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# *In Silico* Discovery of Natural Product Inhibitors of *Burkholderia pseudomallei* Dethiobiotin Synthetase

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## Abstract

Melioidosis, a frequently underdiagnosed yet potentially fatal disease in the Philippines, is caused by *Burkholderia pseudomallei*, a pathogen noted for rapidly acquiring antibiotic resistance. The bacterial enzyme dethiobiotin synthetase (DTBS), which functions as a dimer, is an attractive drug target because of its essential role in biotin biosynthesis. In this study, computer-assisted drug discovery and development (CADDD) was employed to identify natural product inhibitors of the AlphaFold-predicted structure of *B. pseudomallei* DTBS using the COCONUT natural products database. A receptor cavity was mapped and used to generate a pharmacophore model for virtual screening. Phenylalanine–isoleucine–arginine tripeptide was the chemical that fit the pharmacophore the best (pharmacophore fit value 1.58). Molecular docking was used to further assess it, and the result was an interaction energy of -47.17 kJ/mol. Molecular dynamics simulation of the ligand–DTBS complex showed high stability and compactness, with low root mean square deviation and radius of gyration. Key interacting residues displayed minimal fluctuations, and the binding energy was more negative than that of reference co-crystallized DTBS homologs. Short-range interaction energies from Lennard-Jones and Coulombic potentials were –91.17 ± 5.0 kJ/mol and –195.28 ± 7.7 kJ/mol, respectively. The findings point to thermodynamically advantageous binding and the possibility that the top ligand could block DTBS by altering its active dimeric structure, offering a promising avenue for the creation of new anti-melioidosis drugs.

**Keywords:** *Burkholderia pseudomallei*, Dethiobiotin synthetase, AlphaFold, Computer-assisted drug discovery and development, Structure-based pharmacophore, Molecular docking, Molecular dynamics

## Introduction

Melioidosis, or Whitmore's disease, is a potentially fatal infection caused by *Burkholderia pseudomallei*. Acute cases often present with sepsis, abscesses, or pneumonia, while chronic melioidosis may persist for at least two months (Wiersinga *et al*., 2018). Major risk factors include diabetes mellitus, thalassemia, and frequent exposure to contaminated soil, making rice farmers and diabetic patients particularly vulnerable (Suputtamongkol *et al*., 1999; Cheng & Currie, 2005; Selvam *et al*., 2022). Although endemic in Southeast Asia and northern Australia, the disease remains largely underdiagnosed and underreported (San Martin *et al*., 2018; Saito *et al*., 2022; Kaewrakmuk *et al*., 2023). Fatality rates can reach 50% if early diagnosis and treatment are missed (Princess *et al*., 2017; Wiersinga *et al*., 2018).

The causative agent *B. pseudomallei* is a motile, gram-negative soil saprophyte capable of surviving in harsh environmental conditions, including nutrient-deficient, acidic, or basic settings, and even in the presence of disinfectants (Cheng & Currie, 2005; White, 2013). While host antibodies frequently fall short of providing adequate immunity, once within the host, it can live and proliferate within neutrophils and macrophages (Cheng & Currie, 2005). Treatment is further complicated by the bacterium's ability to acquire and stably maintain antibiotic resistance (Schweizer, 2012), reinforcing the need for novel and more effective therapeutic agents.

One promising bacterial drug target is dethiobiotin synthetase (DTBS), a key enzyme in the biotin biosynthesis pathway that catalyzes the conversion of 7,8-diaminopelargonic acid (DAPA) to dethiobiotin (Krell & Eisenberg, 1970; Schumann *et al*., 2021). DTBS is considered essential for bacterial survival, and no human orthologs have been identified, making it a highly specific and "druggable" target (Schumann *et al*., 2021; Khan *et al*., 2022). Previous studies have explored both *in vivo* and *in silico* approaches to identify inhibitors of *B. pseudomallei* and other pathogenic bacteria (Challacombe, 2017; Ross *et al*., 2018; Díaz-Sáez *et al*., 2019; Watkins, 2019; Khan *et al*., 2022).

In this study, computer-aided drug discovery and development (CADDD) was applied to identify natural product inhibitors of *B. pseudomallei* DTBS. Traditional natural product drug discovery is time-consuming and labor-intensive, whereas in silico screening of large natural product libraries offers a faster, more efficient strategy (Yu & MacKerell, 2017). By screening compounds from the Collection of Open Natural Products (COCONUT) database (https://coconut.naturalproducts.net) and evaluating their binding to the AlphaFold-predicted DTBS structure, this work aims to identify promising lead compounds. Such computationally derived candidates provide a foundation for future in vitro and in vivo validation, supporting the development of novel therapies against multidrug-resistant melioidosis.

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## Materials and Methods

This study employed a computer-aided drug discovery and development (CADDD) workflow to identify potential natural product inhibitors of *Burkholderia pseudomallei* dethiobiotin synthetase (Bp DTBS). The approach integrated structure-based pharmacophore modeling, virtual screening of natural product libraries, pharmacokinetic filtering, molecular docking, and molecular dynamics (MD) simulation.

*Retrieval and Validation of the Bp DTBS Structure*

The three-dimensional (3D) model of Bp DTBS (strain 668) was obtained from the AlphaFold Protein Structure Database (https://alphafold.ebi.ac.uk/entry/A3N521). To validate this predicted structure, it was superimposed onto the crystal structure of *Mycobacterium tuberculosis* DTBS (PDB ID: 3FGN) retrieved from the RCSB Protein Data Bank (https://www.rcsb.org/structure/3FGN). Structural quality was evaluated using the ERRAT program in SAVES v6.0 (https://saves.mbi.ucla.edu) and the Verify 3D (Profiles-3D) protocol in Discovery Studio (DS).

*Pharmacophore Modeling and Virtual Screening*

A structure-based pharmacophore was created using the Interaction Generation methodology after the primary ligand-binding cavity of Bp DTBS was discovered in DS. The final pharmacophore model was created by keeping cluster centres of important interaction properties, such as hydrophobic sites, hydrogen bond donors, and hydrogen bond acceptors. A compound library of 406,747 natural products and natural product derivatives from the Collection of Open Natural Products (COCONUT) was first filtered using ADMETlab 3.0 for drug-likeness and pharmacokinetic properties. Screening criteria included no violations of Lipinski's rule of five, >30% predicted human intestinal absorption, F50 (oral bioavailability) <50%, log(brain/blood) > –1, non-inhibition of cytochrome P450 enzymes, absence of PAINS (pan-assay interference compounds), and non-carcinogenic, non-acutely toxic substructures. Compounds passing these filters were virtually screened against the pharmacophore using the Screen Library protocol in DS, retaining only molecules matching at least two pharmacophore features (Ruchin *et al*., 2022; Rudayni *et al*., 2022; Spirito *et al*., 2022; Sugimori *et al*., 2022; Kiedrowicz *et al*., 2023; Kulkarni *et al*., 2023; Dorn *et al*., 2024; Mao *et al*., 2024).

*Molecular Docking*

Top-fitting ligands from the pharmacophore screen were docked to the prepared Bp DTBS model using the CDOCKER module in DS. Interaction energies and overall binding energies were calculated, and compounds were ranked accordingly. Among the 20 highest-ranking ligands, the top candidate was selected based on the most negative interaction energy and the best pharmacophore fit value (Özatik *et al*., 2023; Shahzan *et al*., 2023).

*Molecular Dynamics Simulation*

The Bp DTBS–top ligand complex was subjected to MD simulation using GROMACS 2022.3 on the Computational and Archiving Research Environment (COARE) of the Department of Science and Technology–Advanced Science and Technology Institute (DOST–ASTI). CHARMM36 all-atom force field parameters were applied. The complex was solvated in a TIP3P water-filled dodecahedral box with $Na^+$ counter-ions and subjected to energy minimization. System equilibration was performed under constant volume (NVT) and constant pressure (NPT) ensembles for 1 ns each. A 100 ns production run followed, with coordinates saved every 0.1 ns. Trajectory analyses included root mean square deviation (RMSD), root mean square fluctuation (RMSF), radius of gyration (Rg), and hydrogen bond monitoring to evaluate structural stability and binding mode of the ligand within the active site (AlShammasi *et al*., 2024; Ravoori *et al*., 2024).

## Results and Discussion

This study employed a computer-aided drug discovery strategy to identify natural product inhibitors of *Burkholderia pseudomallei* dethiobiotin synthetase (Bp DTBS). A structure-based pharmacophore was derived from the AlphaFold-predicted Bp DTBS model, which was then used to virtually screen natural products from the COCONUT database. Filtered ligands were docked to the predicted structure, and the top complex was evaluated by molecular dynamics (MD) simulation.

*Validation of the AlphaFold Bp DTBS Structure*

Because no crystal structure of Bp DTBS is available, an AlphaFold model (https://alphafold.ebi.ac.uk/entry/A3N521) was used. AlphaFold predicts protein folds using deep learning informed by multiple sequence alignments and homolog structures (Terwilliger *et al*., 2024). Homologous DTBS crystal structures from *Mycobacterium tuberculosis* (Mtb) and *Helicobacter pylori* have been deposited in the RCSB PDB. Superimposition of the Bp and Mtb DTBS structures gave an RMSD of 7.94 Å **(Figure 1)**, largely attributable to differences in unstructured loop regions and to the fact that AlphaFold predicts a monomer whereas the Mtb enzyme is crystallized as a homodimer (Alexeev *et al*., 1994; Dey *et al*., 2010).

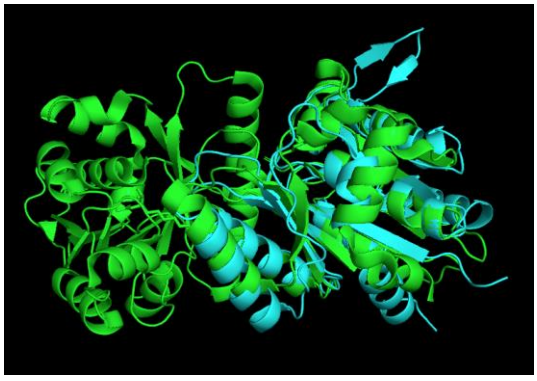


**Figure 1.** Superimposition of the AlphaFold-predicted *B. pseudomallei* DTBS structure (cyan) with the *M. tuberculosis* DTBS crystal structure (green)

Model-quality metrics confirmed the reliability of the predicted fold. ERRAT analysis yielded a 93.2% overall quality factor

(Colovos & Yeates, 1993), and the Verify 3D (Profiles-3D) score was 124.16, exceeding the expected high score of 109.0 (Eisenberg *et al*., 1997). These results indicate that the AlphaFold model is suitable for downstream *in silico* analyses.

*ADMET-Based Filtering of Natural Products*

The 406,747 compounds in the COCONUT database were evaluated with ADMETlab 3.0 (Dong *et al*., 2018; Xiong *et al*., 2021) using standard drug-likeness and pharmacokinetic filters (Lipinski compliance, >30 % intestinal absorption, F50 < 50 %, log brain/blood > –1, non-inhibition of CYP450, absence of PAINS, non-carcinogenic, and no acute-toxicity fragments). Only 2,272 compounds passed, highlighting the stringency of oral drug-likeness criteria and the need for early exclusion of unsuitable candidates (Ferreira & Andricopulo, 2019).

*Pharmacophore Generation and Screening*

A major receptor cavity was identified near the monomer terminus. Although the DTBS active site is normally formed only in the dimer, targeting this pocket could allow ligand-induced conformational changes that disrupt dimerization (Alexeev *et al*., 1994; Dey *et al*., 2010). The pharmacophore comprised 4 hydrogen-bond acceptors, 6 donors, and 14 hydrophobic features. Of the ADMET-filtered compounds, 990 fitted at least two pharmacophore features, with fit scores from 0.00005 to 2.93. Higher fit values indicate closer mimicry of the receptor's interaction environment (Opo *et al*., 2021).

*Molecular Docking*

Docking of the 990 fitted ligands with the CDOCKER protocol (Wu *et al*., 2003) produced 5,196 refined poses from 289 compounds. Among the 20 best-scoring ligands **(Table 1)**, most were small natural peptides or peptide-like molecules, consistent with the antimicrobial activity of many natural peptides (Huan *et al*., 2020; Wang *et al*., 2022). The top ligand, a tripeptide of phenylalanine–isoleucine–arginine **(Figure 2)**, displayed an interaction energy of –55.26 kJ mol$^{-1}$ and a pharmacophore fit value of 1.58.

**Table 1.** Top 20 docking poses: CDOCKER interaction and overall energies (kcal/mol) with corresponding pharmacophore fit values.

| Index | Interaction Energy | Overall Energy | Fit Value |
|---|---|---|---|
| **1666*** | -55.26 | -56.29 | 1.58 |
| **1047** | -50.31 | -50.11 | 0.40 |
| **3636** | -50.05 | -50.38 | 0.63 |
| **3847** | -51.16 | -46.65 | 0.44 |
| **3848** | -49.61 | -46.57 | 0.44 |
| **1048** | -48.15 | -49.01 | 0.40 |
| **1055** | -49.36 | -46.78 | 0.40 |
| **621** | -52.91 | -44.94 | 1.52 |
| **4389** | -50.03 | -45.79 | 0.40 |
| **1054** | -49.20 | -46.80 | 0.40 |
| **1052** | -48.05 | -47.49 | 0.40 |
| **1513** | -47.61 | -47.91 | 0.33 |
| **1056** | -47.81 | -46.74 | 0.40 |
| **3637** | -48.18 | -44.96 | 0.63 |
| **1705** | -50.89 | -42.59 | 0.68 |
| **3640** | -47.93 | -44.18 | 0.63 |
| **3621** | -47.10 | -46.40 | 0.62 |
| **1049** | -46.77 | -48.71 | 0.40 |
| **3032** | -48.59 | -43.08 | 0.57 |

*The selected top ligand for MD simulation

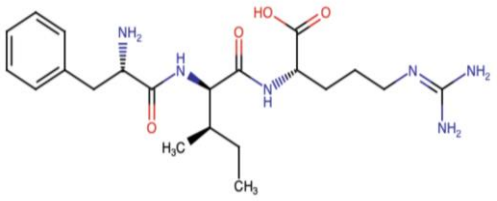
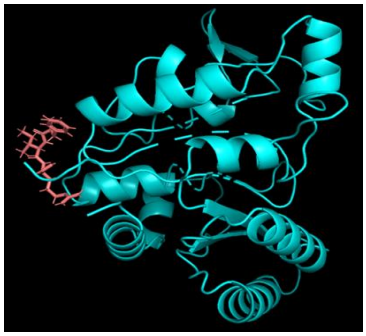


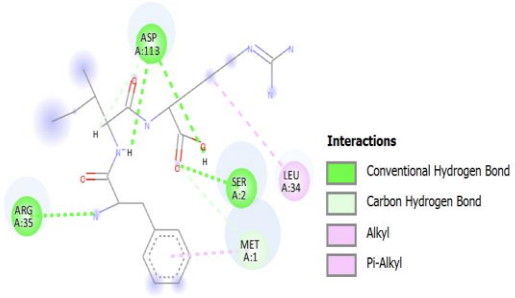

**Figure 2.** Structure of the phenylalanine–isoleucine–arginine tripeptide

*MD Simulation of the Top Ligand–Bp DTBS Complex*

The docked complex **(Figure 3)** was simulated for 100 ns in GROMACS 2022.3 using the CHARMM36 force field. Key hydrogen bonds were observed between ligand carbonyl/amine groups and Asp113, Ser2, and Arg35, with π-alkyl contacts involving Met1 and Leu34.



a

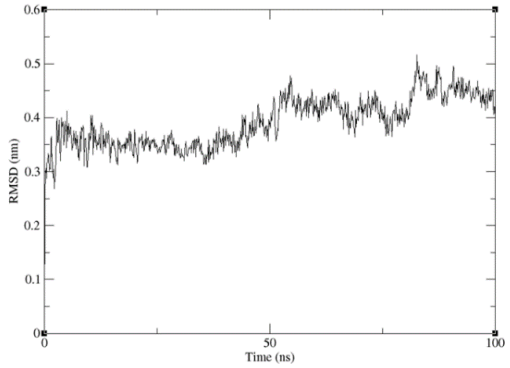



b

**Figure 3.** a) Docked complex of the top ligand with Bp DTBS and b) visualized protein–ligand interactions generated in Discovery Studio

Backbone RMSD averaged 0.393 nm, indicating good structural stability with a slight upward drift suggesting a possible ligand-

induced conformational transition **(Figure 4a)**. The radius of gyration (Rg) decreased to an average of 1.742 nm and stabilized, implying increased protein compactness **(Figure 4b)**. Such ligand-induced compaction has been linked to inhibition of dimer formation in related enzymes (Kumar *et al*., 1980).

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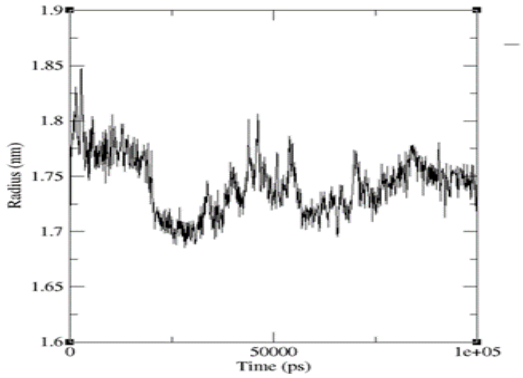
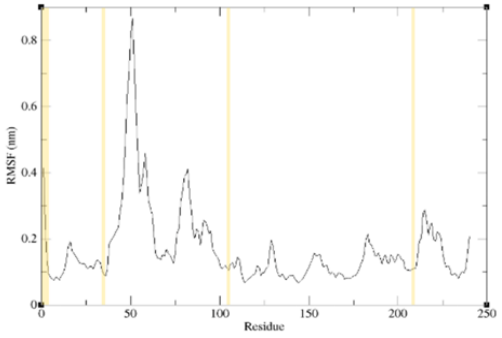


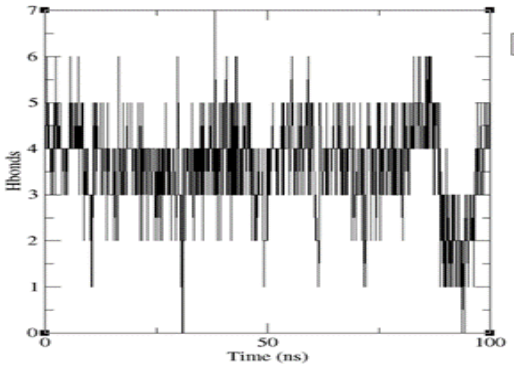

b

**Figure 4.** a) RMSD profile and b) radius of gyration (Rg) profile of the Bp DTBS–ligand docked complex

Residues directly contacting the ligand showed minimal RMSF **(Figure 5a)**, confirming local stability. Larger fluctuations at Gly51 and Pro82 (near ATP/$Mg^{2+}$ binding residues) suggest possible interference with cofactor binding. The ligand maintained ~3–4 hydrogen bonds during most of the simulation **(Figure 5b)**, consistent with stable binding.




a




b

**Figure 5.** a) RMSF profile of the Bp DTBS–ligand docked complex, with residues highlighted that were identified by DS as interacting with the top ligand. b) Number of hydrogen bonds formed during the MD simulation of the Bp DTBS–top ligand complex.

Average Lennard-Jones and Coulombic short-range interaction energies were –91.17 ± 5.0 kJ $mol^{-1}$ and –195.28 ± 7.7 kJ $mol^{-1}$, respectively **(Figure 6)**, indicating strong van der Waals and electrostatic interactions. These values are more negative than those reported for small-molecule ligands of Mtb DTBS (–45.85 to –73.93 kJ $mol^{-1}$); (Rampogu *et al*., 2023), supporting the thermodynamic favorability of the identified tripeptide.

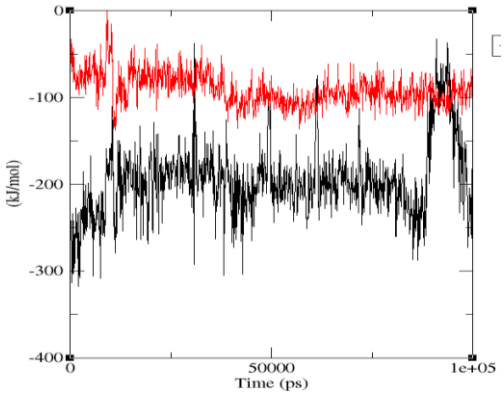



**Figure 6.** Lennard-Jones (red) and Coulombic (black) short-range interaction energy profiles of the Bp DTBS–top ligand docked complex.

The combined pharmacophore screening, docking, and MD data suggest that the phenylalanine–isoleucine–arginine tripeptide binds an allosteric pocket of Bp DTBS with strong, stable interactions and may induce a more compact monomeric structure. Such ligand-induced structural changes could hinder the formation of the enzyme's active homodimer, offering a promising starting point for the development of peptide-based inhibitors against melioidosis.

## Conclusion

*Burkholderia pseudomallei*, the causative agent of melioidosis, can readily acquire chromosomal antibiotic resistance, making infections difficult to treat. This study employed computer-assisted

drug discovery (CADDD) to identify potential inhibitors of *B. pseudomallei* dethiobiotin synthetase (Bp DTBS) from the COCONUT natural products database using ADMET prediction, pharmacophore-based virtual screening, and molecular docking. The majority of the top-ranked choices were short-chain peptides, which is in line with how natural host defence peptides work as antimicrobials. The leading tripeptide ligand, when docked with Bp DTBS and subjected to molecular dynamics simulation, showed stable binding, highly favorable interaction energies, and evidence of ligand-induced conformational changes that could hinder the formation of the enzyme's active dimeric state. These findings highlight the tripeptide as a promising lead for anti-melioidosis drug development. Further *in vitro* and *in vivo* validation, as well as structure-based optimization, are recommended to assess and enhance its therapeutic potential.

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**Conflict of interest:** None

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**Ethics statement:** This study involved only computational analyses of publicly available and computer-generated data and did not include any experiments on humans or animals. Therefore, ethics approval and informed consent were not required.

## References

Alexeev, D., Baxter, R. L., & Sawyer, L. (1994). Mechanistic implications and family relationships from the structure of dethiobiotin synthetase. *Structure, 2*(11), 1061–1072. doi:10.1016/S0969-2126(94)00109-X

AlShammasi, H., Alkhaldi, G., Alharbi, L., & Alyami, M. (2024). Shifts in parental perception of pediatric patients needing dental rehabilitation under general anesthesia post-pandemic. *Turkish Journal of Public Health Dentistry, 4*(1), 29–35. doi:10.51847/jAv4cm0TTn

Challacombe, J. F. (2017). In silico identification of metabolic enzyme drug targets in *Burkholderia pseudomallei* | *bioRxiv*. https://www.biorxiv.org/content/10.1101/034306v2

Cheng, A. C., & Currie, B. J. (2005). Melioidosis: epidemiology, pathophysiology, and management. *Clinical Microbiology Reviews, 18*(2), 383–416. doi:10.1128/cmr.18.2.383-416.2005

Colovos, C., & Yeates, T. O. (1993). Verification of protein structures: patterns of nonbonded atomic interactions. *Protein Science, 2*(9), 1511–1519. doi:10.1002/pro.5560020916

Dey, S., Lane, J. M., Lee, R. E., Rubin, E. J., & Sacchettini, J. C. (2010). Structural characterization of the *Mycobacterium tuberculosis* biotin biosynthesis enzymes 7,8-diaminopelargonic acid synthase and dethiobiotin synthetase. *Biochemistry, 49*(31), 6746–6760. doi:10.1021/bi902097j

Díaz-Sáez, L., Torrie, L. S., McElroy, S. P., Gray, D., & Hunter, W. N. (2019). *Burkholderia pseudomallei* D-alanine-D-alanine ligase; detailed characterisation and assessment of a potential antibiotic drug target. *The FEBS Journal, 286*(22), 4509–4524. doi:10.1111/febs.14976

Dong, J., Wang, N. N., Yao, Z. J., Zhang, L., Cheng, Y., Ouyang, D., Lu, A. P., & Cao, D. S. (2018). ADMETlab: A platform for systematic ADMET evaluation based on a comprehensively collected ADMET database. *Journal of Cheminformatics, 10*(1), 29. doi:10.1186/s13321-018-0283-x

Dorn, G. A., Poznyakovsky, V. M., Danko, N. N., Vladimirovna, P. E., & Tokhiriyon, B. (2024). A study of assessing the impact of pantohematogen, embryotoxicity, and teratogenicity. *International Journal of Veterinary Research and Allied Sciences, 4*(2), 5–13. doi:10.51847/tvX0TaYc7D

Eisenberg, D., Luethy, R., & Bowie, J. (1997). VERIFY3D: Assessment of protein models with three-dimensional profiles. *Methods in Enzymology, 277*, 396–404. doi:10.1016/S0076-6879(97)77022-8

Ferreira, L. L. G., & Andricopulo, A. D. (2019). ADMET modeling approaches in drug discovery. *Drug Discovery Today, 24*(5), 1157–1165. doi:10.1016/j.drudis.2019.03.015

Huan, Y., Kong, Q., Mou, H., & Yi, H. (2020). Antimicrobial peptides: Classification, design, application, and research progress in multiple fields. *Frontiers in Microbiology, 11*, 582779. doi:10.3389/fmicb.2020.582779

Kaewrakmuk, J., Chusri, S., Hortiwakul, T., Kawila, S., Patungkaro, W., Jariyapradub, B., Limvorapan, P., Chiewchanyont, B., Thananchai, H., Duangsonk, K., et al. (2023). Under-reporting cases and deaths from melioidosis: a retrospective finding in Songkhla and Phatthalung Province of Southern Thailand, 2014–2020. *Tropical Medicine and Infectious Disease, 8*(5), 286. doi:10.3390/tropicalmed8050286

Khan, M. A. S., Miah, M. I., & Rahman, S. R. (2022). Subtractive proteomic analysis for identification of potential drug targets and vaccine candidates against *Burkholderia pseudomallei* K96243. *Informatics in Medicine Unlocked, 35*, 101127. doi:10.1016/j.imu.2022.101127

Kiedrowicz, M., Dembowska, E., Banach, J., Safranow, K., & Pynka, S. (2023). Evaluating periodontal health in type 2 diabetics with chronic complications. *Annals of Orthodontics and Periodontics Speciality, 3*, 19–27. doi:10.51847/axdaRLPSoJ

Krell, K., & Eisenberg, M. A. (1970). The purification and properties of dethiobiotin synthetase. *Journal of Biological Chemistry, 245*(24), 6558–6566. doi:10.1016/S0021-9258(18)62570-0

Kulkarni, S., Zope, S., Suragimath, G., Varma, S., & Kale, A. (2023). The influence of female sex hormones on periodontal health: a regional awareness study. *Annals of Orthodontics and Periodontics Speciality, 3*, 10–18. doi:10.51847/v4EFMh6WEf

Kumar, S. A., Murthy, N. S., & Krakow, J. S. (1980). Ligand-induced change in the radius of gyration of cAMP receptor

protein from *Escherichia coli*. *FEBS Letters, 109*(1), 121–124. doi:10.1016/0014-5793(80)81324-X

Mao, J., Zhang, T., Zhang, G., Wang, M., Liu, C., & Wang, M. (2024). The impact of cold storage on the survival and viability of parasitoid bee pupae and whole insects. *International Journal of Veterinary Research and Allied Sciences, 4*(2), 20–26. doi:10.51847/d0aYiMtX37

Opo, F. A. D. M., Rahman, M. M., Ahammad, F., Ahmed, I., Bhuiyan, M. A., & Asiri, A. M. (2021). Structure-based pharmacophore modeling, virtual screening, molecular docking, and ADMET approaches for identification of natural anti-cancer agents targeting XIAP protein. *Scientific Reports, 11*(1), 4049. doi:10.1038/s41598-021-83626-x

Özatik, Ş., Saygılı, S., Sülün, T., & Alan, C. B. (2023). Customized prosthetic solutions for scleroderma-induced microstomia: a semi-digital approach in removable partial denture fabrication. *International Journal of Dental Research and Allied Sciences, 3*(1), 1–7. doi:10.51847/XlJ1uvhGvu

Princess, I., Ebenezer, R., Ramakrishnan, N., Daniel, A. K., Nandini, S., & Thirunarayan, M. A. (2017). Melioidosis: an emerging infection with fatal outcomes. *Indian Journal of Critical Care Medicine, 21*(6), 397–400. doi:10.4103/ijccm.IJCCM_122_17

Rampogu, S., Shaik, B., Kim, J. H., Jung, T. S., Ha, M. W., & Lee, K. W. (2023). Explicit molecular dynamics simulation studies to discover novel natural compound analogues as *Mycobacterium tuberculosis* inhibitors. *Heliyon, 9*(2), e13324. doi:10.1016/j.heliyon.2023.e13324

Ravoori, S., Sekhar, P. R., Pachava, S., Pavani, N. P. M., Shaik, P. S., & Ramanarayana, B. (2024). Perceived stress and depression among oral cancer patients: a hospital-based cross-sectional study. *Turkish Journal of Public Health Dentistry, 4*(1), 1–5. doi:10.51847/FoK9xAl1JW

Ross, B. N., Myers, J. N., Muruato, L. A., Tapia, D., & Torres, A. G. (2018). Evaluating new compounds to treat *Burkholderia pseudomallei* infections. *Frontiers in Cellular and Infection Microbiology, 8*, 210. doi:10.3389/fcimb.2018.00210

Ruchin, A., Alekseev, S., Khapugin, A., & Esin, M. (2022). The fauna and diversity of ground beetles (Coleoptera, Carabidae) in meadow ecosystems. *Entomological Letters, 2*(1), 1–11. doi:10.51847/xiIPPVCe56

Rudayni, H. A., Basher, N. S., Al-Keridis, L. A., Ibrahim, N. A., & Abdelmageed, E. (2022). Exploring the effectiveness of *Ocimum basilicum* extracts in mosquito larvae management. *Entomological Letters, 2*(1), 12–18. doi:10.51847/upImR4jWMM

Saito, N., Solante, R. M., Guzman, F. D., Telan, E. O., Umipig, D. V., Calayo, J. P., Frayco, C. H., Lazaro, J. C., Ribo, M. R., Dimapilis, A. Q., et al. (2022). A prospective observational study of community-acquired bacterial bloodstream infections in Metro Manila, the Philippines. *PLOS Neglected Tropical Diseases, 16*(5), e0010414. doi:10.1371/journal.pntd.0010414

San Martin, P. F. M., Chua, J. C., Bautista, R. L. P., Nailes, J. M., Panaligan, M. M., & Dance, D. A. B. (2018). Melioidosis in the Philippines. *Tropical Medicine and Infectious Disease, 3*(3), 99. doi:10.3390/tropicalmed3030099

Schumann, N. C., Lee, K. J., Thompson, A. P., Salaemae, W., Pederick, J. L., Avery, T., Gaiser, B. I., Hodgkinson-Bean, J., Booker, G. W., Polyak, S. W., et al. (2021). Inhibition of *Mycobacterium tuberculosis* dethiobiotin synthase (MtDTBS): toward next-generation antituberculosis agents. *ACS Chemical Biology, 16*(11), 2339–2347. doi:10.1021/acschembio.1c00491

Schweizer, H. P. (2012). Mechanisms of antibiotic resistance in *Burkholderia pseudomallei*: implications for treatment of melioidosis. *Future Microbiology, 7*(12), 1389–1399. doi:10.2217/fmb.12.116

Selvam, K., Ganapathy, T., Najib, M. A., Khalid, M. F., Abdullah, N. A., Harun, A., Wan Mohammad, W. M., & Aziah, I. (2022). Burden and risk factors of melioidosis in Southeast Asia: a scoping review. *International Journal of Environmental Research and Public Health, 19*(23), 15475. doi:10.3390/ijerph192315475

Shahzan, S., Paulraj, J., & Maiti, S. (2023). Impact of rubber dam use on anxiety levels in children during dental procedures: a randomized controlled study. *International Journal of Dental Research and Allied Sciences, 3*(1), 17–23. doi:10.51847/RmzKyVOff6

Spirito, F. D., Iacono, V. J., Alfredo, I., Alessandra, A., Sbordone, L., & Lanza, A. (2022). Impact of COVID-19 awareness on periodontal disease prevention and management. *Asian Journal of Periodontics and Orthodontics, 2*, 16–26. doi:10.51847/t8D9TJGOCU

Sugimori, T., Yamaguchi, M., Kikuta, J., Shimizu, M., & Negishi, S. (2022). The biomechanical and cellular response to micro-perforations in orthodontic therapy. *Asian Journal of Periodontics and Orthodontics, 2*, 1–15. doi:10.51847/Z9adSJ59rj

Suputtamongkol, Y., Chaowagul, W., Chetchotisakd, P., Lertpatanasuwun, N., Intaranongpai, S., Ruchutrakool, T., Budhsarawong, D., Mootsikapun, P., Wuthiekanun, V., Teerawatasook, N., et al. (1999). Risk factors for melioidosis and bacteremic melioidosis. *Clinical Infectious Diseases, 29*(2), 408–413. doi:10.1086/520223

Terwilliger, T. C., Liebschner, D., Croll, T. I., Williams, C. J., McCoy, A. J., Poon, B. K., Afonine, P. V., Oeffner, R. D., Richardson, J. S., Read, R. J., et al. (2024). AlphaFold predictions are valuable hypotheses and accelerate but do not replace experimental structure determination. *Nature Methods, 21*(1), 110–116. doi:10.1038/s41592-023-02087-4

Wang, L., Wang, N., Zhang, W., Cheng, X., Yan, Z., Shao, G., Wang, X., Wang, R., & Fu, C. (2022). Therapeutic peptides: Current applications and future directions. *Signal Transduction and Targeted Therapy, 7*(1), 1–27. doi:10.1038/s41392-022-00904-4

Watkins, S. (2019). Design, synthesis, and evaluation of potential *Burkholderia pseudomallei* IspF inhibitors. *Graduate Research Theses & Dissertations.* https://huskiecommons.lib.niu.edu/allgraduate-thesesdissertations/2119

White, N. J. (2013). Melioidosis and glanders. In A. J. Magill, D. R. Hill, T. Solomon, & E. T. Ryan (Eds.), *Hunter's Tropical Medicine and Emerging Infectious Disease* (9th ed., pp.

580–583). W.B. Saunders. doi:10.1016/B978-1-4160-4390-4.00071-0

Wiersinga, W. J., Virk, H. S., Torres, A. G., Currie, B. J., Peacock, S. J., Dance, D. A. B., & Limmathurotsakul, D. (2018). Melioidosis. *Nature Reviews Disease Primers, 4*(1), 17107. doi:10.1038/nrdp.2017.107

Wu, G., Robertson, D. H., Brooks III, C. L., & Vieth, M. (2003). Detailed analysis of grid-based molecular docking: a case study of CDOCKER—A CHARMm-based MD docking algorithm. *Journal of Computational Chemistry, 24*(13), 1549–1562. doi:10.1002/jcc.10306

Xiong, G., Wu, Z., Yi, J., Fu, L., Yang, Z., Hsieh, C., Yin, M., Zeng, X., Wu, C., Lu, A., et al. (2021). ADMETlab 2.0: an integrated online platform for accurate and comprehensive predictions of ADMET properties. *Nucleic Acids Research, 49*(W1), W5–W14. doi:10.1093/nar/gkab255

Yu, W., & MacKerell, A. D. (2017). Computer-aided drug design methods. *Methods in Molecular Biology, 1520*, 85–106. doi:10.1007/978-1-4939-6634-9_5