Investigating crucial interactions of the 2-(benzylideneamino)-*N*′-(7-chloroquinolin-4-*yl*) benzohydrazide derivatives and GyrB as potent GyrB inhibitors through molecular docking calculations

B. Kamsri[1], B. Pakamwong[1], P. Thongdee[1], N. Phusi[1], K. Ariyachaokun[2], P. Kamsri[3], A. Punkvang[3], P. Saparpakorn[4], S. Hannongbua[4], K. Suttisintong[5], P. Kittakoop[6,7,8], J. Spencer[9], A. J. Mulholland[10], 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, Thailand
[6]Chulabhorn Research Institute, Kamphaeng Phet 6 Road, Laksi, Bangkok 10210, Thailand
[7]Chulabhorn Graduate Institute, Chemical Biology Program, Chulabhorn Royal Academy, Kamphaeng Phet 6 Road, Laksi, Bangkok 10210, Thailand
[8]Center of Excellence on Environmental Health and Toxicology (EHT),
[9]School of Cellular and Molecular Medicine, Biomedical Sciences Building, University of Bristol, Bristol, BS8 1TD, United Kingdom
[10]Centre for Computational Chemistry, School of Chemistry, University of Bristol, Bristol, BS8 1TS, United Kingdom

*E-mail: pornpan_ubu@yahoo.com

Introduction

Tuberculosis is caused by *Mycobacterium tuberculosis (Mtb)*.

World Health Organization

In 2020
9.9 million people fell ill with TB.
1.5 million people died from the disease.

Anti-TB drugs

First-line drugs

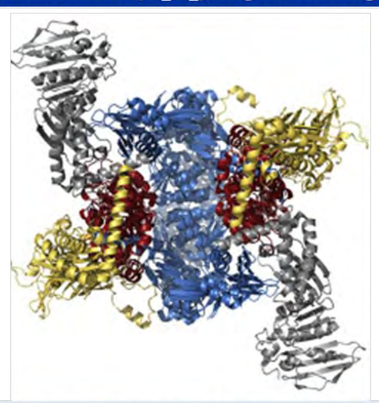
Isoniazid Ethambutol Pyrazinamide

Second-line drugs

Para aminosalicylic acid Kanamycin Fluoroquinolones

DNA gyrase

Heterotetramer (A_2B_2), GyrA and GyrB

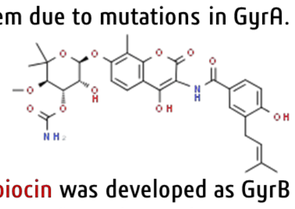


GyrA is involved in the breakage and reunion of DNA.

GyrB promote ATP hydrolysis.

Hydrolysis of ATP to promote initial events involved in the initiation of DNA replication in MTB

Fluoroquinolones as GyrA inhibitors used for treatment of MDR-TB but it show resistance problem due to mutations in GyrA.



Novobiocin was developed as GyrB inhibitor.
withdrawn from the market
-severe safety issues
-poor pharmacological properties

Problem
of TB treatment

Drug Resistant or DR-TB

Multi Drug Resistant (MDR)	Extensively Drug Resistant (XDR)
First-line drugs	First-line drugs Second-line drugs

- very long duration of treatments
- expensive

Material and Methods

2-(benzylideneamino)-N'-(7-chloroquinolin-4-*yl*) benzohydrazide derivatives

Bioorg Med Chem Lett., 2017, 27(8):1859-1866

Chemical structures

cpd01 MIC 6.25 µM
cpd03 MIC 3.12 µM
cpd07 MIC 6.25 µM
cpd08 MIC 0.78 µM
cpd09 MIC 1.56 µM
cpd10 MIC 6.25 µM
cpd12 MIC 25 µM
cpd13 MIC 25 µM

Structure optimization
M062X/6-31G(d,p) method
Gaussian09 program

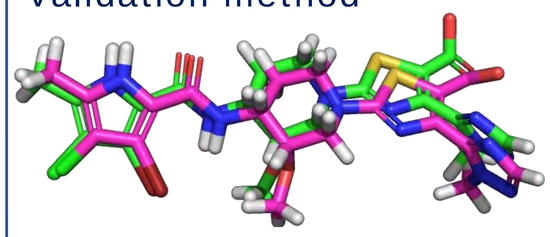
Molecular docking calculations
GyrB ATPase domain (PDB code : 4BAE)
Glide docking (XP mode)

Conclusion

- The crucial interactions showed hydrogen bond interactions via mediated interactions the carbonyl substituent on benzohydrazide with Asp79 residue and nitrogen atom of N-benzylidene with Asn52 residue.
- The 2-(benzylideneamino)-N'-(7-chloroquinolin-4-yl)benzohydrazide derivatives formed hydrophobic interactions with Ile84, Pro85, Val99, Val123 and Val125 residues
- The key structural for binding concepts are fruitful to design new potential GyrB inhibitors against *Mtb*.

Results

Validation method



RMSD = 0.76 Å

Figure 1. Superimposition of pyrrolamides derivatives form X-ray ligand and molecular docking (PDB code: 4BAE)

Table 1. The results of binding energy (Docking score (kcal/mol))

Compounds	Docking score (kcal/mol)
cpd01	-6.1
cpd03	-6.5
cpd07	-6.6
cpd08	-6.6
cpd09	-7.1
cpd10	-6.6
cpd12	-6.1
cpd13	-4.8

The crucial interactions between GyrB and 2-(benzylideneamino) -*N*′-(7-chloroquinolin-4-*yl*) benzohydrazide derivatives

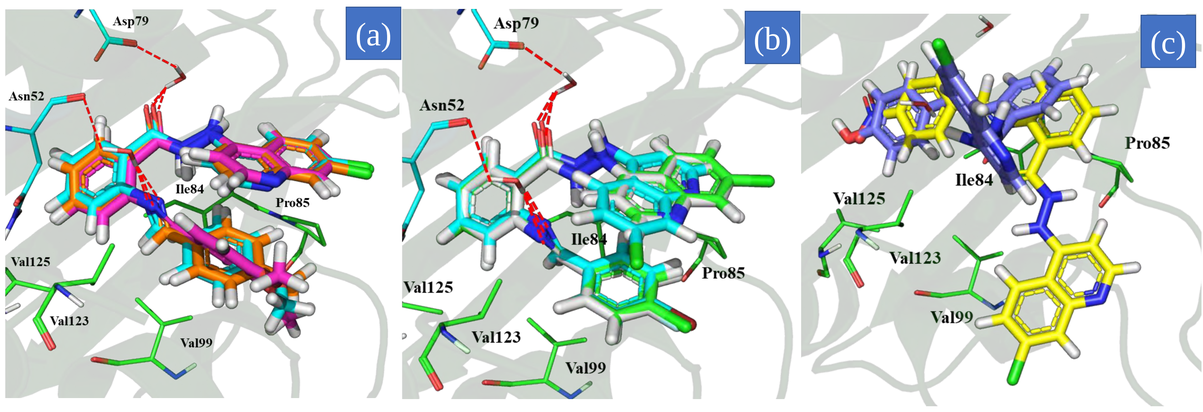
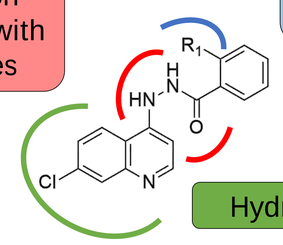


Figure 2. Binding modes and crucial interactions between the GyrB residues and (a) the high active compounds; cpd08(orange), cpd09(blue) and cpd10(pink) (b) the moderate active compounds; cpd01(gray), cpd03(blue) and cpd07(green) and (c) the low active compounds; cpd12(yellow) and cpd13(blue).

Hydrogen bond interaction via mediated interactions with Asp79 and Asn52 residues

Hydrophobic interaction with Ile84, Pro85, Val99, Val123 and Val125 residues



Hydrophobic interactions

Figure 3. Summary of crucial interactions

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