Identification of Pseudomonas pseudomallei FabI1 inhibitors of antimicrobial agents against melioidosis using virtual screening approaches

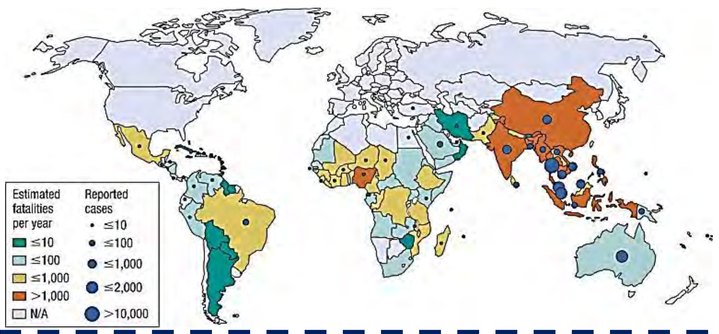
Darunee Sukchit[1], Siripen Modmung[1], Sirintip Sangsawang[1], Chayanin Hanwarinroj[1], Bandit Khamsri[1], Somjintana Taweepanich[1], Chan Inntam[1], Jidapa Sangswan[2], Sasithorn Lorroengsil[2], Pharit Kamsri[3], Auradee Punkvang[3], Jiraporn Leanpolchareanchai[4], Narisara Chantratita[5], Warinthorn Chavasiri[6], Khomson Suttisintong[7], Prasat Kittakoop[8,9,10], Noriyuki Kurita[11], Pornpan Pungpo[1]*

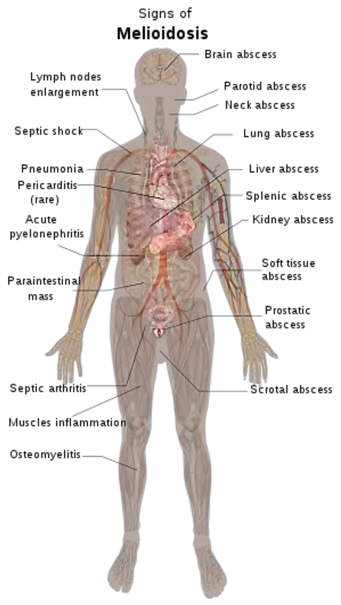
[1] Department of Chemistry, Faculty of Science, Ubon Ratchathani University, Ubon Ratchathani 34190, Thailand
[2] Department of Biological Science, Faculty of Science, Ubon Ratchathani University, Ubon Ratchathani 34190, Thailand
[3] Division of Chemistry, Faculty of Science, Nakhon Phanom University, Nakhon Phanom 48000, Thailand
[4] Faculty of Pharmacy, Mahidol University, 10400 Bangkok, Thailand
[5] Department of Microbiology and Immunology, Faculty of Tropical Medicine, Mahidol University, 10400 Bangkok, Thailand
[6] Department of Chemistry, Faculty of Science, Chulalongkorn University, 10330 Bangkok, Thailand
[7] National Nanotechnology Center, NSTDA, 111 Thailand Science Park, Klong Luang, Pathum Thani, Thailand
[8] Chulabhorn Research Institute, Kamphaeng Phet 6 Road, Laksi, Bangkok 10210, Thailand
[9] Chulabhorn Graduate Institute, Chemical Biology Program, Chulabhorn Royal Academy, Kamphaeng Phet 6 Road, Laksi, Bangkok 10210, Thailand
[10] Center of Excellence on Environmental Health and Toxicology (EHT)
[11] Department of Computer Science and Engineering, Toyohashi University of Technology, Toyohashi 441-8580, Japan

***Email: pornpan_ubu@yahoo.com**

Introduction

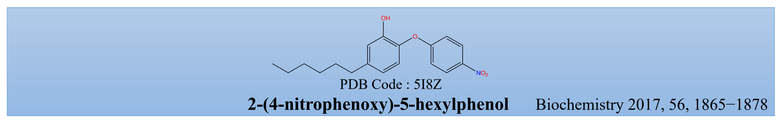
Melioidosis is a complex disease because of its rapid progression and tendency to generate latent infections. The etiologic agent of melioidosis is the gram-negative organism *Burkholderia pseudomallei.* To identify new and potential melioidosis inhibitors, Zinc database was applied to screen novel melioidosis inhibitor. Then, drug-likeness properties and antibacterial predictions were elucidated. Molecular docking calculations using Glide program were performed.





Material and Methods

➢ Flowchart of Virtual Screening



Pharmacophore
ZINC database

Drug-likeness and Medicinal Chemistry properties
Swiss ADME

PASS online predicted anti- Burkholderia pseudomallei

Molecular Docking Calculations
Glide program

Figure 1 The virtual screening process to be melioidosis inhibitors

Results

➢ Virtual Screening

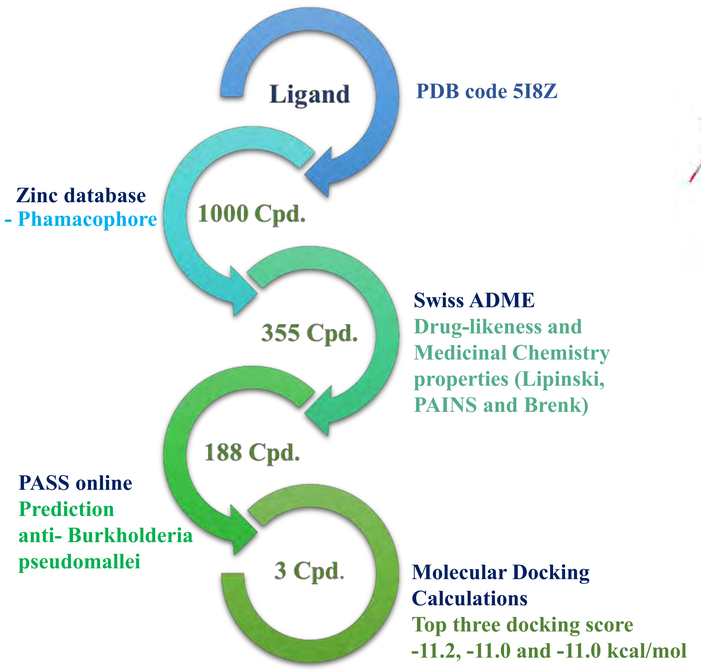
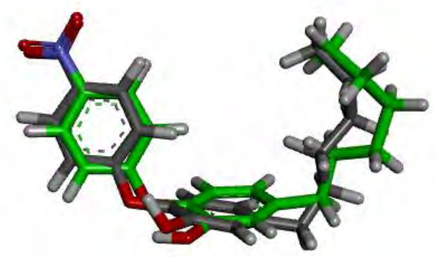


Figure 2 The virtual screening process of melioidosis inhibition from zinc database

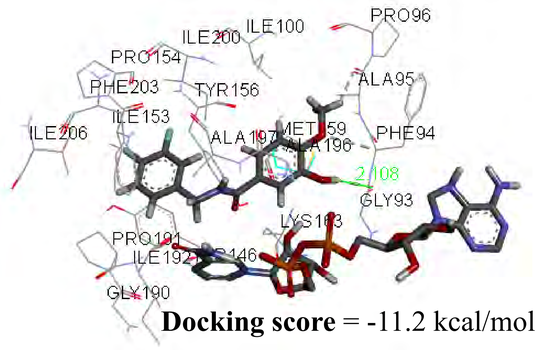
➢ Validation method



RMSD = 1.13 A°

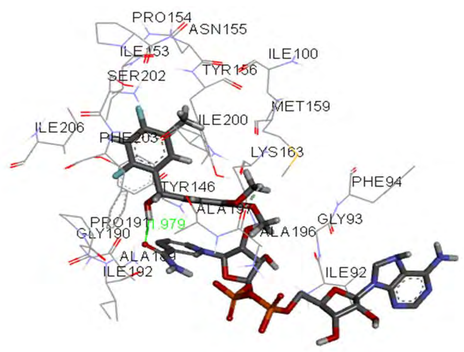
Figure 3. Superimposition of X-ray ligand (Grey) and docked ligand (Green)

➢ Molecular Docking Calculations



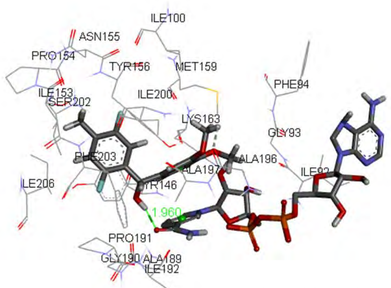
Docking score = -11.2 kcal/mol

Figure 4. The crucial interaction of ZINC93953430 (Compound 1) in FabI1 binding site



Docking score = -11.0 kcal/mol

Figure 5. The crucial interaction of ZINC94081106 (Compound 2) in FabI1 binding site



Docking score = -11.0 kcal/mol

Figure 6. The crucial interaction of ZINC94708668 (Compound 3) in FabI1 binding site

Table 1 Lipinski's rules of five, PAINS, Brenk, Burkholderia pseudomallei, RESISTANT Burkholderia pseudomallei and docking score of hit compounds

Zinc code (Cpd.)	Lipinski					PAINS	Brenk	Burkholderia pseudomallei	RESISTANT Burkholderia pseudomallei	Docking score (kcal/mol)
	MW	Rotatable bond	H-bond acceptors	H-bond donors	MlogP					
ZINC93953430 (1)	293.27	5	5	2	2.85	0	0	0	0.0295	-11.2
ZINC94081106 (2)	294.29	4	5	1	3.35	0	0	0	0.0610	-11.0
ZINC94708668 (3)	294.29	4	5	1	3.35	0	0	0	0.0966	-11.0

Conclusions

- ✓ **Top three compounds which showed docking score closed to x-ray ligand including ZINC93953430 (Compound 1), ZINC94081106 (Compound 2) and ZINC94708668 (Compound 3) were selected.**
- ✓ **The crucial interactions are hydrogen bond interactions with Gly93 residue and NAD^+ cofactor and hydrophobic interactions with Phe94, Ile100, Ile153, Pro154, Met159, Pro191, Ile192, Ala196, Ala197, Ile200, Phe203 and Ile206 residues were found as crucial interactions.**
- ✓ **The integrated results provide fruitful information for discovery of melioidosis inhibitor with highly and more potent.**

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