MOLCULAR DOCKING AND MOLECULAR DYNAMIC SIMULATION OF 1,3-BENZOXAZINE DERIVATIVES AGAINST PENICILLIN BINDING PROTEIN-2A OF METHICILLIN-RESISTANT *Staphlyococcus aureus*

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Methicillin-resistant *Staphylococcus aureus* (MRSA) has a penicillin-binding protein 2a encoded by *mecA* localized on staphylococcal cassette chromosome mec (SCCmec). MRSA has six different types that show resistance to all β-lactam antibiotics. Patients with MRSA infections have higher healthcare costs, have to stay longer in hospital, and eventually died. 1,3-Benzoxazine is a class of heterocyclic compounds that act as antibacterial agents. The molecular docking analyses, molecular dynamics (MD) simulations, dynamic cross-correlation matrix (DCCM) and Molecular mechanics Poisson-Boltzmann surface area (MM-PBSA) were performed to investigate the interactional analyses of PBP2a against the derivatives of 1,3-benzoxazine. Twenty (20) 1,3-benzoxazine derivatives were subjected to molecular docking analyses using MOE software. Moreover, eight previously synthesized symmetrical 1,3-benzoxazine compounds (**21-28**) with known activities against *Staphylococcus aureus*, along with twelve newly designed compounds (**29-40**), were also utilized. The molecular docking results revealed that the 3,4-dihydro-2*H*-1,3-benzoxazine containing 5-methylisoxazole group (compound **28**) showed the least binding energy among the synthesized compounds. Interestingly, it was observed that the 3,4-dihydro-2*H*-1,3-benzoxazine containing a 5-(4-fluorophenyl) isoxazole group (compound **38**) showed lowest binding energy among the newly modified 1,3-benzoxazines. MD simulation was performed for the selected targets, and top ranked compounds, **28** and **38**, were reported. The results of MD analysis confirmed the stability of the penicillin binding protein-2a/ ligand **38** complex based on the results of root-mean-square deviation (RMSD), radius of gyration (Rg), and solvent accessible surface area (SASA) analysis, unlike ligand **28**. The root-mean-square fluctuations (RMSF) results revealed that amino acid fluctuation of binding pocket residues was not observed upon binding of ligand **38**. The binding analysis showed that ligand **28** disturbs the conformational space of the amino acid residues, whereas ligand **38** only affects

the non-local contacts. The hydrogen bond analysis of ligand **38** showed the highest occupancy of hydrogen bond formation with amino acid Asn-545 (84.0 %) and (76.5 %) in both chains (A and B), respectively. In dynamics cross correlation matrix (DCCM) analysis, the binding of ligand **28** induced a large amount of anti-correlation, while ligand **38** only induced a small anti-correlation, depicting the stability. In MM-PBSA and MM-GBSA calculations, most of the poses for ligand **28** showed a higher PB1 value, which revealed the potential cause of the higher fluctuation. On the other hand, the PB and GB components revealed the stability of ligand **38**. The computational results have concluded that ligand **38** is more potent than ligand **28**, and further examinations will be required in the future for confirmation of the *in vitro* and *in vivo* antibacterial activity of ligand **38.**

Keywords: Antibacterial, Molecular Docking, Molecular Dynamic Simulation, MRSA, PBP2a

SDG: GOAL 3: Good Health and Well-Being

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Master Sains

DOK MOLEKUL DAN SIMULASI DINAMIK MOLEKUL TERBITAN 1,3-BENZOKSAZINA TERHADAP PROTEIN PENGIKAT PENISILIN-2A *Staphylococcus aureus* KEBAL METHICILLIN

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Staphylococcus aureus (MRSA) yang tahan kepada methicillin mempunyai protein pengikat penisilin 2a yang dikodkan oleh mecA, disetempatkan pada kromosom kaset *stafilokokus* (SCCmec). Enam jenis yang berbeza telah dikenali dan menunjukkan ketahanan kepada semua antibiotik β-lactam. Jangkitan MRSA membawa kepada peningkatan kos penjagaan kesihatan, penginapan hospital yang lebih lama, dan kematian. 1,3-Benzoksazina adalah satu kelas sebatian heterosiklik dengan potensi yang besar sebagai agen antibakteria. Dok molekul, simulasi dinamik molekul (MD), matriks dinamik korelasi silang (DCCM) dan mekanik molekul kawasan permukaan Poisson-Boltzmann (MM-PBSA) dilakukan untuk menyiasat interaksi PBP2a dengan terbitan 1,3-benzoksazina. Dua puluh (20) terbitan 1,3-benzoksazina telah dianalisa dok molekul menggunakan perisian MOE. Tambahan, lapan (8) 1,3-benzoksazina simetrik (**21-28**) yang telah disintesis sebelum ini dengan aktiviti yang diketahui terhadap *Staphylococcus aureus* bersama-sama dengan dua belas (12) sebatian yang direka baru (**29-40**) juga telah diuji. Hasil dok molekul mendedahkan bahawa 3,4-dihidro-2*H*-1,3-benzoksazina yang mengandungi kumpulan 5-metilisoksazol (sebatian **28**) mempunyai tenaga pengikat terendah di antara sebatian yang telah disintesis. Menariknya, 3,4-dihidro-2*H*-1,3-benzoksazina yang mengandungi kumpulan 5-(4-florofenil)isoksazol (sebatian **38**) mempunyai tenaga mengikat terendah di antara 1,3-benzoksazina yang direka baru. Simulasi MD telah dijalankan untuk sasaran yang dipilih dan sebatian di kedudukan teratas, **28** dan **38**, telah dilaporkan. Keputusan analisis MD mengesahkan kestabilan kompleks pengikat penisilin protein-2a/ligan **38** berdasarkan keputusan sisihan punca min kuasa dua (RMSD), jejari legaran (Rg), dan analisis kawasan permukaan boleh diakses pelarut (SASA) tidak seperti ligan **28**. Keputusan turun naik punca min kuasa dua (RMSF) mendedahkan bahawa tiada turun naik asid amino bagi sisa poket pengikat diperhatikan semasa pengikatan ligan **38**. Analisis pengikatan menunjukkan

bahawa ligan **28** mengganggu ruang konformasi residu asid amino manakala ligan **38** hanya menjejaskan hubungan bukan setempat. Analisis ikatan hidrogen ligan **38** menunjukkan penghunian tertinggi pembentukan ikatan hidrogen dengan asid amino Asn-545 (84.0%) dan (76.5%) dalam kedua-dua rantai (A dan B), masing-masing. Dalam analisis matriks dinamik korelasi silang (DCCM), pengikatan ligan **28** menyebabkan sejumlah besar anti-korelasi manakala ligan **38** hanya mendorong anti-korelasi kecil yang menggambarkan kestabilan. Dalam pengiraan MM-PBSA dan MM-GBSA, kebanyakan pose untuk ligan **28** menunjukkan nilai PB1 yang lebih tinggi, mendedahkan potensi penyebab turun naik yang lebih tinggi. Sebaliknya, komponen PB dan GB mendedahkan kestabilan ligan **38**. Keputusan pengiraan telah menyimpulkan bahawa ligan **38** lebih poten daripada ligan **28**, dan pemeriksaan lanjut diperlukan pada masa hadapan untuk pengesahan aktiviti antibakteria untuk ligan **38** secara i*n vitro* dan *in vivo.*

Kata kunci: Antibakteria, Pengikatan Molekul, Simulasi Dinamik Molekul, MRSA, PBP2a

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LIST OF ABBREVIATIONS

MRSA	Methicillin Resistant *Staphylococcus aureus*
PBP	Penicillin Binding Protein
RMSD	Root Mean Square Deviation
RMSF	Root Mean Square Fluctuation
Rg/RoG	Radius of Gyration
SASA	Solvent Accessible Surface Area
MD	Molecular Dynamic Simulation
NAPS	Pico second
mdp	Molecular Dynamic Parameter file
top	Topology File
PDB ID	Identification of entries in Protein Data Bank

CHAPTER 1

INTRODUCTION

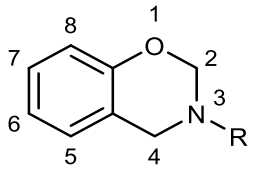
Heterocyclic compounds have received the most interest in scientific research in the field of organic chemistry due to their wide range of biological activity. Most of the pharmaceutically important molecules are heterocycles. The use of heterocycles in medicine is pervasive since they hold the majority of marketed drugs today.

The fused heterocyclic ring system is one of the most important scaffolds in medicinal chemistry and has been commonly found in several natural and non-natural compounds with significant pharmacological properties (Horton *et al.,* 2003).

1,3-Benzoxazine is a class of heterocyclic compounds with great potential as an antimicrobial agent. The privileged structure of 1,3-benzoxazine has been investigated for its biological activity when compared with the standard drugs. Benzoxazine derivatives, especially at 1,3-position, are reported to possess antimicrobial, antifungal, antiproliferative, and antibacterial activities (Sharma *et al.,* 2018; Taira *et al.,* 1992; Burckhalter *et al.,* 1948; Mathew *et al.,* 2010; Alber-Hayta *et al.,* 2006; Macchiaarulo *et al.,* 2002; Khan *et al.,* 2016; Verma *et al.,* 2012). Many substituted 1,3-benzoxazines have been shown to_possess biological activities such as methoxy 1,3-benzoxazine which is present in many pharmaceutically active molecule (Mandzyuk *et al.,* 2020) such as calcium channel antagonists, central nervous system drugs, and analgesics (Dilesh *et al.,* 2013). Moreover, the 1,3-benzoxazines bearing isoxazole group displayed excellent antibacterial and antifungal activity (Rajanarendar *et al.,* 2008). Symmetrical 1,3-Benzoxazines exhibited excellent to moderate antibacterial activity towards the positive bacteria *Staphylococcus aureus,* especially, 1,3-benzoxazine bearing oxazole group (Hassan, 2017).

Staphylococcus aureus that is resistant to the drug methicillin is known as methicillin-resistant *Staphylococcus aureus* (MRSA) (Fluit et al., 2001; Hidron et al., 2008; Sader et al., 2006; Voss et al., 1994). It is a Gram-positive bacterium that is responsible for a group of diseases ranging from simple skin diseases to serious pneumonia and blood bacteria (Qin *et al.,* 2020, Chambers & Deleo, 2009; Grundmann *et al.,* 2006; Klevens *et al., 2007*; Hersh *et al.,* 2008; Hope *et al.,* 2008). Many hospitals do MRSA colonisation checks before admission as an essential infection control measure (Bode et al., 2010; Coia et al., 2006; Huang et al., 2006; Jain et al., 2011; Muto et al., 2003; Robicsek et al., 2008; Siegel et al., 2007).

1,3-Benzoxazine **Figure 1.1** is a molecule that consist of an oxazine ring, a six-membered heterocyclic ring with oxygen and nitrogen atom, which is fused to a benzene ring. The numbering of 1,3-benzoxazine is according to the IUPAC system of heterocyclic compounds, in which the oxygen atom is the prefix followed by the nitrogen atom (Ishida, 2011).



Structure of 3-alkyl-3,4-dihydro-2H-1,3-benzoxazine

Figure 1.1 : General nomenclature of benzoxazine

Inspired by the biological importance and pharmaceutical applications of 1,3-benzoxazine compounds and the continuation of ongoing research on biologically active molecules, and to improve our understanding on the molecular properties of the MRSA-1,3-benzoxazines interaction, a theoretical study comprising molecular docking and molecular dynamics simulation was performed as part of our aim to understand the 1,3-benzoxazine behaviour toward PBP2a from MRSA.

1.1 Problem Statement

Methicillin-resistant *Staphylococcus aureus* (MRSA) has a penicillin-binding protein 2a encoded by *mecA.* PBP2a's low affinity for most β-lactams, leads to resistance to MRSA against many antibiotics. Patients with MRSA infections have to face numerous issues, including increased healthcare costs, longer stays in hospitals, and fatalities. MRSA is considered as an endemic in hospitals worldwide, and patients have had major surgery. Although 50-60% of MRSA patients are merely colonized, indicating symptomless carriage, serious infections such as respiratory tract and bone/joint infections occur. These infections are harder to treat than methicillin-susceptible isolates, and MRSA can readily transmit among patients in the hospital. MRSA control and prevention require awareness among all healthcare professionals and the general public, rapid and dependable detection in the research laboratory, effective monitoring, immediate patient isolation, standard preventive measures, good professional practice by all healthcare workers, effective hospital hygiene programs, and antibiotic stewardship (Hughes-Fitzgerald *et al.,* 2012). Computational methods are essential in solving a wide range of problems across various fields. Using computational methods has increased the discovery of effective ligands to treat MRSA in a shorter time than experimental methods (Lavanya *et al.,* 2016*;* Coates and Hu, 2007). Molecular docking and molecular dynamic (MD) simulations are two commonly used computational methods in drug design, as

they help us predict and understand drug-protein interactions. Today, pharmaceutical industries require these computational methods for drug research because these techniques address different aspects of the drug discovery process and complement each other effectively. Moreover, these approaches are cost effective (Naqvi *et al.,* 2018). Interactions between drugs and proteins guide the rational design of new drug candidates and help optimize existing ones, ultimately improving the efficiency of the drug discovery process and increasing the likelihood of identifying effective therapies for various diseases.

1.2 Goals and Objectives

Based on all the information mentioned above about the biological significance of 1,3-benzoxazine derivatives, this research project aims to:

1. identify 1,3-benzoxazine derivatives with the highest binding affinity and potential antibacterial activity against PBP-2a of methicillin-resistant Staphylococcus aureus (MRSA) through molecular docking studies.
2. assess the stability and dynamics of the top-ranked 1,3-benzoxazine compounds in complex with PBP-2a using molecular dynamics simulations.
3. investigate the potential mechanism of action and binding behavior of the selected 1,3-benzoxazine derivatives, providing insights into their ability to inhibit PBP-2a and suggesting their potential as antibacterial agents against MRSA.

1.3 Scope of the Research

In the current study, the structural basis for the binding affinity and stability of 1,3-benzoxazine compounds within specific protein targets has been investigated through a comprehensive workflow that encompasses molecular docking and molecular dynamics (MD) simulations. Recent advances in computational chemistry and structural biology techniques have opened new avenues for rational drug design, providing an opportunity to understand atomic-level interactions between small molecules and their target proteins.

In the first phase of our research, molecular docking of a set of previously synthesized 1,3-benzoxazine compounds (**21-28**) into their respective protein targets has been performed. Molecular docking, a computational technique, was utilized to predict the binding mode and affinity of these small molecules within the active site of the proteins. These docking studies provided crucial initial insights into the binding preferences and interactions of the compounds with their protein targets.

From the molecular docking studies conducted in the current study, one compound, Compound **28**, was identified as the top hit among the from previously eight synthesized compounds based on its binding affinity and interaction profiles with the protein target. This compound was selected for further analysis.

Continuing with the current study, we proposed a set of new 1,3-benzoxazine compounds (**29-40**) by changing the functional groups of the original compounds (**21-28**). These modifications were aimed at enhancing binding affinity, specificity, and drug-like properties.

The newly modified 1,3-benzoxazine compounds (**29-40**) were subjected to molecular docking studies. This step allowed us to evaluate the binding affinity and interaction profiles of these modified compounds within the active site of the target protein. The goal was to identify potential lead compounds with improved binding properties compared to the original compounds.

As the molecular docking studies of the modified compounds continued, Compound 38 was chosen as the best match based on how well it bound and interacted with the protein target. This compound, along with compound **28**, was selected for further investigation using molecular dynamics simulations.

In the final phase of our research, molecular dynamics simulations were conducted on three protein systems, including the target protein of interest and two complexes involving the top hit compounds (Compounds **28** and **38**). Molecular dynamics simulations provided a dynamic view of protein-ligand interactions over time, enabling us to assess stability, conformational changes, and binding energetics.

The outcomes of the current study hold significant scientific implications. Our holistic approach, which combines molecular docking and molecular dynamics simulations, contributed to a deeper understanding of the binding affinity and stability of 1,3-benzoxazine compounds within specific protein targets. This research will have far-reaching implications in the drug discovery field, offering valuable insights into the rational design of novel therapeutics. By identifying top hit compounds and elucidating their binding mechanisms, we aim to facilitate the development of potential drug candidates with enhanced efficacy and specificity. In conclusion, the current study contributes to the scientific understanding of small molecule-protein interactions by investigating the structural basis for the binding affinity and stability of 1,3-benzoxazine compounds. The results of this study have the potential to drive advancements in the development of novel therapeutics with enhanced efficacy and specificity.

CHAPTER 5

CONCLUSION

Computational methodologies like molecular docking and molecular dynamics (MD) simulations play a pivotal role in exploring intricate ligand-protein interactions. These techniques enable in-depth exploration of molecular behaviours that would otherwise remain hidden. Our study delved into the interactions of synthesized 1,3-benzoxazines (**21-28**) and modified analogs (**29-40**), highlighting compelling insights into their binding activity.

The computed binding energies identified compounds **28** and **38** as notable contenders, boasting binding energies of -7.8 kcal/mol and -8.5 kcal/mol, respectively. Notably, through comprehensive structural analysis, we found that ligand **28** prompts heightened fluctuations in both Chain A and B of the protein, indicating destabilization of the binding interface. In contrast, ligand **38** exhibits a more stable binding profile, strengthening interactions with both Chains A and B.

Calculations of the radius of gyration (Rg) show that when ligand 28 binds to the protein, it causes the protein's structure to expand significantly, which means it is less compact.Conversely, binding of ligand **38** leads to an increase in compactness, supporting its stable binding profile. Surface area calculations (SASA) corroborate this trend, with ligand **28** causing elevated protein core exposure, while ligand **38** induces a more compact, less solvent-exposed protein configuration.

Hydrogen bond analysis indicates ligand **38**'s persistent and stable interaction throughout the 100 ns simulation, in contrast to ligand **28**'s higher hydrogen bond count, hinting at reduced conformational stability. This collective evidence positions ligand **38** as a potential compound with favorable dynamics and binding attributes.

Further substantiating our findings, MM-PBSA and dynamic cross-correlation analysis underscore the distinct activity of ligands **28** and **38**. Ligand **28**'s binding yields substantial anti-correlation, inducing protein fluctuations, potentially impacting its own stability. Meanwhile, ligand **38**'s binding exhibits partial anti-correlation, indicating a more stable binding configuration.

Notably, our conclusion aligns with MM-PBSA and GBSA analyses, showing ligand **38**'s more stable binding. The higher PB and GB components in ligand **38** highlight its stable binding activity. In particular, ligand 38's GBSA configurational space reaches an impressive -34 kcal/mol in the GB1 configuration, where GB1

dominates different poses. This confirms that it has stable interactions with protein residues.

In summary, our comprehensive analysis collectively confirms that ligand **38**'s binding showcases a better interaction with both Chain A and B. But it is also important to consider that the current in-silico analysis is not enough to comment on the stability and potential of ligand **38** to act as a potent drug candidate. Further examinations are required to conclusively talk about ligand **38**'s activity.

5.1 Recommendations for Future Work

Based on the conclusions drawn from this study, several avenues for future research and exploration emerge that can further deepen our understanding of ligand-protein interactions and contribute to drug development endeavours. These prospective directions encompass:

Multiscale Simulations: Employing advanced computational techniques, such as multiscale simulations that integrate quantum mechanics and molecular mechanics, could provide a more accurate representation of the intricate interactions between ligands and proteins. This approach would facilitate a deeper exploration of the binding mechanisms and energetics of ligand **38.**

Longer Timescale Simulations: Extending the simulation duration beyond the current 100 ns timeframe could enable the observation of rare or slow conformational changes within the protein-ligand complex. This prolonged exploration of dynamics might provide insights into binding stability and long-term behavior.

Experimental Validation: Collaborating with experimental researchers to validate the computational findings through techniques like X-ray crystallography, NMR spectroscopy, and biophysical assays would enhance the credibility of the computational predictions and reinforce the robustness of the conclusions.

In summary, the present study opens up a spectrum of promising avenues for future research, ranging from computational techniques to experimental validations, aimed at further elucidating ligand-protein interactions and advancing drug discovery efforts. Each of these directions has the potential to enrich our understanding of molecular behavior and ultimately contribute to the development of effective therapeutic agents.

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