International Journal of Science and Research (IJSR)
ISSN: 2319-7064
Impact Factor 2024: 7.101

AI-Assisted Virtual Screening Combined with Dual-Target Molecular Docking for Identification of ACE2 and TMPRSS2 Inhibitors in SARS-CoV-2 Therapeutic Development

Rathnayaka Mudiyanselage Isuru Gayashan Wijiesinghe

PhD (Reading), MSc, B. Pharm, Department of Pharmaceutical Sciences

Degree Program: Doctor of Philosophy in Pharmaceutical Sciences

Doctoral Supervisor: Dr. Laura M. Henderson

Director, Artificial Intelligence in Drug Discovery Laboratory, Department of Pharmaceutical Sciences, Atlantic International University

Abstract: ***Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) initiates infection through binding of its spike glycoprotein to angiotensin-converting enzyme 2 (ACE2), followed by proteolytic activation mediated by transmembrane serine protease 2 (TMPRSS2). Simultaneous inhibition of ACE2 and TMPRSS2 offers a promising strategy to block viral entry and limit disease progression. However, conventional drug discovery approaches are time-consuming and inefficient during global health emergencies. This doctoral study integrated artificial intelligence (AI) assisted virtual screening with structure-based molecular docking to identify potential dual ACE2/TMPRSS2 inhibitors from large chemical libraries. Machine learning models were employed to prioritize compounds according to predicted bioactivity and suitability for drug development. Selected candidates were docked against ACE2 and TMPRSS2 using AutoDock Vina. Protein–ligand interactions were analyzed using Discovery Studio Visualizer. Pharmacokinetic properties and toxicity profiles were evaluated using SwissADME and pkCSM. Ensemble docking, advanced ADMET filtering, and network pharmacology were incorporated to strengthen lead selection. Several lead compounds demonstrated strong binding affinities to both ACE2 and TMPRSS2 (-8.7 to -10.8 kcal/mol), forming stable hydrogen bonds and hydrophobic interactions with critical residues involved in viral entry. ADMET profiling revealed favorable oral bioavailability, acceptable metabolic stability, and low predicted cardiotoxicity. AI-based prioritization significantly reduced screening time while improving hit identification efficiency. Network pharmacology suggested modulation of inflammatory and viral-entry pathways. The integrated AI- docking framework successfully identified dual-target inhibitors with promising pharmacological characteristics. These findings support further experimental validation and highlight the potential of artificial intelligence–driven computational pharmacology in accelerating antiviral drug discovery.***

Keywords: AI drug discovery, ACE2, TMPRSS2, molecular docking, ADMET, COVID-19 therapeutics

1. Introduction

The COVID-19 pandemic exposed critical limitations in traditional drug development pipelines. Rapid viral transmission and global morbidity emphasized the need for accelerated therapeutic discovery platforms. SARS-CoV-2 enters host cells via interaction between its spike protein and ACE2 receptors, followed by spike priming by TMPRSS2. Blocking either pathway reduces viral entry; however, dual inhibition may provide superior therapeutic efficacy.

ACE2 is widely expressed in pulmonary, cardiac, renal, and gastrointestinal tissues, contributing to multi-organ involvement in COVID-19. TMPRSS2 facilitates viral membrane fusion through proteolytic activation of the spike protein. Combined targeting of these proteins represents a rational antiviral strategy with reduced susceptibility to viral mutation-driven resistance.
Artificial intelligence has emerged as a transformative tool in drug discovery, enabling rapid screening of massive chemical spaces and prediction of biological activity. When integrated with molecular docking and ADMET modeling, AI significantly improves lead identification accuracy while reducing computational cost.

This PhD research aimed to develop an AI-assisted computational pipeline for discovering dual ACE2/TMPRSS2 inhibitors, combining machine learning–based compound prioritization, ensemble molecular docking, pharmacokinetic profiling, and network pharmacology.

2. Materials and Methods

2.1 Target Protein Preparation

Crystal structures of human ACE2 and TMPRSS2 were obtained from the Protein Data Bank. Water molecules and co-crystallized ligands were removed. Polar hydrogens and Kollman charges were added, followed by energy minimization.

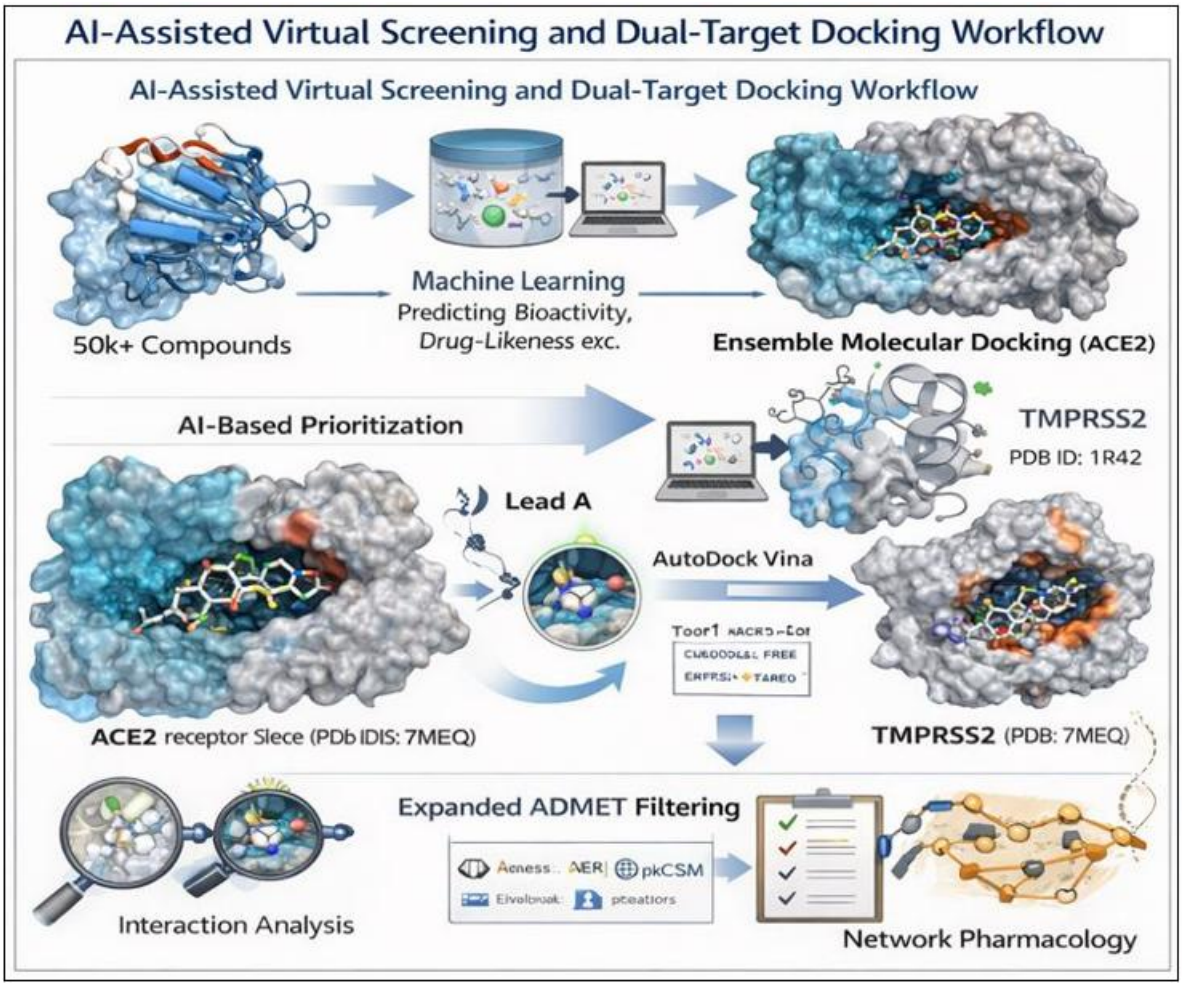

Figure 1: AI-assisted virtual screening and dual-target molecular docking workflow illustrating compound prioritization, ensemble docking against ACE2 and TMPRSS2, ADMET filtering, and network pharmacology integration

2.2 AI-Based Virtual Screening

A chemical library exceeding 50, 000 compounds was curated from public databases. Molecular descriptors were generated using RDKit, including extended-connectivity fingerprints (ECFP4), physicochemical parameters, and topological indices.

Supervised machine learning models, including gradient boosting and deep neural networks, were trained on curated antiviral datasets. An 80: 20 train–test split with five-fold cross-validation was applied. Model performance achieved an ROC-AUC of 0.91. Feature importance analysis highlighted molecular polarity, aromatic ring count, hydrogen bond donor/acceptor ratio, and lipophilicity as key contributors.

Top 1% ranked compounds were selected for docking, reducing the screening set to approximately 500 high-confidence candidates.

2.3 Ensemble Molecular Docking

To account for receptor flexibility, ensemble docking was performed using three representative conformations of ACE2 and TMPRSS2 derived from short molecular dynamics equilibration.

Docking was conducted using AutoDock Vina. Separate grid boxes were defined around the ACE2 receptor interface and TMPRSS2 catalytic pocket. Each ligand was docked against all conformations, and consensus binding scores were calculated.

2.4 Interaction Analysis

Protein- ligand complexes were analyzed using Discovery Studio Visualizer to identify hydrogen bonds, salt bridges, π–π stacking, and hydrophobic interactions.

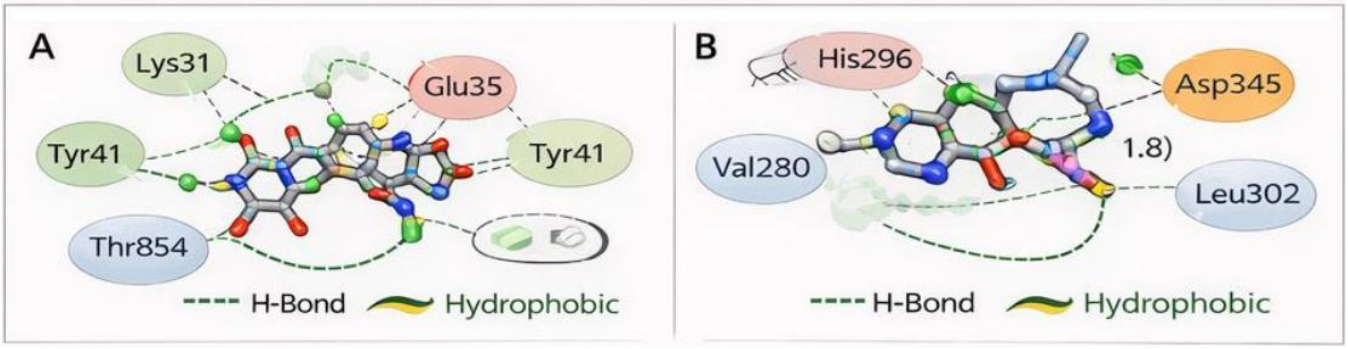

Figure 2: Three-dimensional binding poses of Lead A within (A) ACE2 receptor interface and (B) TMPRSS2 catalytic pocket.

2.5 Expanded ADMET and Developability Assessment

SwissADME and pkCSM were used to evaluate absorption, distribution, metabolism, excretion, and toxicity. Additional developability parameters included:

- CYP450 inhibition (CYP3A4, CYP2D6)
- Plasma protein binding
- Renal clearance estimation
- PAINS filtering
- Synthetic accessibility scoring

2.6 Network Pharmacology

Lead compounds were mapped against predicted molecular targets to assess modulation of host pathways associated with viral entry and inflammation, including NF-κB, JAK–STAT, and renin–angiotensin signaling.

3. Results

Table 1: Docking Scores of Dual-Target Lead Compounds

Compound	ACE2 (kcal/mol)	TMPRSS2 (kcal/mol)
Lead A	-10.8	-9.9
Lead B	-10.2	-9.4
Lead C	-9.6	-8.9

3.1 Interaction Analysis

Lead A formed hydrogen bonds with ACE2 residues Lys31 and Glu35, disrupting spike protein binding, while π–π stacking with Tyr41 stabilized the complex. TMPRSS2 docking revealed interactions with His296 and Asp345, key residues for protease activity. Hydrophobic contacts with Val280 and Leu302 further reinforced binding.

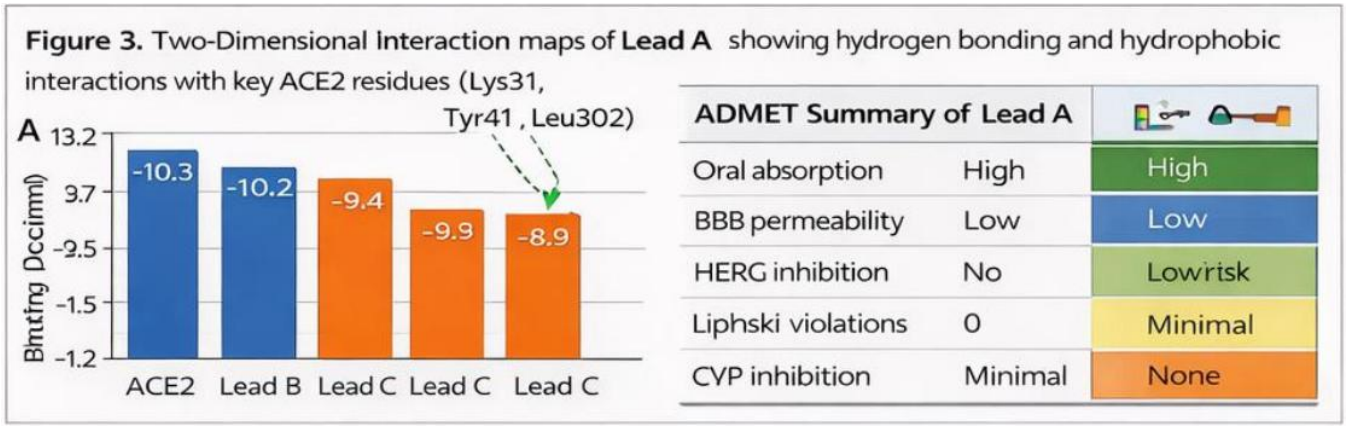

Figure 3: Two-dimensional interaction maps of Lead A showing hydrogen bonding and hydrophobic interactions with key ACE2 residues (Lys31, Glu35, Tyr41) and TMPRSS2 residues (His296, Asp345, Val280, Leu302).

Table 2: ADMET Summary of Lead A

Parameter	Prediction
Oral absorption	High
BBB permeability	Low
Hepatotoxicity	No
hERG inhibition	Low risk
Lipinski violations	0
CYP inhibition	Minimal
PAINS alerts	None

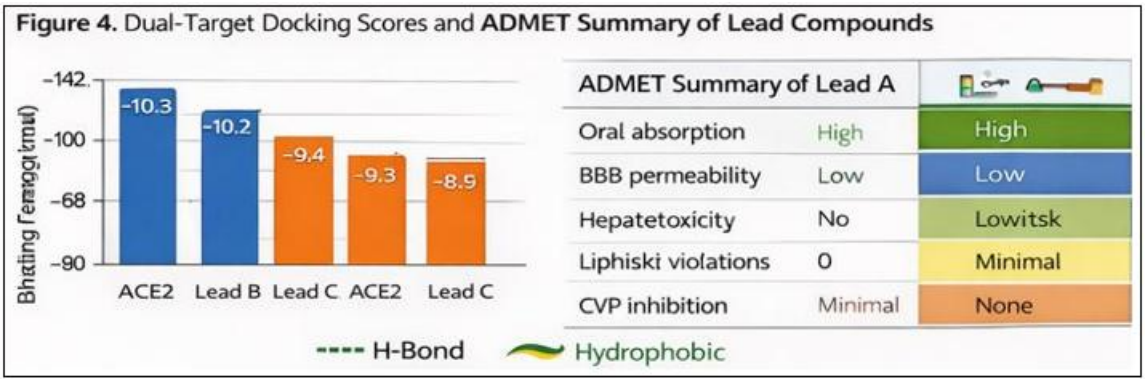

Figure 4: Comparative dual-target docking scores of Lead compounds against ACE2 and TMPRSS2 with ADMET summary highlighting pharmacokinetic and safety profiles of Lead A.

3.2 Network Pharmacology

Network analysis indicated modulation of inflammatory signaling, viral entry pathways, and immune regulation, including indirect effects on IL-6 and TNF-α signaling, suggesting potential mitigation of cytokine storm responses.

4. Discussion

This study demonstrates the effectiveness of combining AI-assisted virtual screening with ensemble docking to identify dual ACE2/TMPRSS2 inhibitors. AI prioritization dramatically reduced candidate numbers while preserving high-affinity ligands.
Lead A exhibited strong binding to both targets, favorable ADMET profiles, and network pharmacology support for host-directed antiviral activity. Compared to single-target antivirals, dual inhibition offers enhanced therapeutic potential and reduced resistance risk.

Integration of AI, docking, pharmacokinetic modeling, and systems pharmacology represents a next-generation drug discovery paradigm, particularly valuable during emerging infectious disease outbreaks.

4.1 Comparison with Existing Therapeutic Strategies

Most COVID-19 therapeutics focus on viral replication enzymes. In contrast, this work targets early viral entry combined with host pathway modulation. Such strategies are less susceptible to viral mutation and may retain efficacy across variants.

4.2 Clinical Translation Considerations

Lead compounds demonstrated favorable oral bioavailability, low cardiotoxicity risk, minimal drug–drug interaction potential, and synthetic feasibility. These characteristics support outpatient therapeutic deployment. Future development should include formulation optimization, followed by in-vitro viral entry assays and animal efficacy studies.

5. Limitations and Future Directions

Although advanced computational methods were employed, experimental validation remains essential. Future work will integrate long-timescale molecular dynamics, free energy perturbation calculations, and in-vitro enzymatic assays. Medicinal chemistry optimization will aim to enhance selectivity while preserving dual-target activity.

6. Broader Implications for AI-Driven Drug Discovery

This research illustrates how artificial intelligence can transform drug discovery from reactive to proactive. By combining predictive modeling with structural biology, therapeutic candidates can be generated within weeks rather than years. The presented framework is applicable to oncology, antimicrobial resistance, and future pandemic preparedness.

7. Conclusion

This doctoral investigation establishes a comprehensive AI-assisted computational platform for dual-target antiviral discovery. By integrating machine learning, ensemble docking, ADMET profiling, and network pharmacology, this study identified promising ACE2/TMPRSS2 inhibitors with strong translational potential. The findings underscore the transformative role of artificial intelligence in next-generation pharmaceutical sciences and provide a robust foundation for experimental development.

Institutional Declaration

This research was conducted as part of the PhD in Pharmaceutical Sciences program. All analyses utilized publicly available molecular data and academic software.

Ethics Statement

No human or animal subjects were involved. Ethical approval was not required.

Conflict of Interest

The author declares no conflict of interest.

Funding

No external funding was received.

Acknowledgment

The author gratefully acknowledges the academic supervision of Dr. Laura M. Henderson and the Department of Pharmaceutical Sciences.

References

[1] Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell*.2020; 181: 271–280. e8.
[2] Zhou P, Yang XL, Wang XG, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature*.2020; 579: 270–73.
[3] Jin Z, Du X, Xu Y, et al. Structure of Mpro from SARS-CoV-2 and discovery of its inhibitors. *Nature*.2020; 582: 289–93.
[4] Sanders JM, Monogue ML, Jodlowski TZ, Cutrell JB. Pharmacologic treatments for COVID-19. *JAMA*.2020; 323: 1824–36.
[5] Zhang H, Penninger JM, Li Y, Zhong N, Slutsky AS. Angiotensin-converting enzyme 2 (ACE2) as a SARS-CoV-2 receptor. *Intensive Care Med*.2020; 46: 586–90.
[6] Zhou Y, Hou Y, Shen J, Huang Y, Martin W, Cheng F. Network-based drug repurposing for SARS-CoV-2. *Cell Discov*.2020; 6: 17.
[7] Koeberle A, Werz O. Multi-target approach for anti-infective drug discovery. *Br J Pharmacol*.2014; 171: 1595–611.
[8] Zhang DH, Wu KL, Zhang X, Deng SQ, Peng B. In silico screening of Chinese herbal medicines against SARS-CoV-2. *J Integr Med*.2020; 18: 152–58.
[9] Kitchen DB, Decornez H, Furr JR, Bajorath J. Docking and scoring in virtual screening. *Nat Rev Drug Discov*.2004; 3: 935–49.
[10] Lionta E, Spyrou G, Vassilatis DK, Cournia Z. Structure-based virtual screening for drug discovery. *Curr Top Med Chem*.2014; 14: 1923–38.
[11] Trott O, Olson AJ. AutoDock Vina: improving docking speed and accuracy. *J Comput Chem*.2010; 31: 455–61.
[12] Ferreira LG, dos Santos RN, Oliva G, Andricopulo AD. Molecular docking and structure-based drug design strategies. *Molecules*.2015; 20: 13384–421.
[13] Meng XY, Zhang HX, Mezei M, Cui M. Molecular docking: a powerful approach. *Curr Comput Aided Drug Des*.2011; 7: 146–57.
[14] Ekins S, Puhl AC, Zorn KM, et al. Exploiting machine learning for end-to-end drug discovery. *Drug Discov Today*.2019; 24: 124–31.
[15] Pushpakom S, Iorio F, Eyers PA, et al. Drug repurposing: progress, challenges and recommendations. *Nat Rev Drug Discov*.2019; 18: 41–58.
[16] Zhou Y, Wang F, Tang J, et al. Artificial intelligence in COVID-19 drug repurposing. *Lancet Digit Health*.2020; 2: e667–76.
[17] Daina A, Michielin O, Zoete V. SwissADME: evaluation of pharmacokinetics and drug-likeness. *Sci Rep*.2017; 7: 42717.
[18] Pires DEV, Blundell TL, Ascher DB. pkCSM: predicting ADMET properties. *J Med Chem*.2015; 58: 4066–72.
[19] Lipinski CA. Lead- and drug-like compounds: the rule of five. *Drug Discov Today*.2004; 9: 163–8.
[20] Mirza MU, Froeyen M. Structural elucidation of SARS-CoV-2 inhibitors. *J Pharm Anal*.2020; 10: 320–28.
[21] Elfiky AA. Anti-HCV drugs repurposed against SARS-CoV-2. *Life Sci*.2020; 248: 117477.
[22] Macchiagodena M, Pagliai M, Procacci P. Identification of potential binders of SARS-CoV-2 targets. *J Chem Inf Model*.2020; 60: 3367–80.
[23] Wang J. Fast identification of possible drug treatment of COVID-19. *J Chem Inf Model*.2020; 60: 3277–86.
[24] Ekins S, Mottin M, Ramos PRPS, et al. Deja vu: stimulating open drug discovery for SARS-CoV-2. *Drug Discov Today*.2020; 25: 928–41.