Virtual screening of novel *M. tuberculosis* PknA/PknB dual inhibitors as anti-tuberculosis agents

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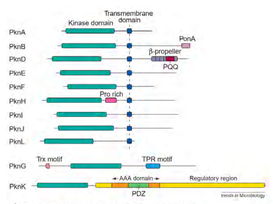
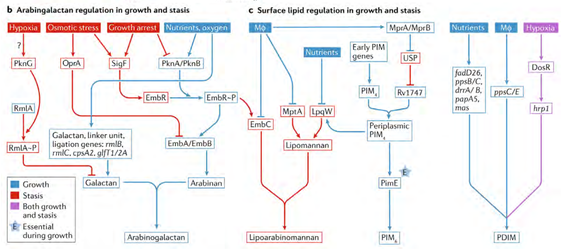
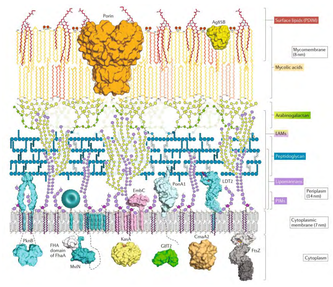
Introduction



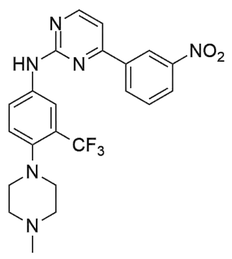
- ❑ **Ser/Thr protein kinases (STPKs) have been interested in anti-tuberculosis drug development.**
- ❑ ***M. tuberculosis* STPK family contains 11 putative eukaryotic-like protein kinases**
- ❑ **PknA and PknB controls the switch between peptidoglycan elongation and septum formation in bacteria.**





Trends Microbiol. 2000, 8(5), 238-244.
Nat Rev Microbiol. 2020, 18(1), 47-59
Tuberculosis report 2021, WHO

Materials and Methods



PknB Ki= 320 nM
CDK2 IC_{50} => 40 μM
S(1) =@ 10 μM = 0.12
MTB MIC = 9.9 μg/mL
THP-1 CC_{50} = 3.89 μM

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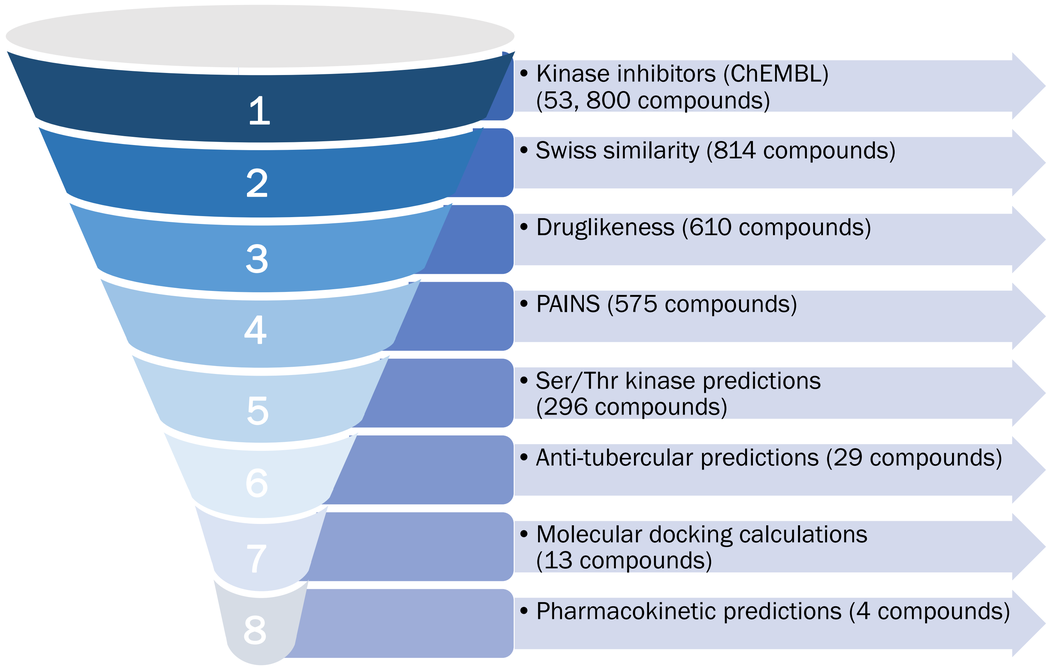


Virtual screening workflow to identify of PknA/PknB dual inhibitors

Results

Biological prediction, docking energy and pharmacokinetic prediction of hit compounds

CHEMBL_ID	PknB		TB		MTB	H37Rv	H37Ra	R-MTB	R-H37Rv	MycoCSM	Caseum FU(%)	MRTD log (mg/kg/day)	Docking energy (kcal/mol)	
													PknA	PknB
CHEMBL1257310	0.286	0.020	0.204	0.164		0.387			0.350	-4.559	1.296	0.067	-6.11	-8.61
CHEMBL1356336	0.199	0.034	0.233	0.130		0.352		0.030	0.043	-4.641	0.198	0.461	-6.17	-8.48
CHEMBL1403777	0.109	0.078	0.217	0.148	0.001	0.050				-4.957	18.565	0.117	-6.93	-8.43
CHEMBL153843	0.115	0.072	0.357	0.046	0.154	0.500	0.039	0.121	0.237	-4.992	0.274	0.475	-6.35	-8.09

Absorption

CHEMBL ID	Water solubility	Caco2 permeability (log Papp in 10^{-6} cm/s)	Intestinal absorption (human) (% Absorbed)	Skin Permeability	P-glycoprotein substrate	P-glycoprotein I inhibitor	P-glycoprotein II inhibitor
CHEMBL1257310	-4.38	0.92	88.96	-2.91	No	No	Yes
CHEMBL1356336	-4.54	1.46	93.65	-2.74	Yes	Yes	Yes
CHEMBL1403777	-2.96	1.20	96.83	-2.74	Yes	Yes	Yes
CHEMBL153843	-4.16	1.00	91.07	-2.77	Yes	Yes	Yes

Distribution

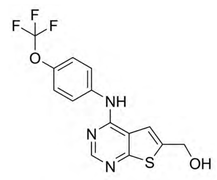
CHEMBL ID	VDss (human) (log L/kg)	Fraction unbound (human) (Fu)	BBB permeability (log BB)	CNS permeability (log PS)
CHEMBL1257310	-0.17	0.15	-0.15	-2.24
CHEMBL1356336	0.10	0.10	0.51	-1.81
CHEMBL1403777	0.46	0.14	-1.21	-3.64
CHEMBL153843	-0.08	0.07	0.07	-1.83

Metabolism & Excretion

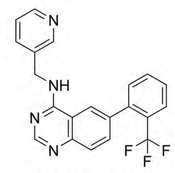
CHEMBL ID	Metabolism							Excretion	
	CYP2D6 substrate	CYP3A4 substrate	CYP1A2 inhibitior	CYP2C19 inhibitior	CYP2C9 inhibitior	CYP2D6 inhibitior	CYP3A4 inhibitior	Total Clearance (log ml/min/kg)	Renal OCT2 substrate
CHEMBL1257310	No	Yes	Yes	Yes	Yes	No	No	0.15	No
CHEMBL1356336	No	Yes	Yes	Yes	Yes	Yes	Yes	0.25	No
CHEMBL1403777	No	Yes	Yes	No	No	No	Yes	0.09	No
CHEMBL153843	Yes	Yes	Yes	Yes	Yes	No	Yes	0.07	No

Toxicity

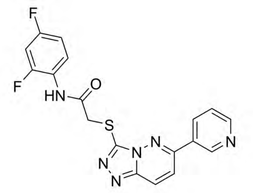
CHEMBL ID	AMES toxicity	MRTD (human) (log mg/kg/day)	hERG I inhibitor	hERG II inhibitor	Oral Rat Acute Toxicity (LD_{50}) (mol/kg)	Oral Rat Chronic Toxicity (LOAEL) (log mg/kg bw/day)	Hepatotoxicity	Skin Sensitisation	*T. Pyriformis* toxicity (log ug/L)	Minnow toxicity (log mM)
CHEMBL1257310	Yes	0.07	No	Yes	2.82	1.50	Yes	No	0.77	1.10
CHEMBL1356336	Yes	0.46	No	Yes	2.69	0.56	Yes	No	0.31	0.72
CHEMBL1403777	No	0.12	No	Yes	2.55	0.84	Yes	No	0.29	-0.87
CHEMBL153843	No	0.48	No	Yes	2.69	0.90	Yes	No	0.68	0.47



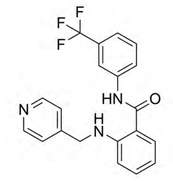
CHEMBL1257310



CHEMBL1356336

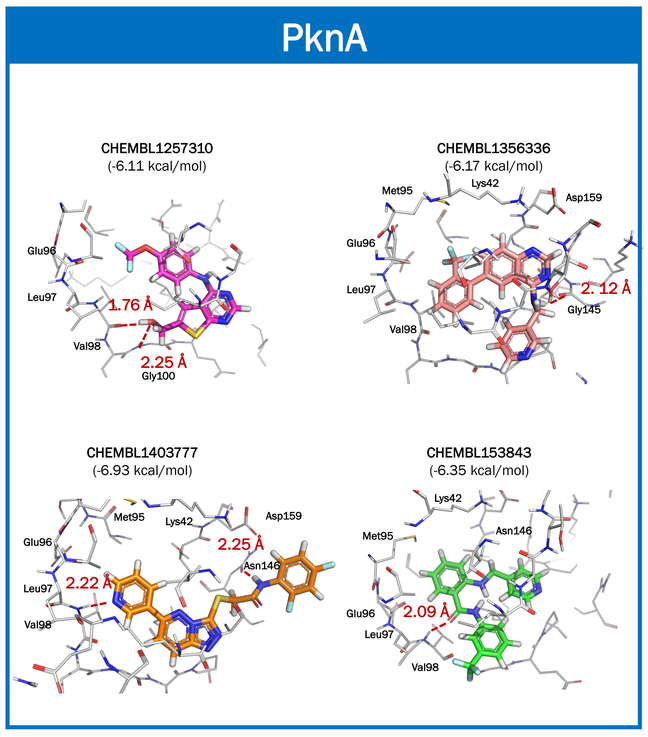


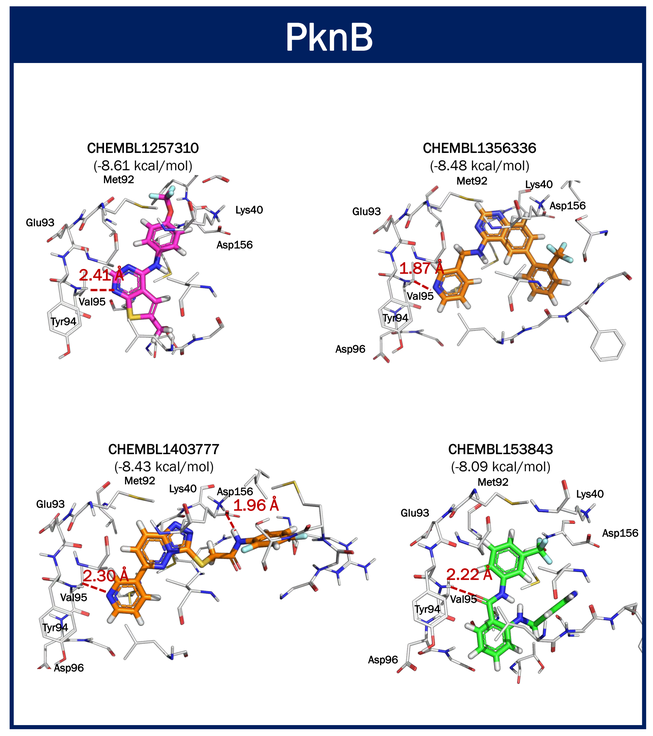
CHEMBL1403777



CHEMBL153843

Binding mode and binding interactions of hit compounds derived from molecular docking calculations





Conclusions

- ❑ Four kinase inhibitors (CHEMBL1257310, CHEMBL1356336, CHEMBL1403777 and CHEMBL153843) were discovered as PknA/PknB dual inhibitors as anti-tuberculosis agents based on virtual screening and pharmacokinetic prediction.
- ❑ The predicted biological evaluation using several methods were confirmed that these finding compounds were promising structure for future validation as anti-tuberculosis agents.
- ❑ Strong binding affinity in the ATP binding site of PknA and PknB was obtained from molecular docking calculations. These hits shared hydrogen bond interaction with Val98 and Val95 backbone for PknA and PknB , respectively as the key interaction for binding.

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