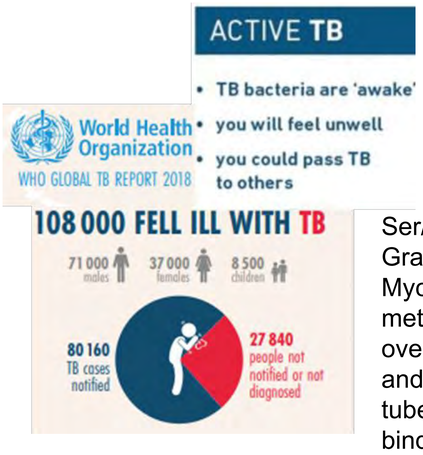
Understanding binding modes and binding interactions of 4-oxocrotonic acid as highly potential PknB inhibitors through computer aided drug design

Chayanin Hanwarinroj[1], Paptawan Thongdee[1], Chan Inntam[1], Somjintana Taveepanich[1], Jidapa Sangswan[2], Sasithorn Lorroengsil[2], Pharit Kamsri[3], Auradee Punkvang[3], Patchreenart Saparpakorn[4], Supa Hannongbua[4], Khomson Suttisintong[5], Prasat Kittakoop[6,7,8], James Spencer[9], Adrian J. Mulholland[10], and Pornpan Pungpo[1,*]

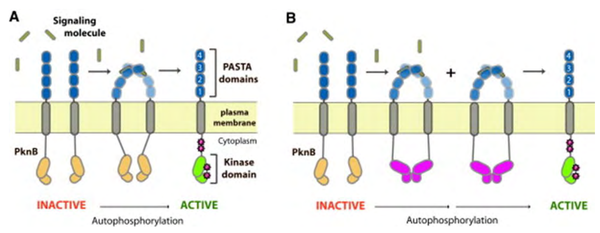
[1]Department of Chemistry, Faculty of Science, Ubon Ratchathani University, Ubon Ratchathani 34190, Thailand
[2]Department of Biological Science, Faculty of Science, Ubon Ratchathani University, Ubon Ratchathani 34190, Thailand[3]Division of Chemistry, Faculty of Science, Nakhon Phanom University, Nakhon Phanom 48000, Thailand
[4]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]School of Cellular and Molecular Medicine, University of Bristol, Bristol, BS8 1TD, United Kingdom
[10]Centre for Computational Chemistry, School of Chemistry, University of Bristol, Bristol, BS8 1TS, United Kingdom
*Email: pornpan_ubu@yahoo.com

Introduction

TB situation in THAILAND



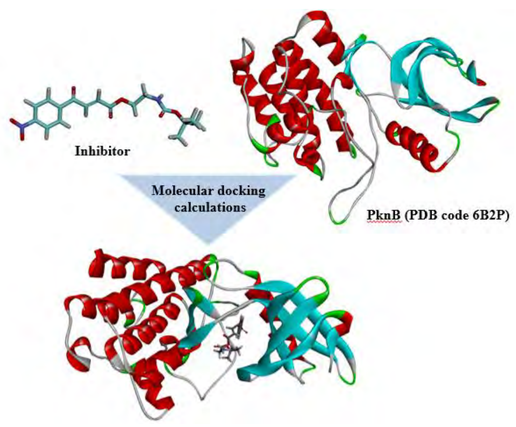
Ref. www.who.int/tb/data

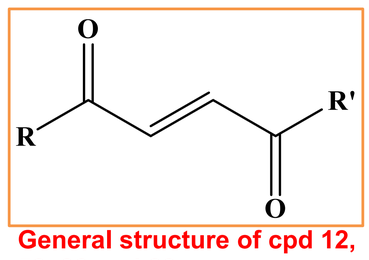


Ref. Structure 18, 606–615,

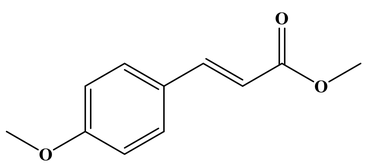
Ser/Thr protein kinase (STPK) highly conserved in Gram-positive bacteria and apparently essential for Mycobacterial viability. Essential for cell division and metabolism, expressed in exponential growth and overexpression causes defects in cell wall synthesis and cell division. This enzyme has been identified as tuberculosis drug development target. This work the binding mode and crucial interactions of 4-oxocrotonic acid derivatives using Autodock 4.2 program

Material and Methods

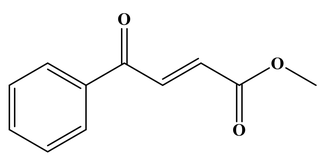




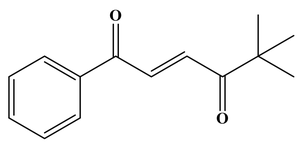
General structure of cpd 12, 52, 82 and 82



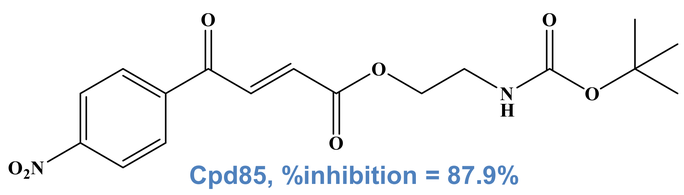
Cpd02, %inhibition = 1.7%



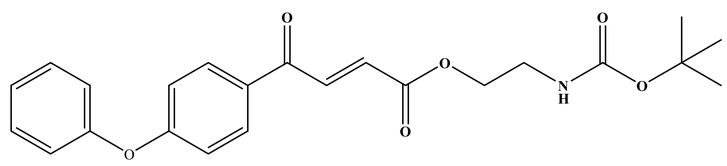
Cpd12, %inhibition = 47.8%



Cpd52, %inhibition = 11.2%



Cpd85, %inhibition = 87.9%

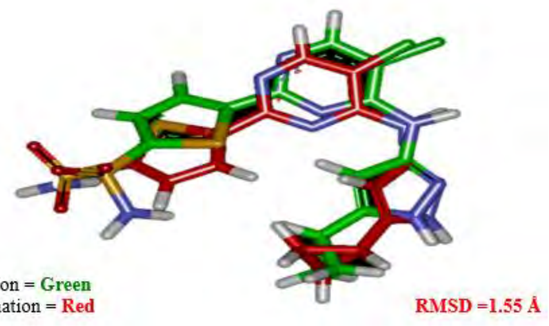


Cpd82, %inhibition = 46.0%

Figure 1. Chemical structure and % inhibition of 4-oxocrotonic acid derivatives
Ref. RSC Adv., 2017, 7, 4763

Results

➢ **Method validation**



➢ **Binding mode and crucial interaction**

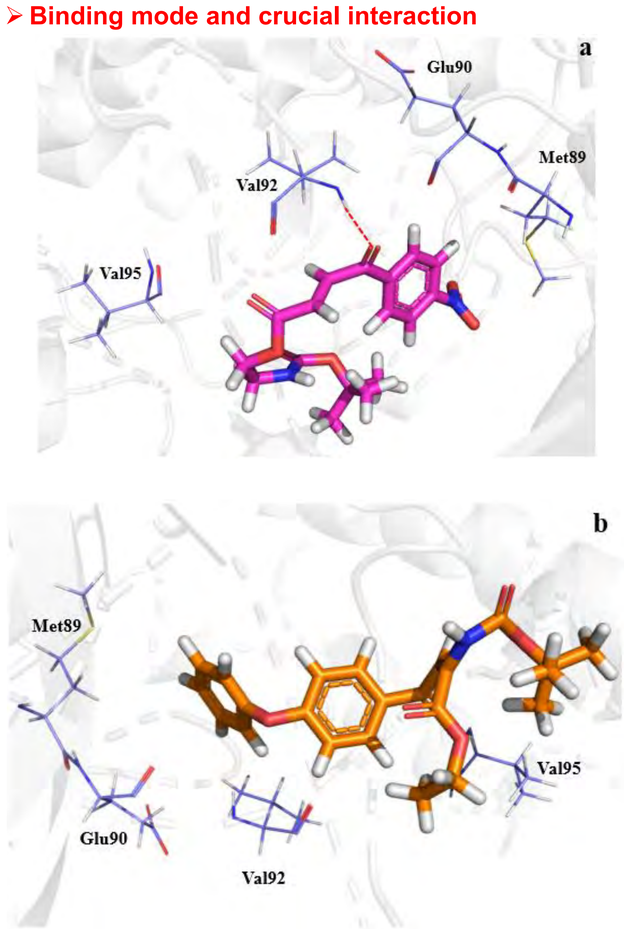


Figure 2. Binding mode and crucial interaction of a) highest active compound (cpd85), b) moderate active compound (cpd 82) and c) less active compound (cpd02)

➢ **Effect of R' position**

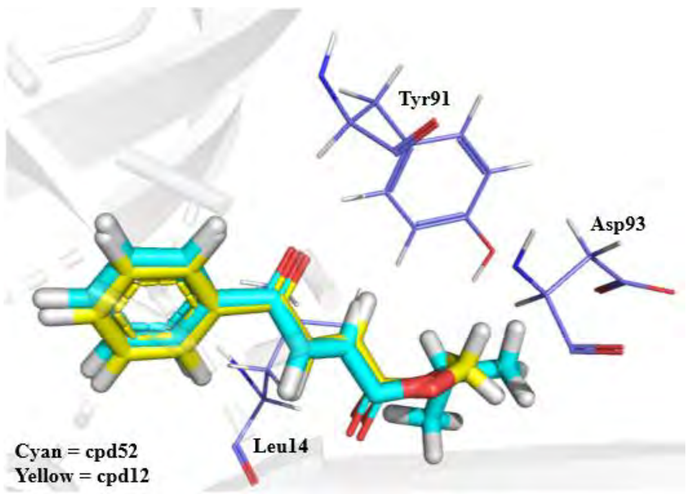


Figure 3. Binding mode and crucial interaction of cpd12 (yellow) and cpd52 (cyan)

➢ **Effect of R position**

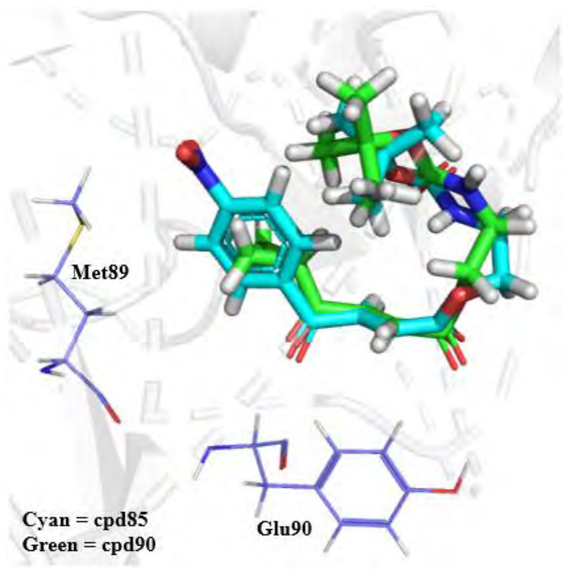


Figure 4. Binding mode and crucial interaction of cpd90 (yellow) and cpd85 (cyan)

Conclusion

Molecular docking calculations was successfully to get better understanding binding modes and crucial interactions of 4-oxocrotonic acid in PknB binding site. The result illustrated the hydrogen bond interaction Glu90, Val92 and Val95 residue. In addition, hydrophobic interaction between ligand and Leu17, Val25, Ala38, Val72, and Val95 residues were found. The obtained result provides beneficially information for further modification of 4-oxocrotonic acid derivatives with highly and more potent against *mycobacterium tuberculosis*.

Acknowledgements

❑ Thailand Graduate Institute of Science and Technology (TGIST) (SCA-CO-2560-4375TH) to C. Hanwarinroj
❑ The Excellence for Innovation in Chemistry (PERCH-CIC)
❑ Faculty of Science, Ubon Ratchathani University
❑ Ubon Ratchathani University
❑ Kasetsart University
❑ Nakhon Phanom University
❑ School of Chemistry, University of Bristol
❑ National Electronics and Computer Technology (NECTEC)