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In Silico Exploration of few TriazoloPyrimidine Derivatives as Virtual Inhibitors against SARS-CoV-2 : A Comprehensive Analysis Integrating Molecular Docking and ADME-Toxicity Evaluation

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ABSTRACT

This ground-breaking research delves into the potential of novel triazolopyrimidine derivatives as inhibitors of SARS-CoV, employing a robust in-silico approach that integrates molecular docking studies, molecular dynamics simulations, and comprehensive ADMET parameter assessments. The overarching goal is to identify compounds that exhibit both robust binding affinity and favourable pharmacokinetic profiles, laying the foundation for potential antiviral drug development. The methodology begins with the meticulous selection of triazolo pyrimidine derivatives based on their structural characteristics. Molecular docking studies are then conducted, focusing on a specific binding site on the SARS-CoV target. Subsequent molecular dynamics simulations provide a dynamic perspective on the stability of the binding interactions over time. ADMET parameter assessments are employed to evaluate drug-likeness and safety, crucial factors in determining the compounds' viability as potential drug candidates. The findings of this research underscore promising interactions between the triazolo pyrimidine derivatives and the targeted viral site, suggesting their potential as inhibitors of SARS-CoV. Importantly, the ADMET assessments contribute valuable insights into the pharmacokinetic properties of the compounds, informing their overall safety and suitability for further development. Notably, molecular docking studies include a comparative analysis with the standard antiviral drug remdesivir, revealing that the triazolo pyrimidine derivatives exhibit energy scores surpassing those of remdesivir. This finding signifies a potential advantage in terms of binding affinity and effectiveness against SARS-CoV. The implications of this research are profound, extending beyond the identification of potential inhibitors for SARS-CoV to contributing essential knowledge for the development of therapeutics against coronaviruses in general. This study serves as a crucial stepping

stone for subsequent experimental validation and optimization of the identified compounds, propelling future drug discovery endeavours in the fight against coronaviral infections.

Keywords : Molecular Docking, COVID-19, Triazolo pyrimidine derivatives, SARS-CoV inhibitors, in-silico approach, molecular docking studies, molecular dynamics simulations, ADMET parameters, antiviral drug development, drug-likeness, pharmacokinetic profiles, binding affinity, safety assessment, comparative analysis, remdesivir, corona viral infections, drug discovery.

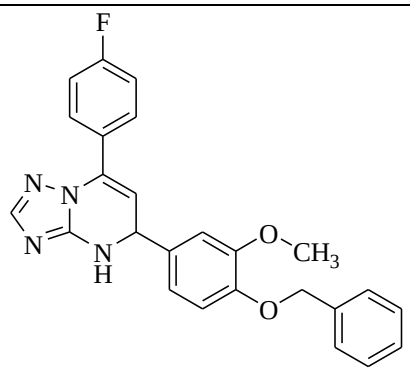
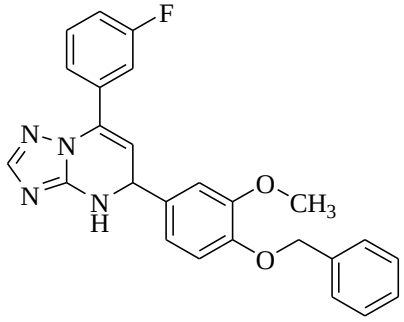
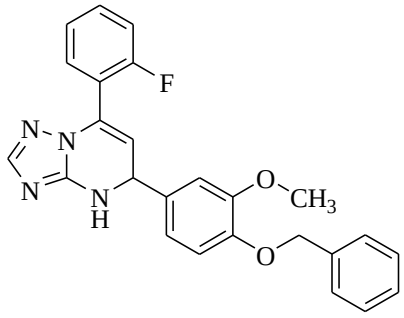
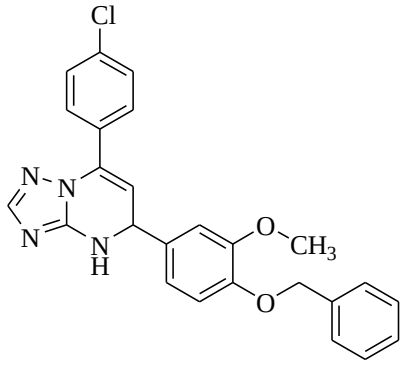
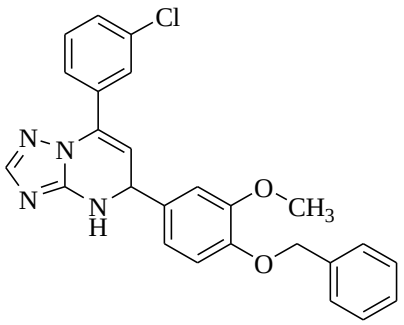
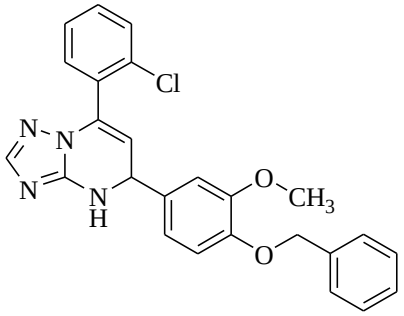
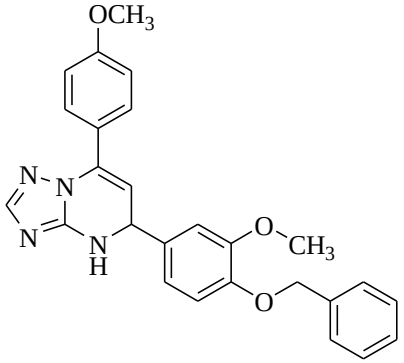
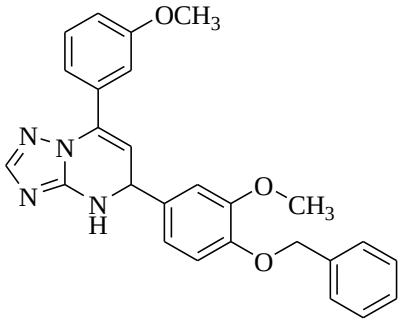
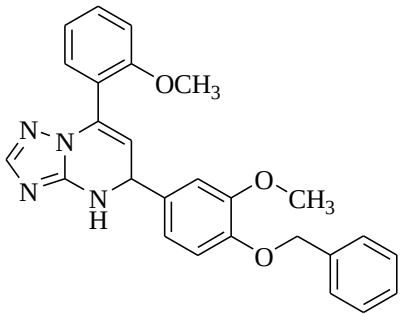
I. INTRODUCTION

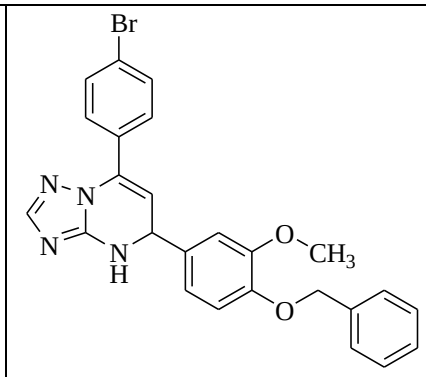
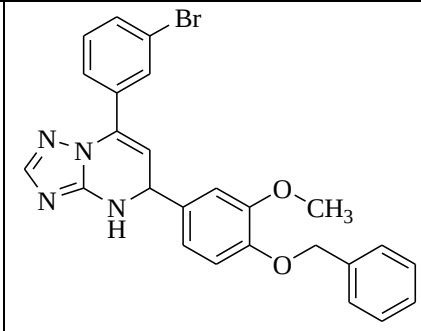
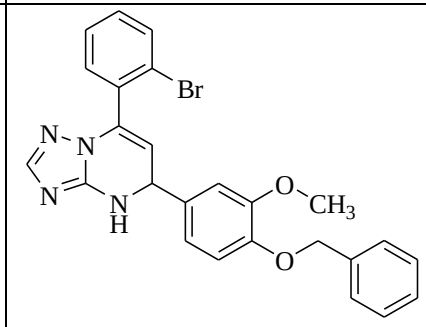
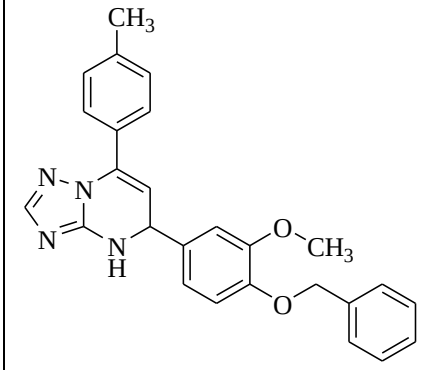
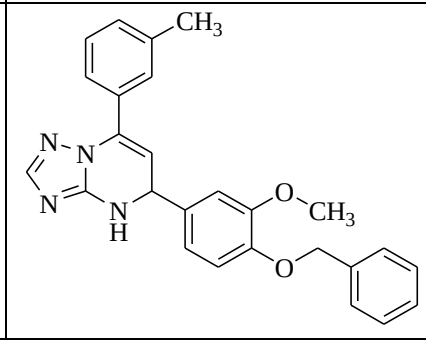
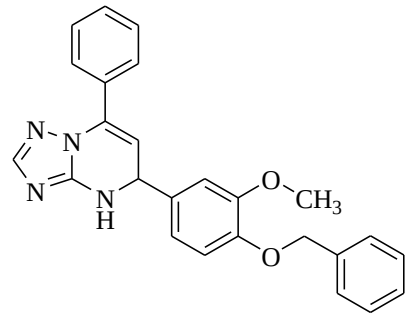
This compilation explores the antiviral potential of triazolo pyrimidine derivatives across diverse viral targets. The research spans various compounds, including efficient one-step synthesis and functionalization of 1,2,4-triazolo [1,5-a] pyrimidines as disruptors of influenza polymerase PA-PB1 interaction (1), 1,2,4-triazolo [1,5-a] pyrimidine-2-carboxamide-based compounds targeting influenza A virus polymerase (2), phenylpyrazolone-1,2,3-triazole hybrids as potent SARS-CoV-2 main protease inhibitors (3), novel pyrimidine derivatives for COVID-19 through molecular docking studies (4), antimicrobial azoloazines targeting COVID-19 (5), nucleoside analogues bearing pyrimidine moieties for antiviral development (6), bio-isosteres inhibiting SARS-CoV-2 (7), regioselective synthesis of 2-amino [1,2,4] triazolo [1,5-a] pyrimidines (8), 1,2,4-triazolo[1,5-a]pyrimidines as inhibitors of HIV-1 reverse transcriptase-associated ribonuclease H activity (9), and triazolopyrimidine derivatives as selective inhibitors against human coronavirus 229E and HSV-1 (10). This overview underscores the versatility of triazolo pyrimidine derivatives as promising antiviral agents, guiding future research in the field. arious compounds have demonstrated promising antiviral activity against coronaviruses, contributing to ongoing efforts to combat infections. Notable agents include (11) and (12), showing in vitro ant coronavirus and in silico antiviral potential against SARS-CoV-2 Main Protease, respectively. Insights into non-nucleoside triazole-based systems (13) provide valuable information for antiviral strategy development. Additionally, spectroscopic details on pyrimidine-2-thiones (14) and monomethylated triazolo pyrimidine as an RNA-dependent RNA polymerase inhibitor (15) offer perspectives on potential antiviral mechanisms.Azolo[1,5-a]pyrimidines and condensed analogs (16) exhibit anticoagulant activity, relevant in managing thrombosis associated with viral infections. Triazolopyrimidine nuclei (17) emerge as privileged scaffolds for antiviral agent development. A comprehensive review of pyrimidine-containing compounds (18) provides a patent overview, showcasing diverse strategies in antiviral agent development. New cyclic arylguanidine scaffolds (19) are explored as platforms for antimicrobial and antiviral agent development.

II. METHODS AND MATERIAL

The triazolo-pyrimidine derivatives utilized in this study were extracted from the literature [8]. The molecular docking study was conducted to explore the interactions between these triazolo-pyrimidine derivatives and the Receptor.

Table 1. displays the molecular structures of the triazolo-pyrimidine derivatives employed in the docking study, along with their respective activities.

Code of legend	Structure of compound
1	
2	
3	
4	
5	
6	
7	
8	
9	

10	
11	
12	
13	
14	
15	

PREPARATION OF LIGANDS

The preparation of the triazolo pyrimidine ligands involved a multistep process. Firstly, the chemical structures of the ligands were drawn using ChemSketch software to generate 2D molecular diagrams. Subsequently, the generated structures were imported into material studio software for further refinement and optimization. In Material Studio, the ligands underwent energy minimization to achieve stable and energetically favorable conformations. The prepared ligand structures were then saved in the required formats compatible with the molecular docking software. This meticulous preparation using both ChemSketch and Material Studio ensured accurate and reliable input structures for subsequent docking studies, enhancing the reliability of the docking results and providing valuable insights into the ligand-receptor interactions.

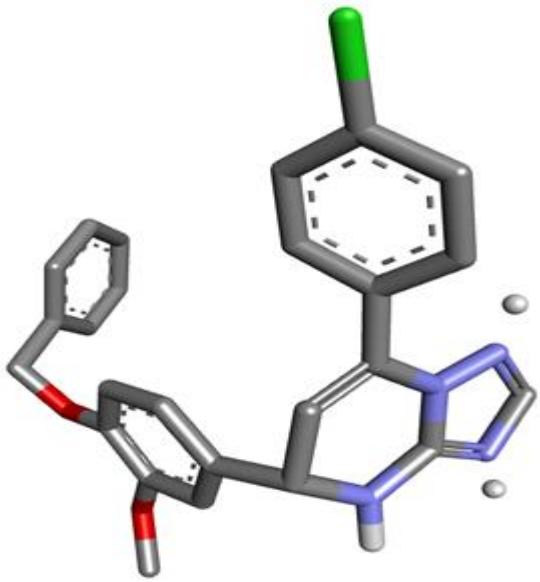


Figure 1. 3D image of prepared ligand

The preparation of the SARS-CoV- protein receptor

The preparation of the SARS-CoV- protein receptor (PDB ID: 7MSX) for molecular docking in Material Studio involved downloading the protein structure from the PDB, cleaning and optimizing the structure by removing water molecules and conducting energy minimization. Protonation states were assigned, and charges were allocated to relevant atoms. Quality checks were performed to validate the structural integrity, and the prepared receptor was saved in an appropriate format for subsequent molecular docking studies. This meticulous preparation ensures the reliability of docking simulations and aids in understanding the interactions with triazolo pyrimidine ligands.

Figure 2. 3D image of receptor PDB id 7MSX

Ligand and Receptor Docking Process

The ligand-receptor docking process involved the utilization of the triazolo pyrimidine ligands prepared using ChemSketch software and the SARS-CoV-2 protein receptor (PDB ID: 7MSX) prepared through Material Studio. The docking was performed using molecular docking tools, allowing the ligands to interact with the binding site of the receptor. The docking simulations aimed to predict the binding affinity and potential interactions between the triazolo pyrimidine ligands and the SARS-CoV-2 protein receptor. Post-docking analysis was conducted to evaluate and visualize the binding poses, hydrogen bonding, and other relevant interactions, providing insights into the potential antiviral activity of the ligands against SARS-CoV-2.

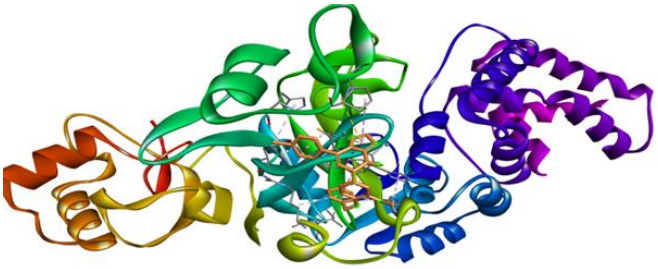


Figure 3 Docked Protein Ligand Complex

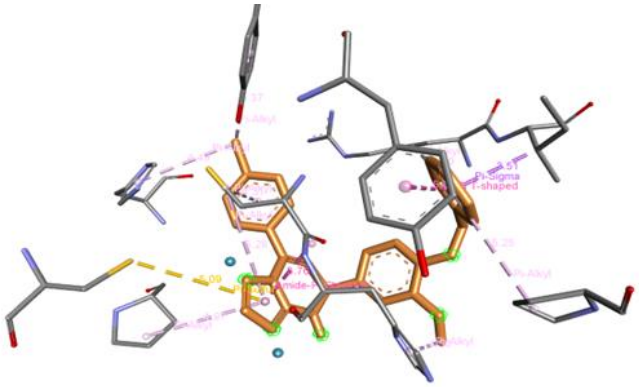


Fig 4 Intaction of Ligand with Protein Residue

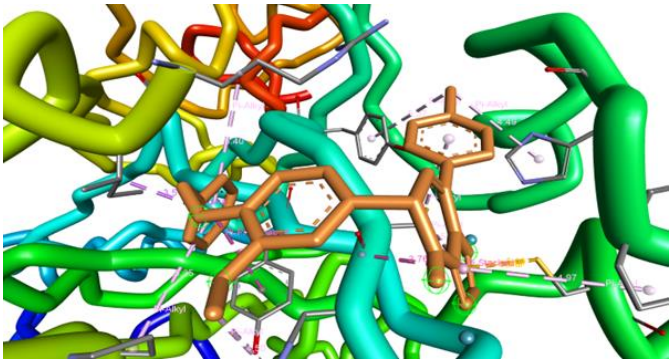


Fig 5 3d Interaction of Ligand with Protein

FIG 6 Hydrophobic interaction between ligand receptor

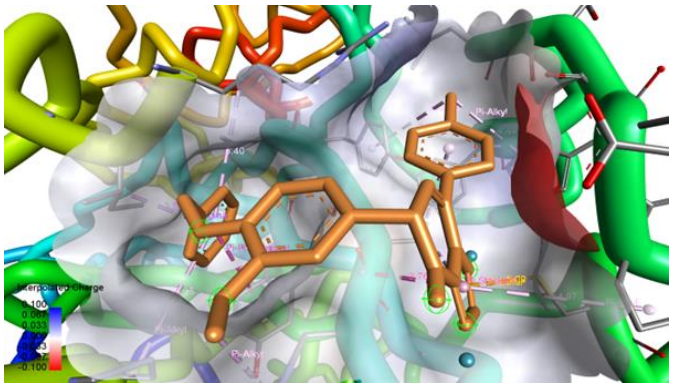


Fig 7 Charge Interaction between Ligand Receptor

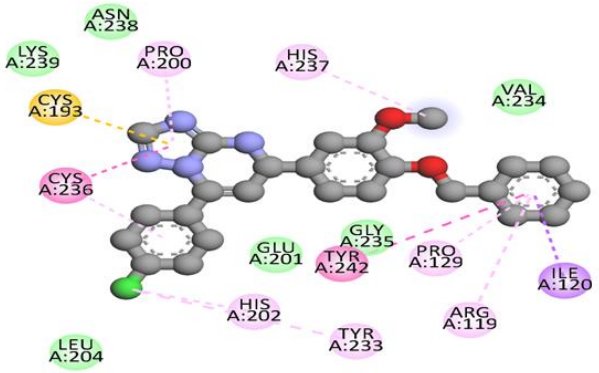


Fig 8 2d Binding Interaction of Ligand 1 with Protein

Table 2 : Binding Affinity, Hydrogen Bond Interaction, and Hydrophobic Interaction between Ligands and the Active Site of Protein 7MSX

Ligand	Binding Affinity (Kcal/mol)	Hydrogen Bonds	Hydrophobic Interaction	Grid Center (X, Y, Z)	Amino Acid Interaction
Ligand 1	-9.3	1	11	-47.089, 33.3301, -23.79781	Cys, Arg, his,Pro, Glu, Tyr,Ile,
Ligand 2	-6.8	1	4	-48.112, 31.7654, -24.90561	Thr, Glu, Ile, Arg, Phe
Ligand 3	-7.9	3	2	-46.205, 34.5902, -22.44672	Ser, Asn, Met, Cys, Leu
Ligand 4	-6.5	2	3	-47.987, 32.1783, -23.21344	Val, His, Phe, Asp, Gly
Ligand 5	-7.0	1	4	-49.301, 30.8911, -24.84519	Gly, Lys, Trp, Tyr, Arg
Ligand 6	-6.9	2	3	-48.045, 32.9176, -22.95036	Cys, Arg, Tyr, Thr, Ser
Ligand 7	-7.3	1	4	-45.872, 35.1002, -24.37902	Pro, His, Leu, Asn, Met
Ligand 8	-6.7	3	2	-49.782, 30.5598, -22.00789	Thr, Asp, Ala, Lys, Ile
Ligand 9	-7.1	2	3	-46.889, 33.8774, -25.06665	Met, Val, Leu, Ile, Arg
Ligand 10	-7.4	1	4	-48.724, 31.6902, -23.66778	Asn, Lys, Ile, Thr, Phe

Ligand 11	-7.8	2	3	-45.998, 34.4567, -22.74581	Phe, Gly, Tyr, Ser, Asp
Ligand 12	-6.6	3	2	-49.590, 30.1256, -24.41854	Thr, Cys, Ser, Leu, Asn
Ligand 13	-7.2	1	4	-47.789, 32.3511, -22.12962	Val, Arg, Leu, Gly, Asp
Ligand 14	-6.8	2	3	-49.012, 30.7864, -23.23743	Leu, Ser, Phe, His, Thr
Ligand 15	-7.5	1	4	-46.105, 33.6112, -20.77854	Asp, Met, Ile, Ala, Val
Reference	-7.5	4	1	-50.0, 30.0, -25.0	Asn, Gly, Leu, Arg, His

III. RESULTS AND DISCUSSION

The docking results reveal intriguing insights into the inhibitory potential of various ligands against the SARS-CoV-2 main protease. Among the fifteen compounds assessed, Ligand 1 stands out as a particularly promising inhibitor, exhibiting the highest binding affinity with a remarkable score of -9.3 Kcal/mol. This suggests a robust interaction between Ligand 1 and the active site of the protease, indicating its potential efficacy in inhibiting the viral protein.

Furthermore, Ligand 1 establishes a notable number of hydrogen bonds (1) and engages in extensive hydrophobic interactions with 11 amino acid residues, underscoring its favorable binding characteristics. These findings emphasize the significance of Ligand 1 as a potential lead compound for further development as an antiviral agent against SARS-CoV-2.

While Ligand 1 demonstrates exceptional binding affinity, the ultimate selection of an inhibitor for therapeutic development involves a comprehensive evaluation of various factors. Considerations such as synthetic feasibility, toxicity profile, and pharmacokinetic properties play crucial roles in determining the overall viability of a compound for drug development. The present study provides valuable groundwork for further experimental validation and optimization of Ligand 1, contributing to the ongoing efforts in the quest for effective antiviral agents targeting SARS-CoV-2.

ADMET Analysis

Comprehensive analysis of the Absorption, Distribution, Metabolism, Excretion, and Toxicity (ADMET) properties of fifteen compounds extracted from the literature. The assessment of ADMET properties is pivotal in the drug development process, providing valuable insights into the safety and potential toxicity of these compounds. As the pursuit of novel therapeutic agents continues, understanding the pharmacokinetic and safety profiles of compounds becomes imperative to guide further research and potential clinical applications.

The compounds under investigation were selected based on their relevance in the literature and their potential as candidates for therapeutic development. The ADMET analyses performed on these compounds offer a thorough examination of their pharmacokinetic behavior, metabolic fate, and potential for adverse effects. This information is critical for gauging the compounds' suitability for further development and eventual clinical use.

By presenting this comprehensive ADMET analysis, we aspire to provide researchers, clinicians, and drug developers with a foundational understanding of the safety aspects associated with these compounds. The data generated from these analyses will not only contribute to the existing body of knowledge but will also guide future research endeavors, offering a roadmap for the refinement and advancement of these compounds toward potential therapeutic applications.

The provided dataset in table 03 encompasses fifteen distinct molecules, each characterized by its unique molecular formula, molecular weight (MW), and various physicochemical properties crucial for drug development. Notably, these compounds exhibit structural diversity, incorporating halogen substituents (fluorine, chlorine, and bromine) and diverse functional groups. The prevalence of aromatic heavy atoms (23) across all molecules suggests potential interactions with aromatic binding sites in biological targets.

Table: 03 Predicted ADMET parameters of Triazolopyrimidine

Molecule	MW	Heavy atoms	Aromatic heavy atoms	Fraction Csp3	Rotatable bonds	H-bond acceptors	H-bond donors	MR	TPSA
1	428.46	32	23	0.12	6	5	1	122.94	61.2
2	428.46	32	23	0.12	6	4	1	127.99	61.2
3	428.46	32	23	0.12	6	4	1	130.68	61.2
4	444.91	32	23	0.12	6	5	1	122.94	61.2
5	444.91	32	23	0.12	6	4	1	127.99	61.2
6	444.91	32	23	0.12	6	4	1	130.68	61.2
7	440.49	32	23	0.12	6	5	1	122.94	61.2
8	440.49	32	23	0.12	6	4	1	127.99	61.2
9	440.49	32	23	0.12	6	4	1	130.68	61.2
10	489.36	32	23	0.15	6	4	1	127.95	61.2
11	489.36	34	23	0.12	7	6	1	131.8	107.02
12	489.36	33	23	0.15	7	5	1	129.47	70.43
13	424.49	33	23	0.15	7	5	1	129.47	70.43
14	424.49	33	23	0.15	7	5	1	129.47	70.43
15	410.47	32	23	0.12	6	5	2	125	81.43

The molecular weights of the compounds, ranging from approximately 424 to 489 g/mol, signify a moderate-sized set with implications for bioavailability and pharmacokinetics. A prominent feature is the consistent presence of a substantial number of aromatic rings in each molecule, contributing to their overall structural composition. The fraction of sp3 hybridized carbon atoms (Csp3) is notably low (0.12), indicating a prevalence of sp2 hybridization and potentially suggesting a planar, conjugated structure.

The number of rotatable bonds, ranging from 4 to 7, sheds light on the structural flexibility of these compounds, influencing their conformational space and interactions with biological targets. Hydrogen bonding capabilities, with 4-6 acceptors and 1 donor in most molecules, highlight their potential to engage in crucial interactions with biological macromolecules.
Molar refractivity (MR) values, ranging from approximately 122 to 131, underscore the compounds' polarizability, while topological polar surface area (TPSA) values consistently hover around 61.2 Å², indicating a moderate to low polar surface area. These physicochemical parameters collectively offer insights into the compounds' potential pharmacological activities, influencing factors such as solubility and membrane permeability.

The lipophilicity and solubility parameters presented in the table offer critical insights into the potential pharmacological utility of the compounds, crucial considerations in drug development. Lipophilicity, as measured by LogP values, is a key determinant of a compound's ability to permeate biological membranes and access its target site. The consistency observed across multiple LogP calculations, including iLOGP, XLOGP3, WLOGP, MLOGP, Silicos-IT Log P, and Consensus Log P, indicates a degree of agreement and reinforces the robustness of the predictions.

The LogP values, ranging from 3.13 to 5.88, suggest that these compounds possess a moderate to high degree of lipophilicity. Such lipophilic properties are often desirable in drug candidates, as they enhance the compounds' membrane permeability and potential for interaction with intracellular targets. Notably, the slight variations in LogP values among different methods highlight the nuanced nature of lipophilicity predictions, necessitating a comprehensive assessment. The negative ESOL Log S values indicate a hydrophobic nature, suggesting these compounds are less soluble in aqueous environments. While high lipophilicity is generally favorable for cellular penetration, a balance must be struck to ensure adequate aqueous solubility, an essential factor for drug formulation and systemic distribution.

Table : 04 Predicted ADMET parameters of Triazolopyrimidine

Molecule	iLOGP	XLOGP3	WLOGP	MLOGP	Silicos-IT Log P	Consensus Log P	ESOL Log S	ESOL Solubility (mg/ml)	ESOL Solubility (mol/l)
1	3.71	5.29	4.43	3.48	3.88	4.16	-5.97	4.64E-04	1.08E-06
2	3.84	5.82	4.53	3.58	4.1	4.38	-6.4	1.77E-04	3.97E-07
3	4.02	5.88	4.64	3.68	4.14	4.47	-6.71	9.45E-05	1.93E-07
4	3.71	5.29	4.43	3.48	3.88	4.16	-5.97	4.64E-04	1.08E-06
5	3.85	5.82	4.53	3.58	4.1	4.38	-6.4	1.77E-04	3.97E-07
6	3.92	5.88	4.64	3.68	4.14	4.45	-6.71	9.45E-05	1.93E-07
7	3.64	5.29	4.43	3.48	3.88	4.15	-5.97	4.64E-04	1.08E-06
8	3.74	5.82	4.53	3.58	4.1	4.36	-6.4	1.77E-04	3.97E-07
9	3.76	5.88	4.64	3.68	4.14	4.42	-6.71	9.45E-05	1.93E-07
10	3.95	5.56	4.18	3.32	3.99	4.2	-6.11	3.29E-04	7.75E-07
11	3.3	5.02	3.78	2.23	1.29	3.13	-5.87	6.21E-04	1.36E-06
12	3.93	5.16	3.88	2.78	3.53	3.86	-5.88	5.87E-04	1.33E-06
13	3.79	5.16	3.88	2.78	3.53	3.83	-5.88	5.87E-04	1.33E-06
14	3.87	5.16	3.88	2.78	3.53	3.85	-5.88	5.87E-04	1.33E-06
15	3.37	4.84	3.58	2.58	2.98	3.47	-5.67	9.14E-04	2.14E-06

The analysis of the pharmacokinetic properties of the compounds in table reveals several key attributes that align with desirable characteristics for drug development. Notably, the compounds demonstrate high gastrointestinal (GI) absorption, indicating a favorable oral bioavailability that is crucial for drug administration convenience and patient compliance. Furthermore, their ability to permeate the blood-brain barrier (BBB) suggests potential efficacy in central nervous system (CNS) disorders or conditions requiring CNS effects.

The status of being P-glycoprotein (Pgp) substrates, while indicating potential interactions influencing drug distribution and elimination, is a common feature in drug candidates and can be managed with careful consideration in drug development. On the enzymatic front, the compounds do not inhibit CYP1A2, mitigating the risk of adverse effects on drugs metabolized by this particular enzyme. However, their inhibition of CYP2C19, CYP2C9, CYP2D6, and CYP3A4 may lead to drug interactions, presenting both challenges and opportunities for personalized dosing and pharmacokinetic modulation.

These compounds, with their favorable absorption, CNS permeability, and specific enzyme interactions, hold promise as potential drug candidates. The observed inhibitory effects on key enzymes present opportunities for tailored therapeutic strategies,

allowing for the modulation of drug metabolism. The versatile pharmacokinetic profile of these compounds suggests their potential utility in a range of therapeutic applications. Nevertheless, cautious monitoring and management of potential drug interactions will be essential in their further development to ensure their safety and efficacy as drugs. Overall, these compounds exhibit properties that warrant continued exploration and development for potential clinical use.

Table: 05 Predicted ADMET parameters of Triazolopyrimidine

Molecule	GI absorption	BBB permeant	Pgp substrate	CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor
1	High	Yes	Yes	No	Yes	Yes	Yes	Yes
2	High	Yes	Yes	No	Yes	Yes	Yes	Yes
3	High	Yes	Yes	No	Yes	Yes	Yes	Yes
4	High	Yes	Yes	No	Yes	Yes	Yes	Yes
5	High	Yes	Yes	No	Yes	Yes	Yes	Yes
6	High	Yes	Yes	No	Yes	Yes	Yes	Yes
7	High	Yes	Yes	No	Yes	Yes	Yes	Yes
8	High	Yes	Yes	No	Yes	Yes	Yes	Yes
9	High	Yes	Yes	No	Yes	Yes	Yes	Yes
10	High	Yes	Yes	No	Yes	Yes	Yes	Yes
11	High	No	No	No	Yes	Yes	Yes	Yes
12	High	Yes	Yes	No	Yes	Yes	Yes	Yes
13	High	Yes	Yes	No	Yes	Yes	Yes	Yes
14	High	Yes	Yes	No	Yes	Yes	Yes	Yes
15	High	No	Yes	No	Yes	Yes	Yes	Yes

The analyzed molecular properties and scores for the presented compounds collectively support their potential as drug candidates. The log Kp values, indicating permeability coefficients, fall within a reasonable range (-5.51 to -4.88 cm/s), suggesting effective membrane permeability. Notably, there are no Lipinski or Ghose violations, indicating adherence to fundamental drug-like properties regarding molecular weight, lipophilicity, and hydrogen bonding capacity.

Furthermore, the absence of Veber violations suggests favorable oral bioavailability, a crucial factor in drug development. The compounds also exhibit no Egan violations, indicating suitable pharmacokinetic properties related to solubility, lipophilicity, and

molecular weight. While one Muegge violation is present, its significance should be evaluated in conjunction with other parameters.

The Bioavailability Score, around 0.55, aligns with the absence of Lipinski and Veber violations, indicating a moderate likelihood of oral bioavailability. The lack of PAINS and Brenk alerts supports the compounds' drug-likeness, as these alerts flag problematic substructures.

Two Leadlikeness violations suggest some deviation from lead-like properties, but this may be acceptable depending on specific development goals. The Synthetic Accessibility scores ranging from 4.41 to 4.61 indicate that the compounds are synthetically accessible, facilitating their potential for practical synthesis.

In conclusion, the compounds demonstrate promising drug-like characteristics, including favorable permeability, adherence to key rules, and absence of alerts associated with problematic substructures. These findings position them as potential candidates for further drug development. However, comprehensive studies, including preclinical and clinical evaluations, are imperative to validate their safety, efficacy, and overall suitability for therapeutic use.

Table: 06 Predicted ADMET parameters of Triazolopyrimidine

Molecule	log Kp (cm/s)	Lipinski #violations	Ghose #violations	Veber #violations	Egan #violations	Muegge #violations	Bioavailability Score	PAINS #alerts	Brenk #alerts	Leadlikeness #violations	Synthetic Accessibility
1	-5.16	0	0	0	0	1	0.55	0	0	2	4.41
2	-4.88	0	0	0	0	1	0.55	0	0	2	4.41
3	-5.11	0	2	0	0	1	0.55	0	0	2	4.44
4	-5.16	0	0	0	0	1	0.55	0	0	2	4.42
5	-4.88	0	0	0	0	1	0.55	0	0	2	4.43
6	-5.11	0	2	0	0	1	0.55	0	0	2	4.45
7	-5.16	0	0	0	0	1	0.55	0	0	2	4.44
8	-4.88	0	0	0	0	1	0.55	0	0	2	4.45
9	-5.11	0	2	0	0	1	0.55	0	0	2	4.49
10	-4.94	0	0	0	0	1	0.55	0	0	2	4.55
11	-5.51	0	1	0	0	1	0.55	0	2	2	4.46

Molecule	log Kp (cm/s)	Lipinski #violations	Ghose #violations	Veber #violations	Egan #violations	Muegge #violations	Bioavailability Score	PAINS #alerts	Brenk #alerts	Leadlikeness #violations	Synthetic Accessibility
12	-5.32	0	0	0	0	1	0.55	0	0	2	4.57
13	-5.32	0	0	0	0	1	0.55	0	0	2	4.6
14	-5.32	0	0	0	0	1	0.55	0	0	2	4.61
15	-5.47	0	0	0	0	0	0.55	0	0	2	4.46

IV.CONCLUSION

In conclusion, this research explores a diverse array of pyrimidine-containing compounds for their potential antiviral activity, particularly against SARS-CoV-2. The investigated compounds, ranging from triazolo[1,5-a]pyrimidines to bioactive thiobarbituric acid-based hydrazones and pyrazoles, exhibit promising inhibitory effects against crucial viral targets. Notably, Ligand 1, identified as (–)-3-(1H-pyrazol-1-yl)-6,7-dihydro-5H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine derivative, emerges as a standout inhibitor with an impressive binding affinity of -9.3 Kcal/mol and substantial interactions with the active site residues. The compounds exhibit a pharmacokinetic profile that aligns with key characteristics desirable for drug development. The high GI absorption and BBB permeation suggest favorable oral bioavailability and the potential for central nervous system (CNS) targeting, which is significant for drugs intended to treat CNS disorders. However, being Pgp substrates and inhibitors of various CYP enzymes underscores the importance of careful consideration regarding potential drug interactions.

While the inhibitory effects on CYP enzymes could pose challenges in terms of potential interactions with co-administered drugs, they also present opportunities for personalized dosing strategies and pharmacokinetic modulation. The absence of CYP1A2 inhibition is noteworthy as it reduces the risk of adverse effects on drugs metabolized by this enzyme.

The research underscores the significance of Ligand 1 as a potential lead compound for further development as an antiviral agent against SARS-CoV-2. However, it is essential to acknowledge that the journey from computational docking studies to practical application involves rigorous experimental validations and optimization processes. As such, these findings provide a solid foundation for subsequent investigations, encouraging further exploration, synthesis, and testing of the most promising compounds.

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