural studies have revealed that VP40 exists in multiple oligomeric states, each associated with distinct functions. [6, 7] As a dimer, VP40 regulates viral RNA synthesis and trafficking, whereas the octameric form is involved in intracellular signaling and host immune modulation. [8-10] Computational and experimental studies have demonstrated that VP40 engages with host phospholipids, such as phosphatidylserine (PS), through its lipid-binding domain, which is critical for its localization to the plasma membrane and subsequent virion formation. [11] Mutational analyses of VP40 have identified key residues responsible for its membrane association, self-assembly, and interaction with other viral components. Given its indispensable role in viral replication and pathogenesis, VP40 represents an attractive target for antiviral intervention. [12, 13] Recent advancements in molecular docking and computational drug discovery approaches have enabled the identification of small molecules capable of disrupting VP40 function, thereby inhibiting MARV replication. [2, 13] Despite the significant role of VP40 in MARV biology, no FDA-approved antiviral drugs specifically targeting this protein are currently available. [14] Therefore, further research on VP40 inhibitors, including the exploration of novel chemical scaffolds such as sulphonyl hydrazide derivatives, is critical for developing effective therapeutic strategies against Marburg virus infection. Understanding the molecular mechanisms of VP40-mediated viral egress and host interactions will not only enhance our knowledge of *Filoviridae* pathogenesis but also contribute to the rational design of targeted antiviral compounds to mitigate the impact of MARV outbreaks. [2, 13, 15] Sulphonyl hydrazides are an important class of heterocyclic compounds known for their diverse biological activities, including antiviral, antibacterial, and anticancer properties. [16] Structurally, these compounds contain a sulphonyl ($-SO_2$) group attached to a hydrazide ($-NH-NH_2$) moiety, which allows them to form stable interactions with various biomolecular targets. Their potential as antiviral agents has gained significant attention in recent years due to their ability to interact with viral proteins, thereby inhibiting key stages of viral replication. [17] No FDA-approved antiviral drugs specifically targeting this protein are currently available. Therefore, further research on VP40 inhibitors, including the exploration of novel chemical scaffolds such as sulphonyl hydrazide derivatives, is critical for developing effective therapeutic strategies against Marburg virus infection. The bojectives of the current study is to investigate the molecular interactions of sulphonyl hydrazide derivatives with MARV VP40 using computational docking techniques and to compare the docking results with known MARV VP40 inhibitors for validation.

2. METHODOLOGY

2.1. Software used for Molecular docking

The computational, modelling, and simulation tools required for molecular docking in the recent work are Chem Draw, Chem3D, Open Babel, Auto Dock tools, PyMol, and Discovery Studio Visualisation. These applications enable ligand optimisation and docking with particular targeted enzymes.

2.2. General methodology of molecular docking

By employing the molecular docking protocol, [18] the binding interaction mechanism of the synthesized sulfonyl hydrazide derivatives was examined for competitive and non-competitive inhibition of the mark enzyme of viral protein (vp40) of marburg virus (illustrated in **Figure 1**). Proteins' three-dimensional crystal structures were obtained from the Protein Databank. The title proteins were first prepared theoretically using Auto Dock MGL tools, and for ease of calculation, inhibitors, co-factors, heteroatoms, and all water molecules were eliminated for optimization. For additional research, the most stable docking conformer with the lowest binding energy was chosen. PyMol, Auto Dock vina, Discovery Studio Visualization, and other programs were used to visualize the mechanism of proteins-ligand complex interactions, their pictures, and the docking poses of the tested compounds against target enzymes [19].

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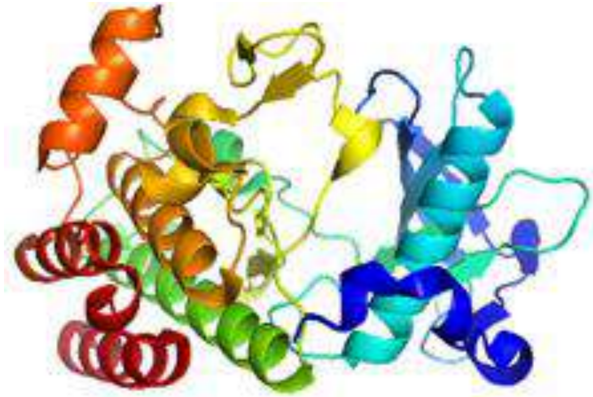

Figure 1. 3D crystal structure of MARV VP40

2.3. Optimization of Sulphonyl-hydrazides SM1-SM5

The selected compounds were fully optimized before docking. Avogadro, Gaussian 09 software, B3LYP theory, and 6-31g basis sets based on DFT were used [20] to optimize the chosen derivatives, SM1-SM5 in figure 2

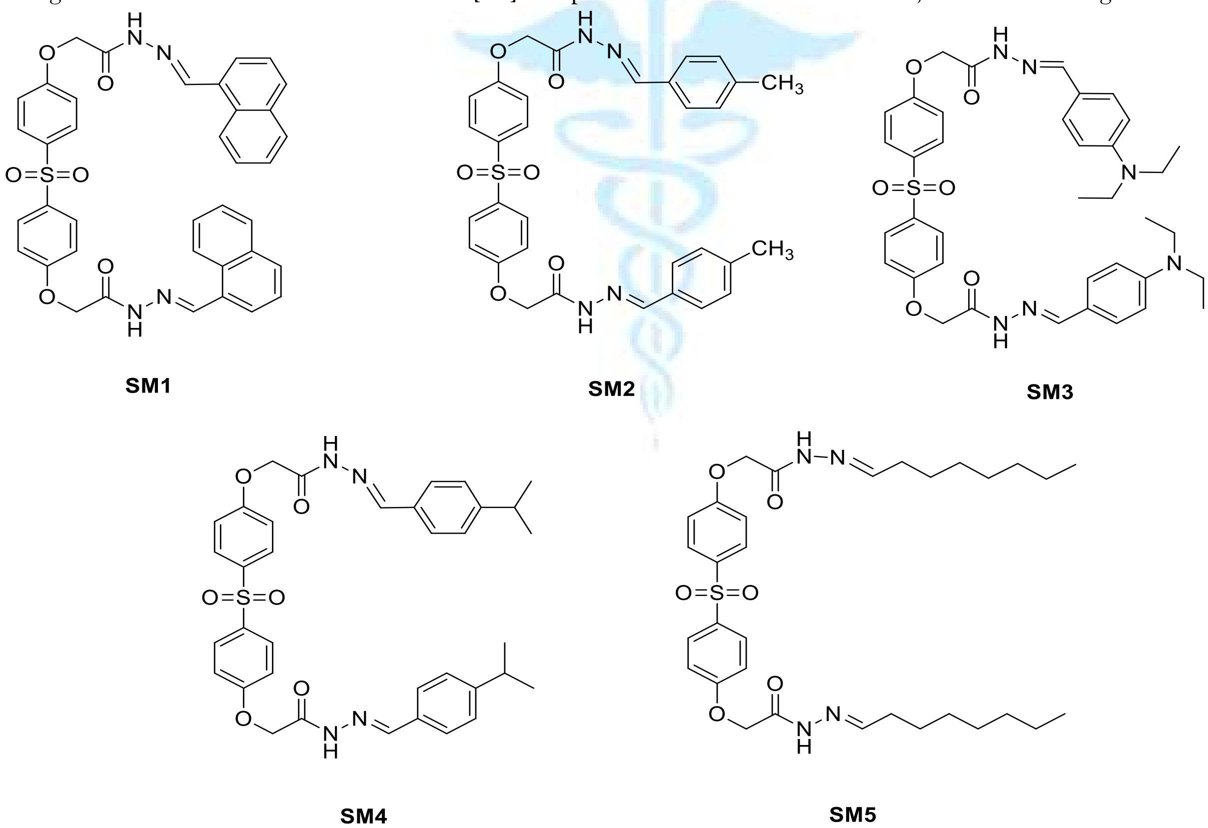

Figure 2. Structural formulae of compounds SM1-SM5

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2.4. Molecular docking of ligands with Marburg virus (VP40)

Molecular docking is a crucial technique for observing how inhibitors and target proteins interact, through the use of MGL tools, Auto Dock vina, the optimized compound of the selected compounds (shown in Figure 2) were theoretically docked in the active region of the target receptors namely Marburg virus (VP40). Ten conformers for compounds have been generated in which the most stable conformations were picked for additional examination. After the docking process, the inhibitor-protein interactions were observed in PyMol and BIOVIA Discovery Studio, which aid in the visualization of hydrophobic interactions, aromatic interactions, π-π interactions and ligand-receptor bonding via hydroge

3. RESULTS

3.1. Interaction of SM1-SM5 with viral protein (VP40) of MARV residues

SM1-SM5 are strongly interacted with the residues in active pocket of VP40 given in Figure 3-7. The interacting residues and their binding energies are given in table 1.

Table 1. Binding energies and interacting residues of SM1-SM5 against viral protein (VP40)

ligands	Binding score (kcal/mol)	Residue involved in hydrogen bonding
SM1	-17.48	CYS-47, CYS-41
SM2	-16.01	GLN-461
SM3	-15.66	CYS-41, ARG469, TYR-130
SM4	-14.73	TYR-130, GLY-45, CYS-47
SM5	-10.13	GLN-44, ARG-61, ARG-83 ARG-79, ARG-79
Ibrofen	-8.81	CYS-41

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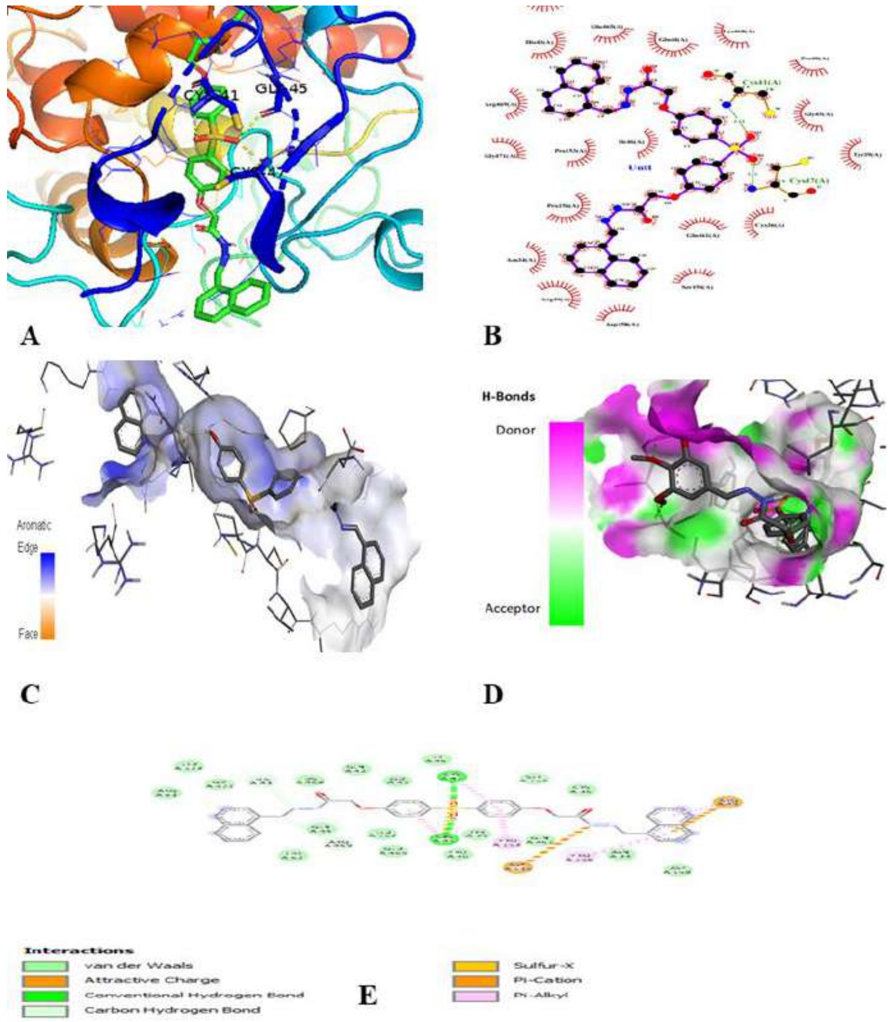

Figure 2.. Binding pose of SM1 with VP40, (A) 3D interactions, (B) interacting amino acids (C) Aromaticity (D), hydrogen bonding, and (E) 2D interactions

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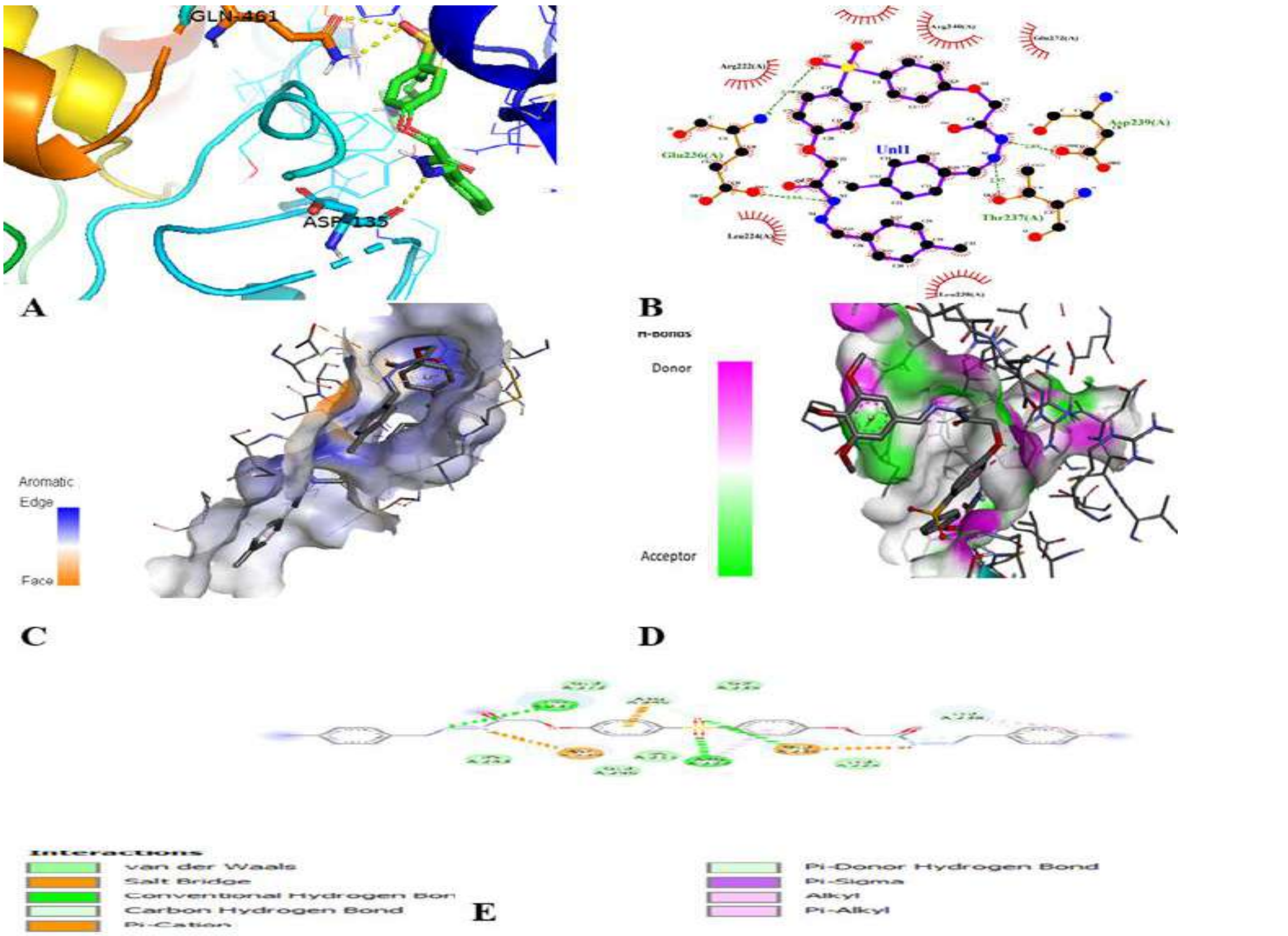

Figure 4. Binding pose of SM2 with VP40, (A) 3D interactions, (B) interacting amino acids (C) Aromaticity (D), hydrogen bonding, and (E) 2D interactions

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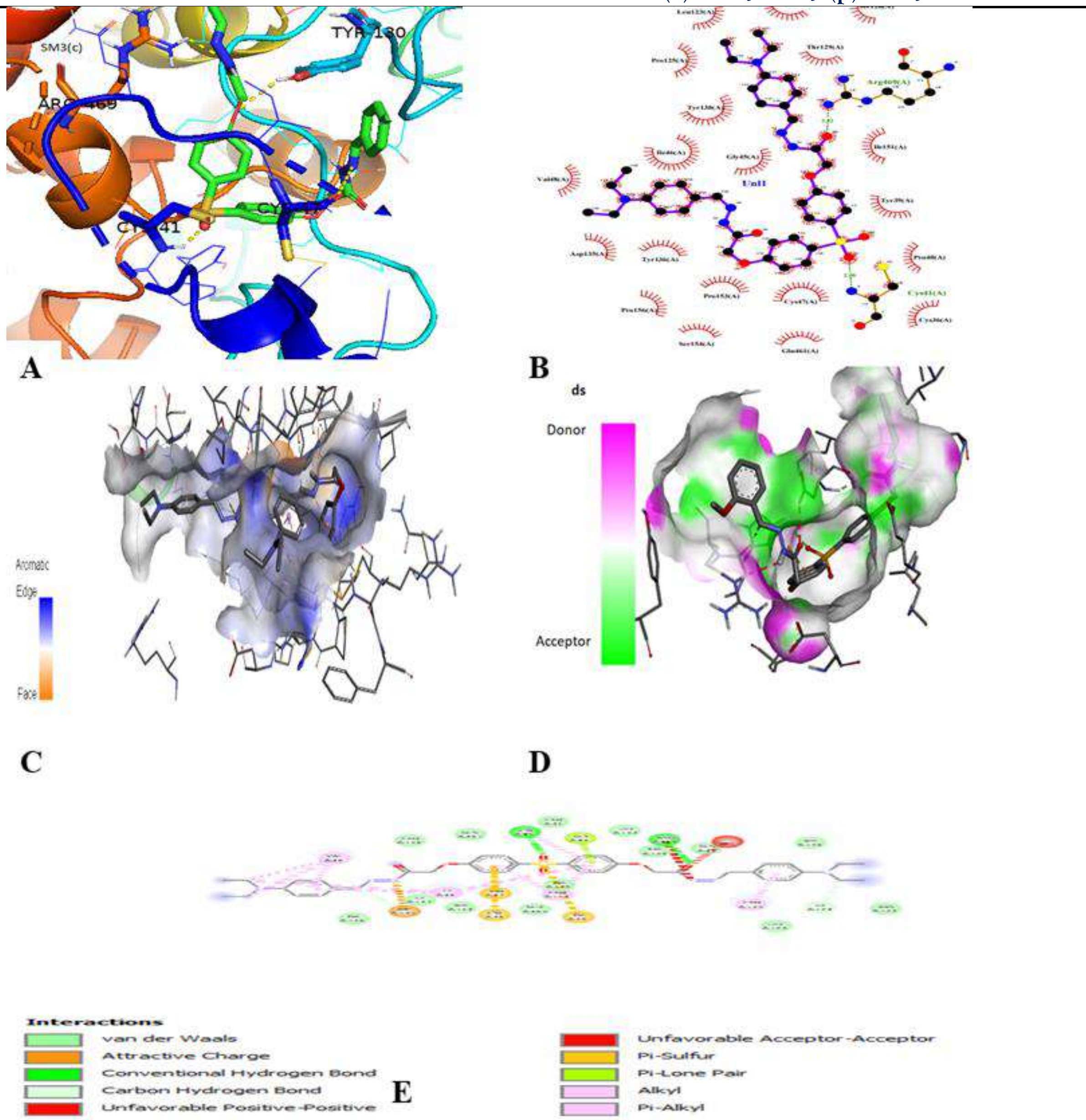

Figure 5. Binding pose of SM3 with VP40, (A) 3D interactions, (B) interacting amino acids (C) Aromaticity (D), hydrogen bonding, and (E) 2D interactions

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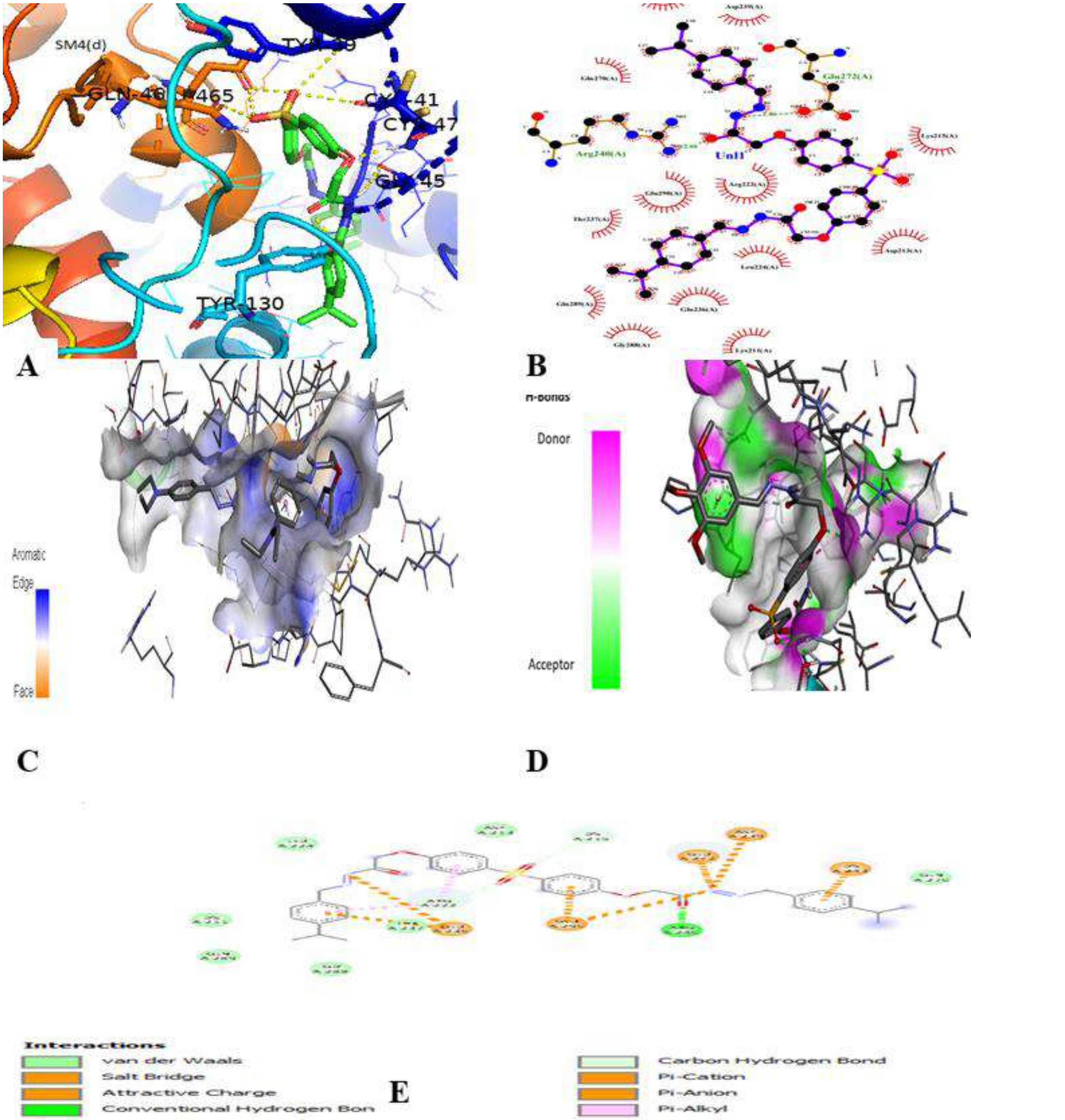

Figure 6. Binding pose of SM4 with VP40, (A) 3D interactions, (B) interacting amino acids (C) Aromaticity (D), hydrogen bonding, and (E) 2D interactions

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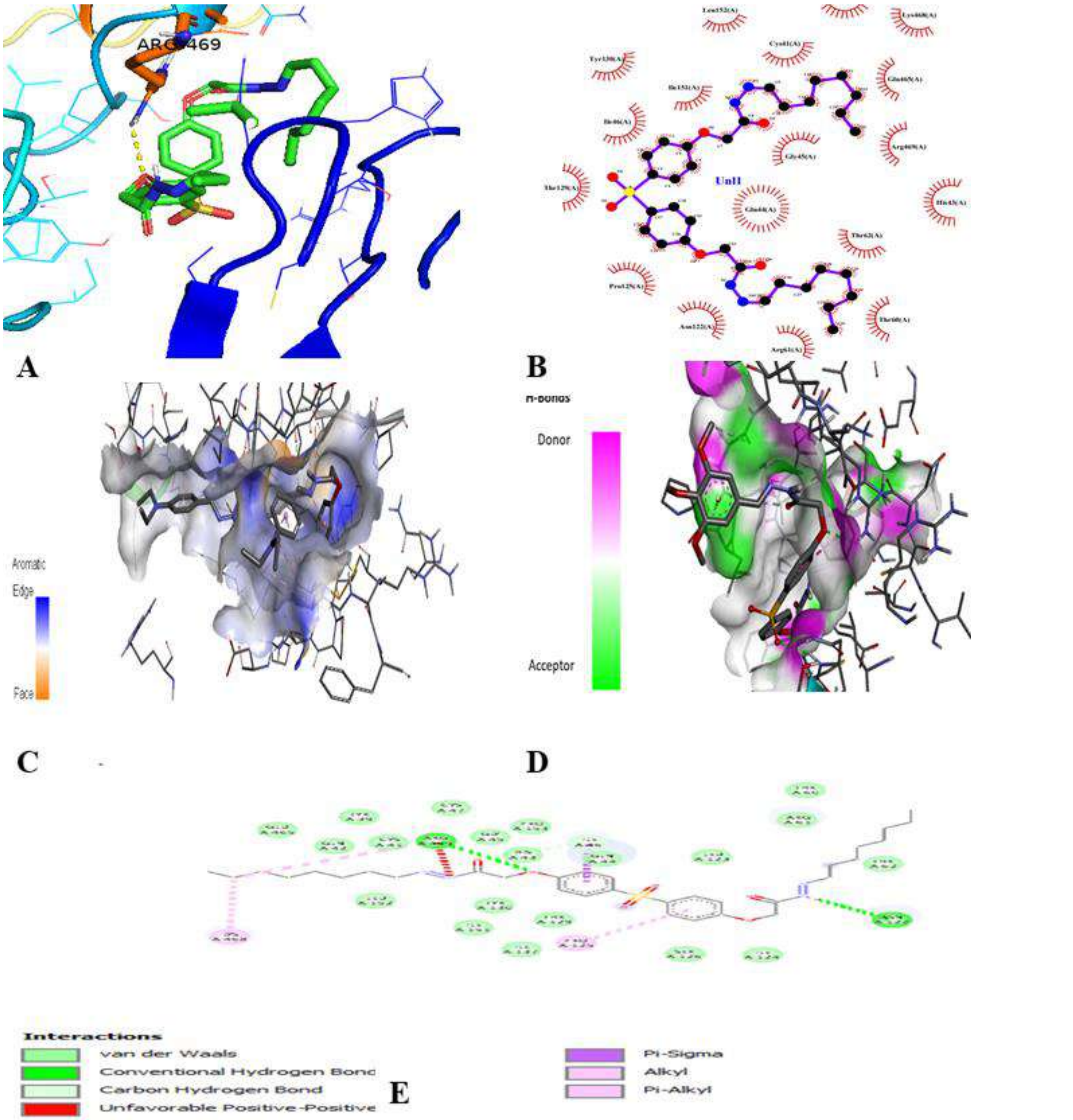

Figure 7. Binding pose of SM5 with VP40, (A) 3D interactions, (B) interacting amino acids (C) Aromaticity (D), hydrogen bonding, and (E) 2D interactions

4. DISCUSSIONS

Open chain and closed chain sulphones and hydrazide containing supramolecular compounds are biologically active. In this study we have selected some of synthetic supramolecular compounds containing sulphones and hydrazide, **SM (1-5)**. The discovery of targeted potential drugs for inflammation in human body are still big challenge for modern world. The literature study shows that the drugs containing hydrazide, sulphones moieties are the competent drugs [21, 22]. So, to intervene in these challenges we are investigating the inhibition potential of the synthetic supramolecular compounds **SM (1-5)** against the targeted proteins MARV. Molecular docking studies were performed to explain the possible binding interactions modes of the selected supramolecular compounds containing sulphones and hydrazide moiety **SM (1-5)** with targeted protein MARV. **Figure 3-7.**

4.1. Molecular docking study of (SM1-SM5)

The literature studies shows that structural variation link between the active site of MARV plays a key role in designing of targeted inhibitors [23]. Molecular docking investigation of **(SM1-SM5)** against MARV was carried out to predict binding and orientation nature of selected compounds in active packet of Marburg virus (VP40). Auto dock study were used for docking, which successfully docked the title compounds **(SM1-SM5)** in the active pocket of Marburg virus (VP40). Binding energy, and residue involved in hydrogen bonding are summarized in **Table 1**. Among the selected compound **SM1-SM5** exhibit docking score of -17.48 kcal/mol, -16.01 kcal/mol, -15.60 kcal/mol, -14.73 kcal/mol, -10.13 kcal/mol against MARV. The description of **SM1** were selected according to lowest binding energy pose. **SM1** compound fitted best into MARV active binding sites. **SM1** form Hydrogen bonding (S=O…HN, S=O…HN) interaction with CYS-47 and CYS-41 residues of MARV with bonds distances 2.1Å and 2.3Å but also one weak π…π interaction (S=O…O=N, 2.5Å)GLY-45 given in **Figure 3** and to demonstrate **SM2** was also selected according to lowest binding energy pose, compound **SM2** fitted best into MARV active binding sites. SM2 form Hydrogen bonds with GLN-461 (S=O…HN, 2.6Å) residues of MARV and form weak π…π interactions (S=O…O=S,2.8Å)GLN-461,(N…O=N,3.0Å)ASP-135 given in **Figure 4** Interaction study of MARV with **SM3** possess three hydrogen bonds with CYS-41 (S=O…HN, 2.1Å), ARG-469 (C=O…HN, 2.3Å), TYR-130 (O…HO, 2.6Å) residues and form weak π…π interactions (N…O=N,.3.5Å) ARG-469 given in **Figure 5**. The interaction pattern of **SM4** was selected according to lowest binding energy pose SM4 fitted best into MARV active binding sites which allows compound **SM4** to form Hydrogen bonding with (C=O…HO, 2.0Å) TYR-130, (NH…O=N, 2.3Å) GLY-45, (O…HN, 1.9Å) CYS-47 residues of MARV and form weak π…π interactions (S=O…O=N,3.4Å)CYS-41,(S=O…O=N,3.4Å)TYR-39 (S=O…O=S,2.4Å)GLU-465(S=O…O=S,2.4Å) GLN-461 shown in **Figure 6.** SM5 exhibit only one hydrogen bond (O…HN, 2.8Å) with ARG-469 and having no π…π interactions given in **Figure 7** The commercially available drug standard Ibrofen which having binding energy -8.81 kcal/mol against MARV [24]. Among the tested compounds, SM1 (-17.48 kcal/mol) exhibit best inhibitory activity against MARV as compared to other tested compounds and as well as standard Ibrofen. 2D interaction, Hydrogen bonding pocket and aromatic interactions Figure of SM1-SM5 are given in **Figure 3-7**

5. CONCLUSION

Sulphones and hydrazone-containing synthetic open chain supramolecular compounds that we have chosen include **SM (1-5)**. Molecular docking shows that supramolecular compounds **SM1-SM5** exhibit binding energy –10.13kcal/mol to -17.48kcal/mol against MARV.(VP$)) Compare with standard drug Ibrofen which having binding energy -8.81 kcal/mol against MARV. The above-mentioned compounds show better inhibitory activity against Marburg virus (VP40). These inhibitors will be useful in future against Marburg virus (VP40).

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Conflict of Interest

The authors declare no conflict of interest

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References

1. Letafati, A., et al., *Marburg Virus Disease: A Narrative Review.* Health Science Reports, 2025. **8**(5): p. e70669.
2. Liang, J., et al., *Chaperone-assisted selective autophagy targets filovirus VP40 as a client and restricts egress of virus particles.* Proceedings of the National Academy of Sciences, 2023. **120**(2): p. e2210690120.
3. Zhuo, Y., et al., *Pathogenicity and Virulence of Filoviruses.* Global Virology V: 21st Century Vaccines and Viruses, 2025: p. 761-780.
4. Liang, J., et al., *WWOX-mediated degradation of AMOTp130 negatively affects egress of filovirus VP40 virus-like particles.* Journal of Virology, 2022. **96**(6): p. e02026-21.
5. Shepley-McTaggart, A., et al., *Ubiquitin ligase SMURF2 interacts with filovirus VP40 and promotes egress of VP40 VLPs.* Viruses, 2021. **13**(2): p. 288.
6. Amiar, S., et al., *Lipid-specific oligomerization of the Marburg virus matrix protein VP40 is regulated by two distinct interfaces for virion assembly.* Journal of Biological Chemistry, 2021. **296**.
7. Hayat, M., et al., *Identification of prospective Ebola Virus VP35 and VP40 protein inhibitors from Myxobacterial natural products.* Biomolecules, 2024. **14**(6): p. 660.
8. Wu, L., et al., *The two-stage interaction of Ebola virus VP40 with nucleoprotein results in a switch from viral RNA synthesis to virion assembly/budding.* Protein & Cell, 2022. **13**(2): p. 120-140.
9. Narkhede, Y.B., et al., *Elucidating residue-level determinants affecting dimerization of Ebola virus matrix protein using high-throughput site saturation mutagenesis and biophysical approaches.* The Journal of Physical Chemistry B, 2023. **127**(29): p. 6449-6461.
10. Almeida-Pinto, F., R. Pinto, and J. Rocha, *Navigating the complex landscape of ebola infection treatment: A review of emerging pharmacological approaches.* Infectious diseases and therapy, 2024. **13**(1): p. 21-55.
11. Cioffi, M.D., et al., *Role of phosphatidic acid lipids on plasma membrane association of the Ebola virus matrix protein VP40.* Biochimica et Biophysica Acta (BBA)-Molecular and Cell Biology of Lipids, 2024. **1869**(3): p. 159464.
12. Khan, S., Z. Fakhar, and A. Ahmad, *Targeting ebola virus VP40 protein through novel inhibitors: exploring the structural and dynamic perspectives on molecular landscapes.* Journal of Molecular Modeling, 2021. **27**(2): p. 49.
13. Saeed, M., et al., *Identification of novel inhibitors against VP40 protein of Marburg virus by integrating molecular modeling and dynamics approaches.* Journal of Biomolecular Structure and Dynamics, 2025. **43**(8): p. 3942-3955.
14. Saadh, M.J., et al., *From protein to immunology: comprehensive insights into Marburg virus vaccines, mechanism, and application.* Archives of Microbiology, 2025. **207**(4): p. 1-35.
15. Bodmer, B.S., T. Hoenen, and L. Wendt, *Molecular insights into the Ebola virus life cycle.* Nature Microbiology, 2024. **9**(6): p. 1417-1426.
16. Laxmikeshav, K., P. Kumari, and N. Shankaraiah, *Expedition of sulfur-containing heterocyclic derivatives as cytotoxic agents in medicinal chemistry: A decade update.* Medicinal Research Reviews, 2022. **42**(1): p. 513-575.
17. Rahman, F.U., et al., *Thiourea Derivatives, Simple in Structure but Efficient Enzyme Inhibitors and Mercury Sensors.* Molecules, 2021. **26**(15): p. 4506.
18. Patil, M., et al., *New urea derivatives as potential antimicrobial agents: Synthesis, biological evaluation, and molecular docking studies.* Antibiotics, 2019. **8**(4): p. 178.

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

19. Khan, M., et al., *Syntheses, in vitro urease inhibitory activities of urea and thiourea derivatives of tryptamine, their molecular docking and cytotoxic studies.* Bioorganic Chemistry, 2019. **83**: p. 595-610.

20. Bielecki, J. and E. Lipiec, *Basis set dependence using DFT/B3LYP calculations to model the Raman spectrum of thymine.* Journal of Bioinformatics and Computational Biology, 2016. **14**(01): p. 1650002.

21. Kajal, A., et al., *Therapeutic potential of hydrazide as anti-inflammatory agents.* International journal of medicinal chemistry, 2014. **2014**.

22. Singh, S.K., D.L. Luisi, and R.H. Pak, *Antibody-drug conjugates: design, formulation and physicochemical stability.* Pharmaceutical research, 2015. **32**: p. 3541-3571.

23. Rao, P. and E.E. Knaus, *Evolution of nonsteroidal anti-inflammatory drugs (NSAIDs): cyclooxygenase (COX) inhibition and beyond.* Journal of pharmacy & pharmaceutical sciences, 2008. **11**(2): p. 81s-110s.

24. Mousa, T.H., Z.M.J. Al-Obaidi, and S.L. Alkhafaji, *Molecular docking studies and evaluation of the anti-inflammatory activity of ibuprofen-tranexamic acid codrug.* Latin American Journal of Pharmacy, 2021. **40**(special issue): p. 128-134.