Insight into binding mode and crucial interaction of aminopyrimidine derivatives as potential PknB inhibitors using molecular docking calculations

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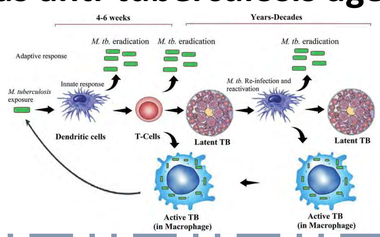
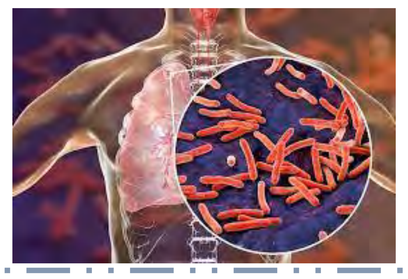
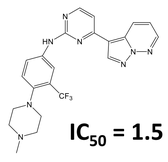
Introduction

Tuberculosis caused by *mycobacterium tuberculosis* that it is major global public health concern. Protein serine/threonine kinase B or PknB is an attractive drug development target because of its central importance in several critical signaling cascades. Here, molecular docking calculations were applied to investigate the binding mode and crucial interactions of aminopyrimidine derivatives in PknB binding pocket as anti-tuberculosis agents.





Material and Methods



IC_{50} = 1.5 µM

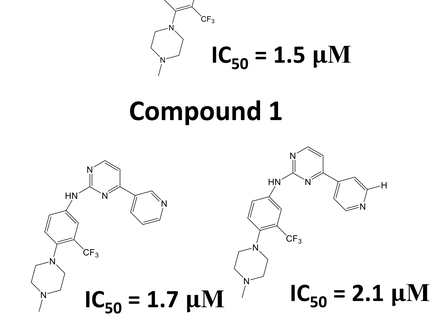
Compound 1

Aminopyrimidine derivatives

The 3D structures of aminopyrimidine derivatives were built by Gaussview 5.08 program and were optimized by M062X/6-31G(d,p) method (Gaussian09 program).

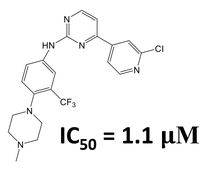
Molecular docking calculations

The initial conformation of all compounds were docked to PknB binding pocket (PDB code: 6B2P) using molecular docking calculations (Glide XP program).

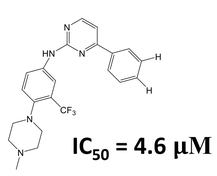


IC_{50} = 1.7 µM — Compound 2

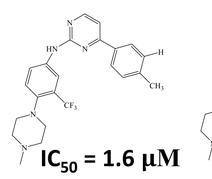
IC_{50} = 2.1 µM — Compound 3



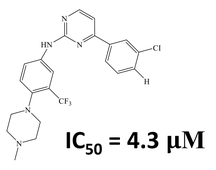
IC_{50} = 1.1 µM — Compound 4



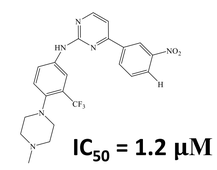
IC_{50} = 4.6 µM — Compound 5



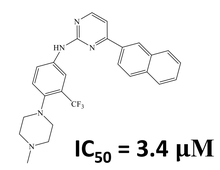
IC_{50} = 1.6 µM — Compound 6



IC_{50} = 4.3 µM — Compound 7



IC_{50} = 1.2 µM — Compound 8



IC_{50} = 3.4 µM — Compound 9

Wlodarchak N.; Feltenberger JB.; Ye ZQ.; Beczkiewicz J.; Procknow R,; Yan G, et al. "Engineering Selectivity for Reduced Toxicity of Bacterial Kinase Inhibitors Using Structure-Guided Medicinal Chemistry" *Acs Medicinal Chemistry Letters*., **2021**, *12(2)*, 228-35.

Results

❑ Validation method

RMSD = 1.08 Å

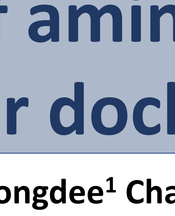
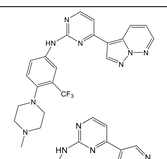
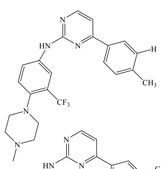
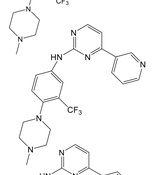
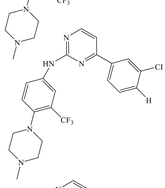
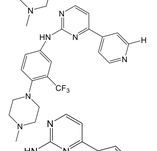
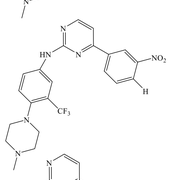
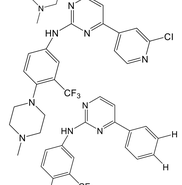
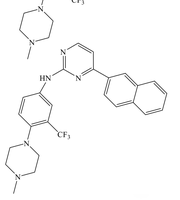
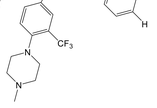


Figure1 superimposition between ligand from molecular docking calculation (yellow) and X-ray ligand (red) (PDB code: 6B2P)

❑ Molecular docking studies

Table 1 The results of binding energy form molecular docking calculations.

Cpd.	Structures	Binding energy (kcal/mol)	Cpd.	Structures	Binding energy (kcal/mol)
1		-8.041	6		-6.569
2		-7.489	7		-7.505
3		-6.404	8		-7.017
4		-5.697	9		-7.712
5		-6.559			

❑ Binding mode and crucial interactions

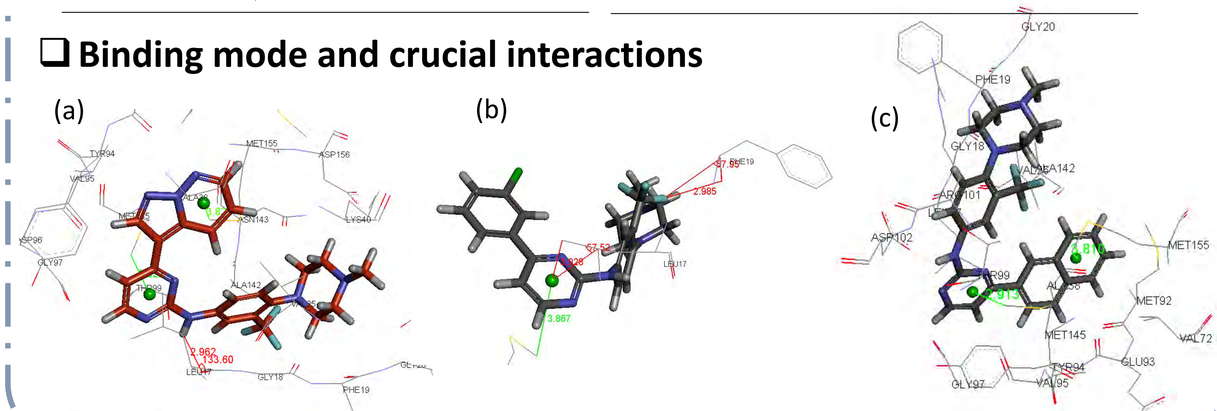


Figure2 the crucial interactions of cpd1 (a), cpd7 (b) and cpd9 (c) in PknB binding pocket

Conclusions

- ❑ Hydrogen bond interaction with Val95 residue
- ❑ Pi-sigma interactions with Met145 and Met155 residues
- ❑ Hydrophobic interactions with Leu17, Phe19, Ser23, Val25, Ala38, Val72, Met92 and Ala142 residues
- ❑ Based on the obtained result could be guideline for rational design novel PknB inhibitor as anti-tuberculosis agents.

Acknowledgements

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- ❑ Faculty of Science, Nakhon Phanom University
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