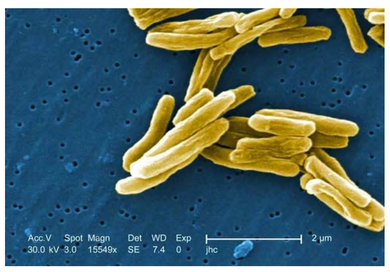
Discovery of novel and potential InhA inhibitors based on virtual screening approaches

N. Phusi[1], T. Pornprom[1], C. Hanwarinroj[1], C. Inntam[1], S. Taveepanich[1], J. sangswan[2], S Lorroengsil[2], P. Kamsri[3], A. Punkvang[3], P. Saparpakorn[4], S. Hannongbua[4], K. Suttisintong[5], P. Kittakoop[6,7,8], N. Kurita[9], J. Spencer[10], A. J. Mulholland[11], and P. 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]*Department of Chemistry, Faculty of Science, Kasetsart University, Bangkok 10900, Thailand*
[5]*National Nanotechnology Center, NSTDA, 111 Thailand Science Park, Klong Luang, Pathum Thani 12120, Thailand*
[6]*Chulabhorn Research Institute, Kamphaeng Phet 6 Road, Laksi, Bangkok 10210, Thailand*
[7]*Chulabhorn Graduate Institute, Chulabhorn Royal Academy, Bangkok 10210, Thailand*
[8]*Center of Excellence on Environmental Health and Toxicology (EHT)*
[9]*Department of Computer Science and Engineering, Toyohashi University of Technology, Tempaku-cho, Toyohashi, Aichi, 441-8580, Japan*
[10]*School of Cellular and Molecular Medicine, University of Bristol, Bristol, BS8 1TD, United Kingdom*
[11]*Centre for Computational Chemistry, School of Chemistry, University of Bristol, Bristol, BS8 1TS, United Kingdom*

*Email: pornpan_ubu@yahoo.com

INTRODUCTION



-Tuberculosis or TB is caused by *Mycobacterium tuberculosis*.

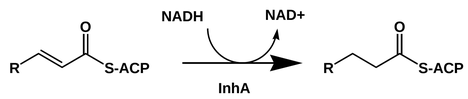
-In 2021, WHO report, about 9.9 million people around the world fell ill with TB and 1.5 million people died from the disease.

-In addition, mutation and drug resistant are the serious problem for treatment.

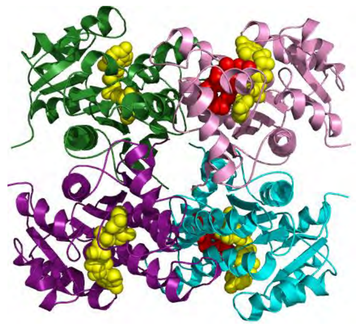
-Therefore, the effective drugs are urgently required.

Enoyl-ACP Reductase or InhA

Excellent target for the development of new anti-TB agents

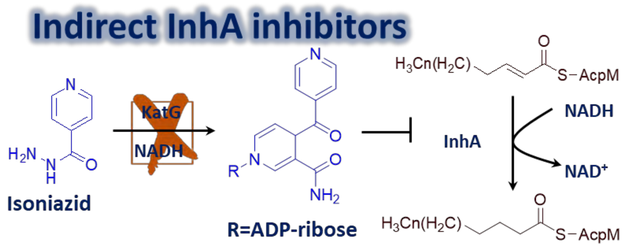


The biochemical mechanism of the InhA enzyme



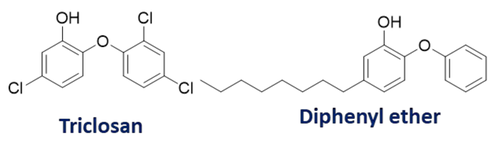
- ❑The InhA is a key enzyme catalyzing the reduction of long-chain trans-2-enoyl-ACP in the type II fatty acid biosynthesis pathway of *M. tuberculosis*.
- ❑Inhibition of InhA terminates the biosynthesis of the mycolic acids, central constituents of the mycobacterial cell wall
- ❑The InhA has been identified as the target of isoniazid

Indirect InhA inhibitors

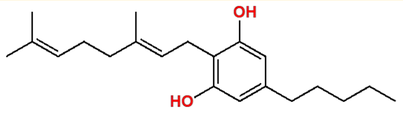


❑ Mutations of Kat G

Direct InhA inhibitors



MATERIAL & METHODS



Cannabigerol (CBG)
IC_{50} 5.2 ± 0.1 µM
Molecules 2019, 24, 2567

1. 50% similarity search — Specs database
2. Drug-likeness properties — Swiss ADME software
3. Molecular Docking Calculations — AutoDock4.2 program, PDB Code : 3FNH
4. Biological testing search — PubChem software

Hit compound

RESULTS

50% similarity search from Specs database (6 compounds)

↓

Lipinski and PAINS (5 compounds)

↓

Docking score -6.94 to -9.02 kcal/mol (5 compounds)

↓

Biological testing search by PubChem (3 compounds)

↓

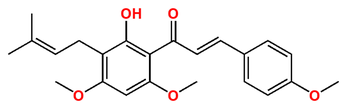
Hit compound (3 compounds)

Ligand based virtual screening

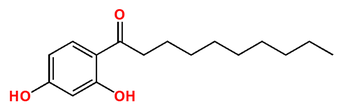
Structure based virtual screening

In silico based anti-tuberculosis activity

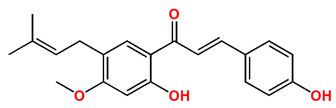
Figure 1 The virtual screening process of InhA inhibition from specs database.



AA-504/21163099 (Cpd.1)



AK-087/42718139 (Cpd.2)



AK-693/21159010 (Cpd.3)

Figure 2 Structure of hit compounds form virtual screening.

Table 1 Lipinski's five rules, PAINS, and docking score of hit compounds.

Cpd.	Lipinski					PAINS	Docking score (kcal/mol)
	MW	Rotatable bond	H-bond acceptors	H-bond donors	MlogP		
CBG	312.53	9	2	2	6.60	0	-8.00
1	382.45	8	5	1	2.79	0	-8.56
2	264.36	9	3	2	2.74	0	-6.94
3	338.40	6	4	2	2.92	0	-9.01

Molecular weight (MW) is less than 500 g/mol
Rotatable bonds is less than 10 bonds
Number of H-bond acceptors is less than 10
Number of H-bond donors is less than 5
MlogP is less than 4.15

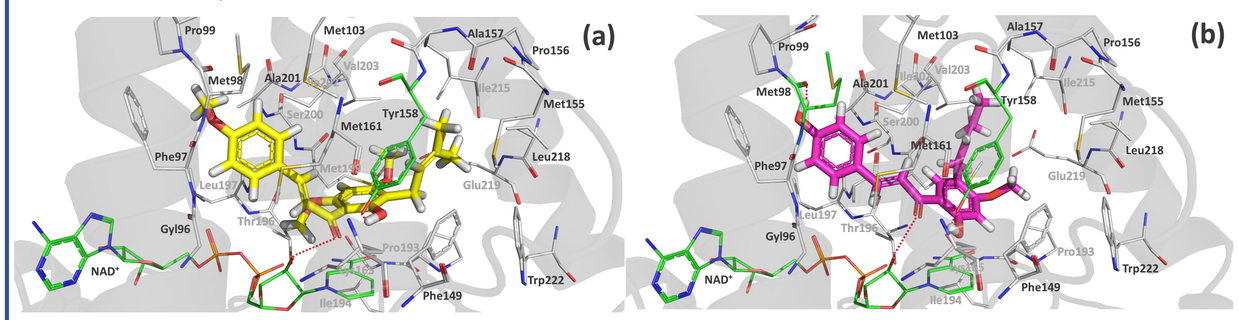


Figure 3 The binding mode and binding interactions of Cpd.1 (a) and Cpd.3 (b) in InhA binding pocket.

CONCLUSIONS

The work presented here demonstrates that ligand based, and structure based virtual screening to identify novel InhA inhibitors with potential to act as antituberculosis agents. Discovery of novel InhA inhibitor by docking calculation, Lipinski rule of five, PAINS, and biological testing search by PubChem were used to screen candidates from Specs databases. A total of 3 hit compounds were obtained. The crucial interaction of hit compounds interacted with hydroxy group of Met98, Tyr158 and NAD^+ cofactor by hydrogen bond interaction. In addition, hydrophobic interactions with Phe97, Met98, Met103, Phe149, Met155, Met161, Pro193, Met199, and Ile202 residues were found. Therefore, the virtual screening provides useful information for rational design new and more potent InhA inhibitors as anti-tuberculosis agents.

ACKNOWLEDGMENTS

-Thailand Graduate Institute of Science and Technology (TGIST) (SCA-CO-2563-12135-TH) to N. Phusi
-The Thailand Research Fund (RSA5980057)
-The RGJ Advanced Programe (RAP60K0009)
-Center of Excellence for Innovation in Chemistry (PERCH-CIC)
-Ubon Ratchathani University
-The Faculty of Science, Ubon Ratchathani University
-Faculty of Science, Kasetsart University
-The University of Bristol
-The National Electronics and Computer Technology Center (NECTEC)
-The National Nanotechnology Center (NANOTEC)