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ENGINEERING AND TECHNOLOGY
COLLOQUIUM



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PREFACE

Welcome to the 2nd International Science, Engineering and Technology Colloquium 2025 (ISETC 2025)!

It is with great pleasure that we present this year's colloquium, a distinguished gathering of scholars, researchers, and professionals dedicated to the advancement of applied sciences. Held virtually on 9th July 2025, ISETC 2025 serves as a platform to highlight cutting-edge research, foster meaningful networking, encourage collaborations, and explore innovative solutions to global challenges.

This year's theme, "The Power of Scientific Innovation: Intelligent Solutions for a Sustainable World" highlights our shared goal to solve global challenges through applied science. It celebrates innovation as a key to building a more sustainable and resilient future. We're proud to feature keynote speakers and presenters who bring fresh insights, bold ideas, and breakthroughs shaping tomorrow's world.

We would like to extend our heartfelt appreciation to the Faculty of Applied Sciences, Universiti Teknologi MARA, Perak Branch, Tapah Campus, for their outstanding support and assistance throughout the planning and execution of the event. Their dedication has been instrumental to the success of this colloquium. We would like to sincerely thank all participants and researchers for their valuable contributions. We also appreciate the reviewers for their careful evaluations and helpful feedback. Your hard work and support mean a lot to us.

As editors, we are proud to present this collection of proceedings. It is an honour to bring together the interesting and meaningful work of our speakers and authors. We hope the ideas shared will lead to new discoveries, encourage more research, and help solve global challenges through science and innovation.

Warm regards,

Dr. Emi Norzehan Mohamad Mahbob

Dr. Saiyidah Nafisah Hashim

Ms. Lili Widarti Zainuddin

Ms. Nurul Nazwa Mohammad

Ms. Rozaina Saleh

ISETC 2025 Proceedings Editors

EXPLORATION OF HETEROCYCLIC LIGANDS BINDING TO THE RBD-ANGIOTENSIN INTERFACE IN THE SARS-CoV-2 OMICRON VARIANT: A COMPUTATIONAL STUDY

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Abstract: Introduction. The SARS-CoV-2 Omicron variant, characterized by a multitude of mutations within its receptor-binding domain (RBD), demonstrates an augmented affinity for the human ACE2 receptor, thereby enhancing its infectivity and capacity for immune evasion. This investigation explores the efficacy of heterocyclic compounds to impede the RBD-ACE2 interaction through a high-throughput blind docking methodology. **Method.** A comprehensive total of 63 heterocyclic ligands were subjected to docking against the Omicron RBD employing AutoDock, with 5,000 iterations conducted for each compound. Five pivotal binding regions—Mpocket, Apocket, and the accessory binding sites ABS-1, ABS-2, and ABS-3—were delineated and assessed in relation to binding free energy and docking frequency. **Result.** Mpocket exhibited the most advantageous binding profile, characterized by the lowest average binding energy (-4.00 kcal/mol) and a high docking frequency (27.85%). ABS-1 further demonstrated significant accessibility (33.78% of total runs). Compounds such as Phenoxazole (FEB = -6.41 kcal/mol), Acridine (FEB = -5.94 kcal/mol), and Phenazine (FEB = -5.67 kcal/mol) revealed pronounced binding affinities and consistent interactions, particularly with the residues SER 496 and ARG 403. Two-dimensional (2D) and three-dimensional (3D) interaction analyses supported the structural compatibility of these ligands with Mpocket, while ABS-2 surfaced as a promising secondary binding site due to its elevated ligand accessibility. **Conclusion.** These outcomes endorse the potential of heterocyclic scaffolds as inhibitors aimed at the RBD-ACE2 interface binding sites.

Keywords: *Heterocyclic compounds, molecular docking, Omicron variant, receptor binding domain (RBD), SARS-CoV-2*

INTRODUCTION

The COVID-19 pandemic, instigated by the SARS-CoV-2 virus, has been described by the emergence of numerous variants of concern (VOCs), each exhibiting mutations that affect viral infectivity, immune evasion, and resistance to therapeutics (Aleem et al., 2021; Tay et al., 2021). Jawad et al. (2022) executed molecular dynamics simulations to examine the influence of Omicron-specific mutations on the RBD-ACE2 interaction (Jawad et al., 2022). Their results elucidated that the Omicron RBD exhibits a greater binding affinity to ACE2 compared to the wild-type strain, predominantly due to augmented electrostatic interactions introduced by mutations such as Q493R, Q498R, and N501Y (Jawad et al., 2022; Kim et al., 2022). These mutations establish new salt bridges with ACE2, thereby enhancing binding affinity and potentially contributing to the increased transmissibility of the variant. While certain mutations (e.g., K417N, G446S) diminish binding, others compensate by fortifying the interaction, culminating in a net enhancement of binding stability (Bate et al., 2022).

MATERIALS AND METHODS

The crystal structures corresponding to the Cryo-EM structure of the SARS-CoV-2 Omicron spike protein (PDB = 7T9J) were systematically downloaded and formatted into PDBQT format for subsequent analyses. Subsequently, the structures of 63 heterocycles were meticulously designed using Marvin Sketch 24.3.0 and also prepared in PDBQT format. The grid parameters for the receptor-binding domain (RBD) were established at coordinates 201.026, 174.545, 269.71 (x,y,z), with a grid box dimension of 86 x 126 x 84. The docking free energy binding (FEB) values were quantified in kcal/mol. The docking run yielding the lowest binding free energy from AutoDock® was selected and

preserved as PDB files. BIOVA Discovery Studio was employed for the visualization of 2D binding interactions, whereas PyMol version 2.5.2 facilitated the three-dimensional visualization of ligand-receptor interactions.

RESULTS AND DISCUSSION

Potential Binding Sites on the Receptor-Binding Domain

Among the identified sites, Mpocket demonstrated the most favorable binding characteristics, with the lowest average binding energy of -4.00 kcal/mol and a high clustering frequency (27.85%), suggesting a strong and consistent ligand affinity. This indicates that Mpocket may serve as a highly promising target site for ligand binding, potentially interfering with the RBD-ACE2 interaction critical for viral entry. ABS-1 also emerged as a significant binding region, accounting for the highest percentage of total docking runs (33.78%), despite a slightly less favorable binding energy (-3.57 kcal/mol) compared to Mpocket. This high frequency suggests that ABS-1 is a highly accessible and frequently targeted site during docking simulations, which may reflect its structural exposure or favorable geometry for ligand accommodation. ABS-3 showed a moderate binding profile with an average energy of -3.79 kcal/mol and 9.60% of total runs, indicating a secondary but potentially relevant binding site. In contrast, ABS-2 and Apocket exhibited lower docking frequencies (3.58% and 6.07%, respectively) and less favorable binding energies, suggesting these regions may be less accessible or less energetically favorable for ligand interaction.

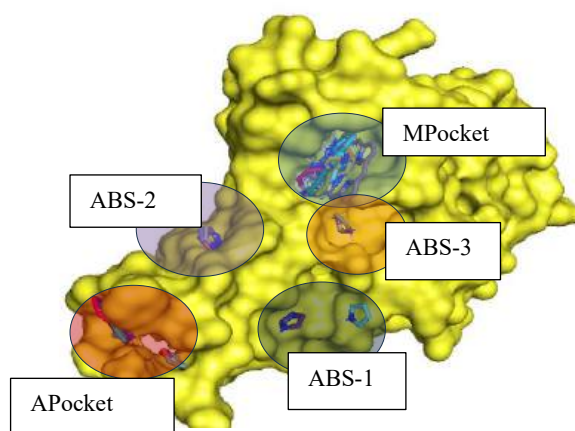


Figure 1. The position of Mpocket, Apocket, ABS-1, ABS-2 and ABS-3 on the RBD SARS-CoV-2 Omicron variant

Binding Free Energy of Heterocyclic Ligands at the Identified RBD-Angiotensin Interface Sites

Compounds such as Phenoxazole (FEB = -6.41 kcal/mol), Phenothiazine (FEB = -6.02 kcal/mol) and Acridine (FEB = -5.94 kcal/mol), demonstrated exceptionally low binding free energies, suggesting strong and stable interactions with the Mpocket site. These molecules likely form favourable non-covalent intermolecular interactions—such as hydrogen bonds, π - π stacking, and hydrophobic contacts—within the binding pocket, contributing to their high affinity. In parallel, heterocycles like Indolizine (FEB = -4.26 kcal/mol), Benzothiophene (FEB = -4.74 kcal/mol), and Dithiane (FEB = -3.46 kcal/mol) exhibited high docking frequencies, indicating that these ligands consistently occupy the Mpocket site across multiple docking conformations. This suggests a high degree of structural compatibility and accessibility to the binding region, which is crucial for effective inhibition of the RBD-ACE2 interaction.

Among the compounds evaluated, Oxazole demonstrated the highest docking frequency (16.10%), suggesting a strong tendency to occupy the Apocket site across multiple conformations. However, its binding free energy was relatively moderate (-2.68 kcal/mol), indicating that while it frequently binds, the interaction may not be highly stable. In contrast, 1,4-benzodiazepine and 3-benzazepine exhibited stronger binding affinities (-4.63 and -4.52 kcal/mol, respectively), but with lower docking frequencies (8.98% and 6.50%). These results suggest that while these ligands

may form more stable interactions when bound, their access or fit to the Apocket site may be more limited or conformation dependent.

Among the compounds analyzed, 1,2,3-oxadiazole (ABS-2) stood out with the highest docking frequency (69.90%), indicating a strong and consistent preference for the ABS-2 site. Despite a moderate binding energy of -3.76 kcal/mol, its high frequency suggests excellent compatibility with the binding pocket, making it a promising candidate for further optimization. Acridine derivatives such as Isoxazole and 2-pyrazoline, also targeting ABS-2, showed moderate docking frequencies (20.62% and 10.82%, respectively) with relatively favorable binding energies, reinforcing the potential of ABS-2 as a druggable site. In contrast, compounds targeting ABS-1, such as 2-imidazoline, 1,2,3-triazole, and 3-pyrroline, exhibited lower docking frequencies (ranging from 3.56% to 7.42%) and slightly weaker binding energies. This suggests that ABS-1 may be more structurally restrictive or less accessible, though still viable for ligands with optimized conformational flexibility. Imidazolidine, the sole compound targeting ABS-3, showed the lowest docking frequency (3.58%) among the group, indicating limited accessibility or weaker interaction potential at this site. However, its binding energy (-3.58 kcal/mol) suggests that once bound, the interaction may be reasonably stable.

Binding Affinity and Interaction Profiles

At the Mpocket site, the interaction profile was dominated by both hydrogen bonding and van der Waals contacts. The most frequently observed hydrogen bond donor/acceptor was SER 496, appearing in 29 compounds, highlighting its central role in polar stabilization of ligand binding. Other residues such as HIP 505, TYR 453, and ARG 403 also contributed to hydrogen bonding, albeit at lower frequencies. The van der Waals interaction landscape was even more extensive, with TYR 495, ARG 403, PHE 497, HIP 505, and TYR 501 emerging as the most recurrent contact residues. These residues form a hydrophobic and aromatic-rich environment that supports π - π stacking and shape complementarity, essential for stabilizing diverse heterocyclic scaffolds. Notably, ARG 403 was also the most frequently involved residue in unfavourable interactions, albeit in only a few cases, suggesting that while it is a key contact point, its spatial orientation may occasionally lead to steric clashes or electrostatic repulsion depending on ligand conformation.

In the Apocket site, the interaction profile was more selective. Hydrogen bonding was observed with residues such as LYS 478, ASN 477, and PHE 486, indicating a polar and potentially solvent-exposed binding environment. Van der Waals interactions were primarily mediated by PRO 479, CYX 480, and GLY 485, suggesting a more flexible or loop-dominated region. No unfavourable interactions were detected in Apocket, reinforcing its compatibility with small, polar ligands. However, the overall interaction density was lower than in Mpocket, consistent with its role as a secondary or allosteric binding site.

The accessory binding sites (ABS-1, ABS-2, and ABS-3) exhibited distinct interaction patterns. In ABS-1, hydrogen bonding was primarily mediated by ARG 457 and TYR 473, while van der Waals contacts involved LEU 455, TYR 421, and PHE 456. ABS-2 showed strong hydrogen bonding with ARG 493 and PHE 490 and van der Waals interactions with TYR 489 and PRO 491, indicating a well-defined and ligand-accessible pocket. ABS-3, though less frequently targeted, involved hydrogen bonding with TYR 495 and GLH 406, and van der Waals contacts with ILE 418 and TYR 453. Interestingly, unfavourable interactions were only observed in ABS-3, specifically involving ASN 417 and ARG 403, suggesting that this site may be more structurally constrained or sensitive to ligand orientation.

CONCLUSIONS

This study identified Mpocket and ABS-1 as key binding sites on the SARS-CoV-2 Omicron RBD through blind docking of heterocyclic compounds. Binding free energy analysis highlighted Phenoxazole, Acridine, and Phenazine as top candidates with strong affinities. Interaction profiling revealed critical non-covalent contacts, particularly involving SER 496 and ARG 403. These findings, supported by 2D and 3D visualization, underscore the potential of heterocyclic scaffolds for antiviral development and provide a structural basis for targeting the RBD-ACE2 interface in Omicron variant inhibition.

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Prof. Madya Dr. Nur Hisham Ibrahim
Rektor
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Sekian, terima kasih.

"BERKHIDMAT UNTUK NEGARA"

Saya yang menjalankan amanah,

Setuju.

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