Molecular Modeling Analysis for Purposing Depsidones and Diaryl Ethers from The Endophytic Fungus *Corynespora cassiicola* L36 Against *Burkholderia pseudomalle* FabI1

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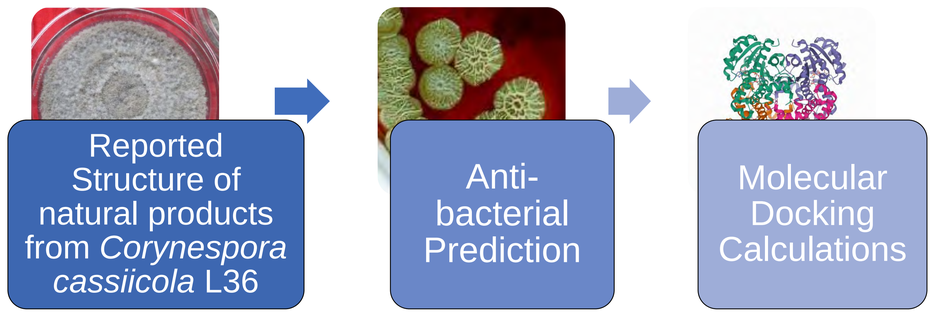
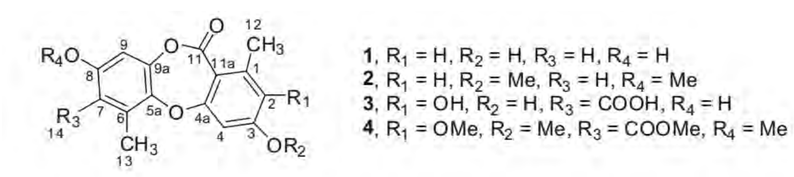
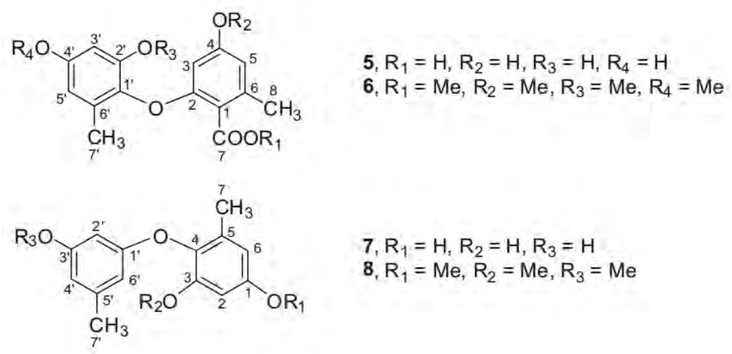
Introduction

Melioidosis is a serious infectious disease caused by the environmental Gram-negative bacillus *Burkholderia pseudomallei* (*B. pseudomallei*). Melioidosis, is associated with a high case fatality rate in Thailand, due in part to difficulties in clinical recognition and diagnostic confirmation of the disease. Incidence of melioidosis is increasing in Northeast Thailand. *B. pseudomallei* are intrinsically resistant to antibiotics. Therefore, the potential drug to overcome drug resistant is urgently required. This study, FabI1 has been identified as novel drug target for anti- *B. pseudomallei* drug. Therefore, we aims to identify of novel FabI1 inhibitors from Thai medicinal plant to over come antibiotic resistant of *B. pseudomallei* and used as new anti-melioidosis agents.

Materials and Methods







Conclusions

- Five compounds based on were identified as potential FabI1 inhibitors which displayed the biological activity prediction against resistant- *Burkholderia pseudomallei* (0.0294 - 0.2629).
- The binding affinity based on docking score raining from -5.15 to -6.92 kcal/mol.
- 2,3',4-Trihydroxy-5',6-dimethyldiphenyl ether was highest binding affinity which shown H-bond interaction with NH and an oxygen carbonyl of Gly96 backbone in FabI1 binding site.

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Results

Anti-*B. pseudomallei* prediction and the docking score

Table 1 Anti-*B. pseudomallei* prediction and the docking score of FabI1 inhibitors

Cpd.	*Burkholderia pseudomallei*	RESISTANT *Burkholderia pseudomallei*	Docking score (kcal/mol)
1	-	0.098	-5.15
2	-	-	-
3	-	0.1017	-6.88
4	-	-	-
5	0.0392	0.2629	-5.95
6	-	-	-
7	-	0.2247	-6.92
8	-	0.0294	-5.87

Drug-likeness properties

Table 2 Drug-likeness properties of FabI1 inhibitors

Descriptor	1	3	5	7	8
Molecular Weight	272.26	332.26	290.27	246.26	288.34
LogP	3.04	2.44	2.91	3.21	4.12
#Rotatable Bonds	0	1	3	2	5
#Acceptors	5	7	5	4	4
#Donors	2	4	4	3	0
Surface Area	114.56	134.67	120.04	104.72	124.77

ADMET properties

Table 3 The predicted ADMET properties of FabI1 inhibitors

Model Name	1	3	5	7	8	Unit
Absorption						
Water solubility	-3.63	-3.22	-2.99	-3.06	-5.07	log mol/L
Caco2 permeability	1.01	1.00	0.41	0.80	1.27	log Papp in 10^{-6} cm/s
Intestinal absorption (human)	92.09	54.92	59.09	91.75	97.43	% Absorbed
Skin Permeability	-2.79	-2.74	-2.74	-2.77	-2.59	log Kp
P-glycoprotein substrate	Yes	Yes	Yes	Yes	No	
P-glycoprotein I inhibitor	No	No	No	No	No	
P-glycoprotein II inhibitor	No	No	No	No	No	
Distribution						
VDss (human)	-0.13	0.07	-0.97	0.02	0.07	
Fraction unbound (human)	0.22	0.27	0.22	0.20	0.13	Fu
BBB permeability	-0.12	-1.47	-1.25	-0.88	-0.02	log BB
CNS permeability	-1.97	-3.42	-3.13	-2.12	-1.57	log PS
Metabolism						
CYP2D6 substrate	No	No	No	No	No	
CYP3A4 substrate	No	No	No	No	Yes	
CYP1A2 inhibitior	Yes	No	No	Yes	Yes	
CYP2C19 inhibitior	Yes	No	No	Yes	Yes	
CYP2C9 inhibitior	No	No	No	Yes	Yes	
CYP2D6 inhibitior	No	No	No	No	No	
CYP3A4 inhibitior	No	No	No	No	No	
Excretion						
Total Clearance	0.60	0.69	0.65	0.57	0.75	log ml/min/kg
Renal OCT2 substrate	No	No	No	No	No	
Toxicity						
AMES toxicity	Yes	Yes	No	Yes	No	
Max. tolerated dose (human)	0.59	1.12	1.24	0.24	1.30	log mg/kg/day
hERG I inhibitor	No	No	No	No	No	
hERG II inhibitor	No	No	No	No	No	
Oral Rat Acute Toxicity (LD_{50})	2.34	2.51	2.42	2.26	2.36	mol/kg
Oral Rat Chronic Toxicity (LOAEL)	1.60	2.23	2.80	1.86	2.12	log mg/kg_bw/day
Hepatotoxicity	No	No	No	No	No	
Skin Sensitisation	No	No	No	No	No	
T.Pyriformis toxicity	0.42	0.29	0.29	0.60	1.04	log ug/L
Minnow toxicity	1.11	1.67	0.76	0.55	-0.43	log mM

The binding mode and binding interactions

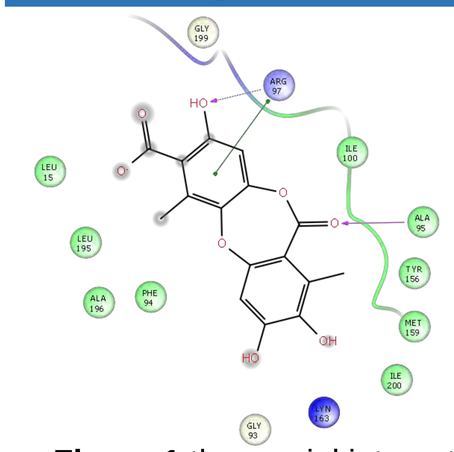

Figure 1 the crucial interaction compound 3 in FabI1 binding pocket

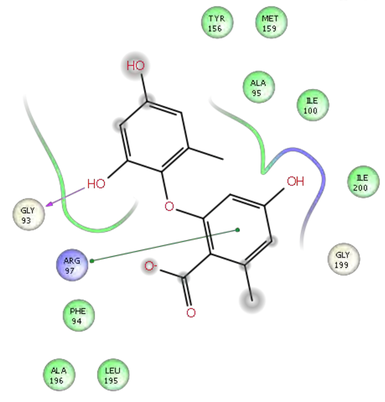

Figure 2 the crucial interaction compound 5 in FabI1 binding pocket

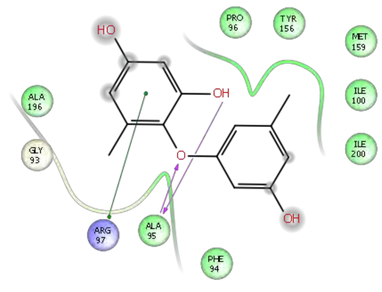

Figure 3 the crucial interaction compound 7 in FabI1 binding pocket