Molecular docking study of benzosuberone-thiazole derivatives for rational design of novel GyrB inhibitors as anti-tuberculosis agents

Bongkochawan Pakamwong[1], Bundit Kamsri[1], Paptawan Thongdee[1], Naruedon Phusi[1], Somjintana Taveepanich[1], Jidapa sangswan[2], Pharit Kamsri[3], Auradee Punkvang[3], Patchreenart Saparpakorn[4], Supa Hannongbua[4], Jiraporn Leanpolchareanchai[5], Khomson Suttisintong[6], Prasat Kittakoop[7,8,9], James Spencer[10], Adrian J. Mulholland[11], Pornpan Pungpo[1,*]

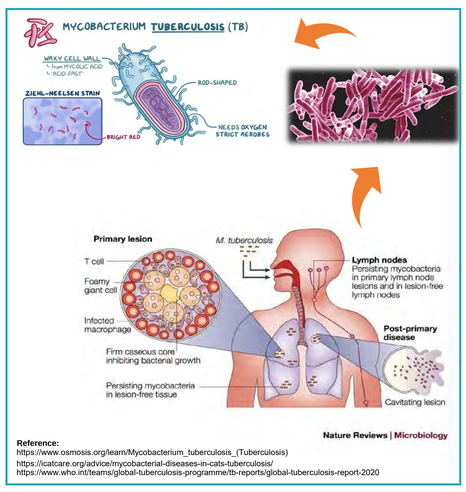
[1]Department of Chemistry, Faculty of Science, Ubon Ratchathani University, Ubon Ratchathani 34190, Thailand
[2]Department of Biological Science, Faculty of Science, Ubon Ratchathani University, Ubon Ratchathani 34190, Thailand
[3]Division of Chemistry, Faculty of Science, Nakhon Phanom University, Nakhon Phanom 48000, Thailand
[4]Department of Chemistry, Faculty of Science, Kasetsart University, Bangkok 10900, Thailand
[5]Department of Pharmacy, Faculty of Pharmacy, Mahidol University, Bangkok 10400, Thailand
[6]National Nanotechnology Center, National Science and Technology Development Agency, Pathum Thani 12120, Thailand
[7]Chulabhorn Research Institute, Bangkok 10210, Thailand
[8]Chulabhorn Graduate Institute, Chemical Biology Program, Chulabhorn Royal Academy, Bangkok 10210, Thailand
[9]Center of Excellence on Environmental Health and Toxicology (EHT)
[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

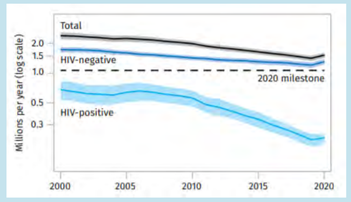
Tuberculosis (TB), caused by *Mycobacterium tuberculosis* (*M. tuberculosis*), has remained a major global health problem.

World Health Organization

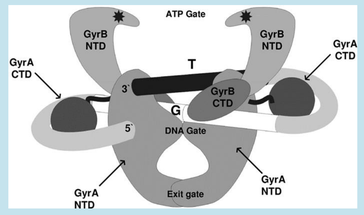
The Global TB Report 2021
- 9.9 million people around the world fell ill with TB
- 1.5 million people died from the disease



Reference:
https://www.osmosis.org/learn/Mycobacterium_tuberculosis_(Tuberculosis)
https://icatcare.org/advice/mycobacterial-diseases-in-cats-tuberculosis/
https://www.who.int/teams/global-tuberculosis-programme/tb-reports/global-tuberculosis-report-2020



Global trends in the estimated number of TB deaths, 2000-2020



DNA gyrase

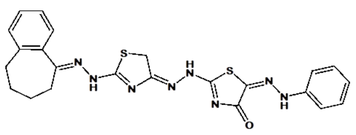
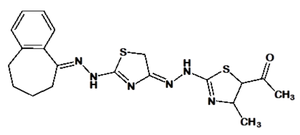
Therefore, discover of new potential GyrB inhibitors are urgent to overcome this drug resistant problem.

DNA Gyrase is an attractive target for antibacterial which is an essential enzyme that has roles in the fundamental biological processes of replication, transcription and recombination. Mutations of DNA gyrase affected to fluoroquinolone drug resistance in GyrA domain are the main problem of treating tuberculosis. GyrB domain has been identified as a suitable target to overcome the fluoroquinolone drug resistant.

MATERIALS AND METHOD

Structure and biological activities of two selected benzosuberone-thiazole derivatives from literature (Bioorg. Chem. 104 (2020) 104316.) summarized in **Table 1**. Molecular docking calculations using the Maestro 10.2 program was performed to predict the potent inhibitors in the GyrB binding pocket (PDB code 4BAE).

Table 1. Two chemical structures and their biological activity of benzosuberone-thiazole derivatives

Compounds	Structure	MIC (ug/ml)		IC_{50} (μM)
		Sensitive *M. tuberculosis*	Resistant *M. tuberculosis*	M.TB DNA gyrase ATPase assay
22		0.12	0.98	5.61
27		0.24	1.95	9.76

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- Faculty of Science, Kasetsart University
- School of Chemistry, University of Bristol
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RESULTS

Validation of the molecular docking calculations

The molecular docking calculations predicted the binding mode, binding interactions and binding energy of 4BAE ligand in GyrB binding site with the root-mean square deviation (RMSD) of 0.86 angstrom in **Figure1**.

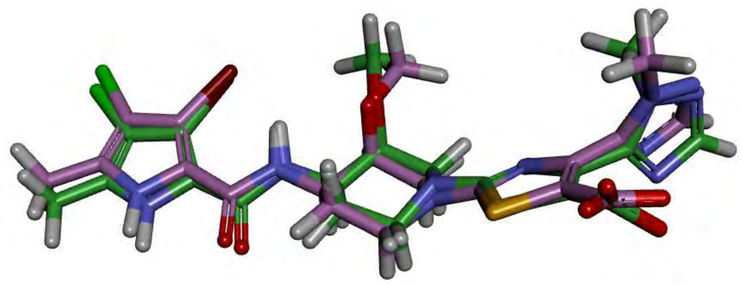
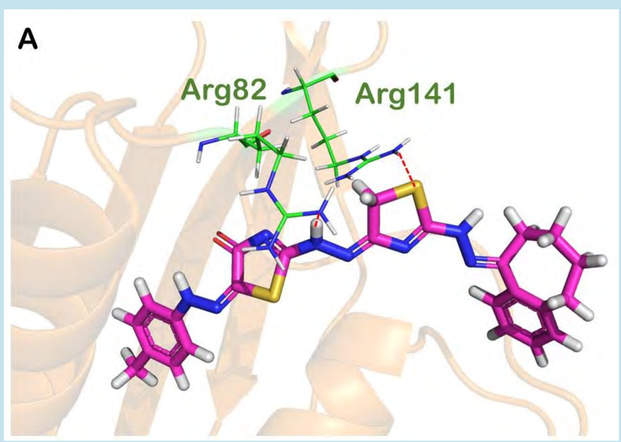


Figure 1. Superimposition of the X-ray crystal structure (green) and docked conformation (pink) of the 4BAE adduct in the GyrB binding pocket.

Molecular docking analysis



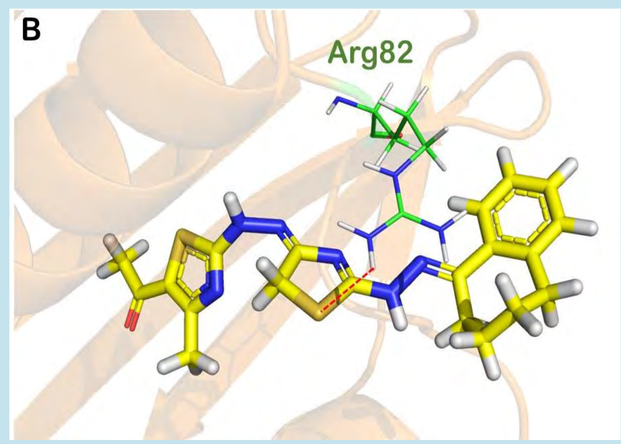
Compound 22

Glide docking score -4.583

Hydrogen bond interactions :

-Hydrogen atom of NH group with nitrogen atom of **Arg82**

-Sulfur atom of thiazole moiety with hydrogen atom of **Arg141**



Compound 27

Glide docking score -3.374

Hydrogen bond interaction :

-Sulfur atom of thiazole moiety with hydrogen atom of **Arg82**

Figure 2. Binding mode, binding interaction and binding energy of compound 22 (A) and 27 (B) obtained molecular docking calculations. Red line showed hydrogen bond interactions.

Compound 22 has two hydrogen bond interactions to correlate with low glide docking score.

CONCLUSIONS

Molecular docking calculations was used to evaluate binding mode, binding interaction and binding energy between benzosuberone-thiazole derivatives with GyrB pocket. The result revealed the hydrogen bond interactions of compound 22 and 27 with Arg82 residue in the GyrB pocket. Another hydrogen bond interaction was found to bind between compound 22 with Arg141 residue of the GyrB active site. Based on the results provide better understanding crucial interactions of benzosuberone-thiazole derivatives with GyrB pocket for rational design new and more potent GyrB inhibitors as novel anti-tuberculosis agents.