Flavans from *Desmos cochinchinensis* as Highly Potent FabI1 Inhibitors of *Burkholderia pseudomallei*: *In silico* based Rational Design Approaches

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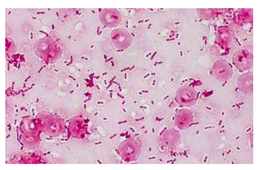
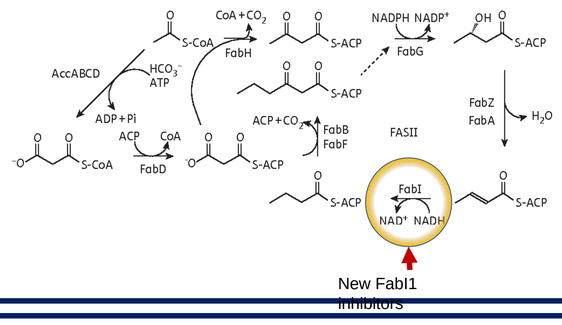
Introduction

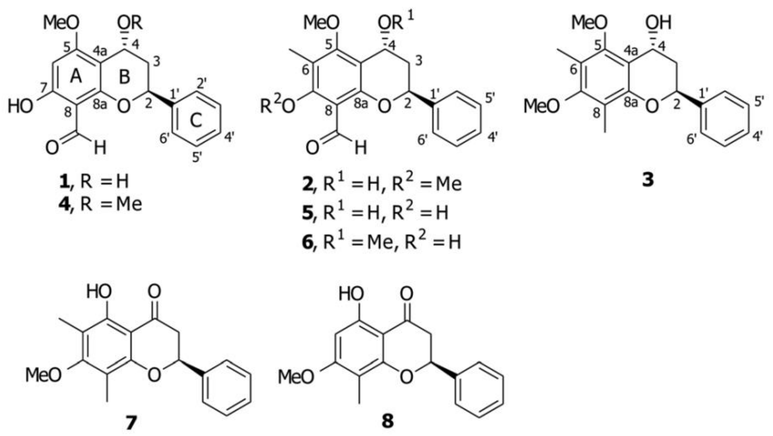
Burkholderia pseudomallei (*B. pseudomallei*) is a Gram-negative soil-dwelling bacillus that causes melioidosis, a frequently fatal infectious disease, in tropical and subtropical regions. Melioidosis is highly endemic in Thailand. Incidence of melioidosis is increasing in Northeast Thailand. *B. pseudomallei* are intrinsically resistant to antibiotics such as penicillin, ampicillin, first- and second-generation cephalosporins, gentamicin, tobramycin, and streptomycin. 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 herb to over come antibiotic resistant of *B. pseudomallei*.



B. pseudomallei



Materials and Methods



Reported Structure of Flavans from *Desmos cochinchinensis*

Anti-bacterial Prediction

Molecular docking Calculations

Results

The docking score, anti-*B. pseudomallei* prediction, and drug-likeness properties

Table 1 The docking score, anti-*B. pseudomallei* prediction, and drug-likeness properties of Cpd.7 and Cpd.8

Cpd.	docking score (kcal/mol)	RESISTANT *B. pseudomallei*	Molecular Weight (g/mol)	LogP	#Rotatable Bonds	#Acceptors	#Donors	Surface Area
7	-10.074	0.0204	298.34	3.72	2	4	1	128.86
8	-8.495	0.0912	284.31	3.42	2	4	1	122.49

ADMET properties

Table 2 The predicted ADMET properties of Cpd.7 and Cpd.8

Model Name	7	8	Unit
Adsorption			
Water solubility	-4.37	-4.04	(log mol/L
Caco2 permeability	1.34	1.33	log Papp in 10^6 cm/s
Intestinal absorption (human)	94.92	93.79	% Absorbed
Skin Permeability	-3.13	-3.06	log Kp
P-glycoprotein substrate	No	No	
P-glycoprotein I inhibitor	No	No	
P-glycoprotein II inhibitor	No	No	
Distribution			
VDss (human)	0.23	0.06	log L/kg
Fraction unbound (human)	0.09	0.10	Fu
BBB permeability	-0.41	-0.41	log BB
CNS permeability	-1.86	-1.934	log PS
Metabolism			
CYP2D6 substrate	No	No	
CYP3A4 substrate	No	No	
CYP1A2 inhibitior	Yes	Yes	
CYP2C19 inhibitior	Yes	Yes	
CYP2C9 inhibitior	Yes	Yes	
CYP2D6 inhibitior	No	No	
CYP3A4 inhibitior	Yes	Yes	
Excretion			
Total Clearance	0.17	0.17	log ml/min/kg
Renal OCT2 substrate	No	No	
Toxicity			
AMES toxicity	Yes	Yes	
Max. tolerated dose (human)	0.28	0.18	log mg/kg/day
hERG I inhibitor	No	No	
hERG II inhibitor	No	Yes	
Oral Rat Acute Toxicity (LD50)	2.45	2.35	mol/kg
Oral Rat Chronic Toxicity (LOAEL)	1.79	1.85	log mg/kg_bw/day
Hepatotoxicity	No	No	
Skin Sensitisation	No	No	
T.Pyriformis toxicity	1.03	1.03	log ug/L
Minnow toxicity	-0.34	0.16	log mM

The binding mode and binding interactions

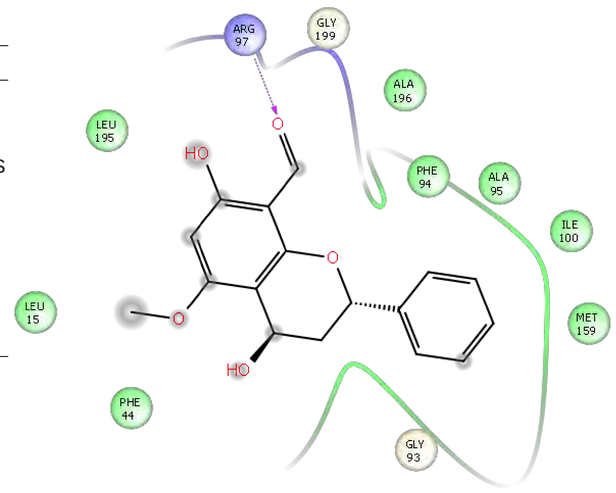


Figure 1 the crucial interaction of (2S)-5-Hydroxy-7-methoxy-6,8-dimethylflavanone (7) in FabI1 binding pocket

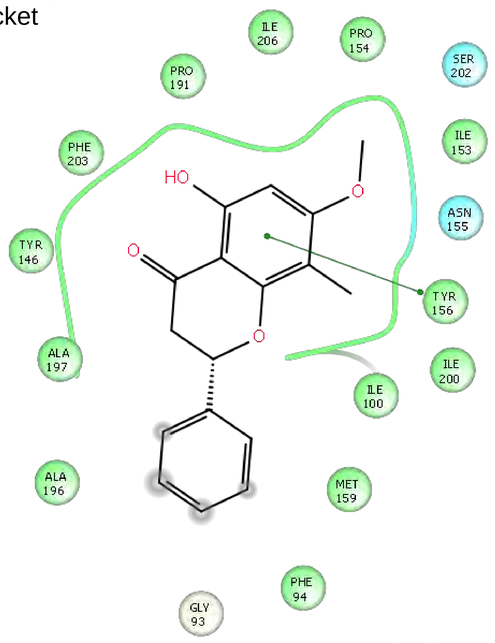


Figure 2 the crucial interaction of (2S)-5-hydroxy-7-methoxy-8-methyl-2-phenyl-2,3-dihydrochromen-4-one (8) in FabI1 binding pocket

Conclusions

- (2S)-5-Hydroxy-7-methoxy-6,8-dimethylflavanone (7) and (2S)-5-hydroxy-7-methoxy-8-methyl-2-phenyl-2,3-dihydrochromen-4-one (7) extracted from *Desmos cochinchinensis* were promising compounds with the anti-bacterial prediction against *resistant-B. pseudomallei* ranging from 0.0204-0.0912.
- The highest binding affinity was found between flavan compound 7 (-10.07 kcal/mol) with *B. pseudomallei* FabI1 and hydrogen bond interaction between hydroxyl (OH) with an oxygen carbonyl backbone of Gly93 and pi-pi interaction of phenyl ring with Phe203 sidechain were suggested as the crucial interaction for binding.

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