The data on MIC determination of *Mycobacterium tuberculosis* against different compounds

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Siriraj Med J 2009;61:56-59
E-journal: http://www.sirirajmedj.com

Tuberculosis (TB) remains the global public health problem. Current estimates suggest that one-third of the world's population are infected, with 9 million new TB cases and 2 million deaths from TB each year[1], posing a continued health and financial burden in various parts of the world.

TB is caused mainly by *Mycobacterium tuberculosis*. The unique structure of the cell wall allows it to lie dormant as a latent infection. The slow growth rate of the organism and prolonged treatment of the disease, make TB difficult to eradicated. Furthermore, the increase in immuno-suppressed individuals due mainly to AIDS, rendering individuals more susceptible to TB infection, or allowing a latent infection to activate[2,3], has led to large increases in TB incidence.

The current first-line drugs for treatment of TB were introduced more than 50 years ago and the treatment requires the combination of the drugs to improve efficacy, prevent resistance, and overcome intrinsic resistance. Moreover, adverse effects of the drugs and the long time required for treatment make patients non-compliant and contribute to drugs resistance. Therefore, concomitant with the resurgence of TB has been the occurrence of multidrug-resistant (MDR) disease and more seriously, extensively drug resistant (XDR) disease which have usually caused treatment failure. All the above reasons means the new anti-TB drugs are urgently needed, especially the ones with novel mechanisms of action to treat MDR, XDR and which can be used in shorter treatment regimens than the current agents.

Research into new anti-TB drugs has developed since the late 1990s, which has resulted in a number of new drug candidates entering clinical trials in recent years. However, more new anti-TB drugs have been required. A variety of compounds have been evaluated to search for anti-TB activity. This report presents the initiative phase that reviews only the in vitro data on the minimum inhibitory concentration (MIC) of compounds against *M. tuberculosis* (Table 1).

Notably, the compounds with anti-TB activity should be considered for their drug like properties and studied further for development as candidates for new TB drugs e.g. ease of synthesis, avoid high molecular weight, very polar, highly lipophilic, and avoid cross resistance with existing drugs, activity against more *M. tuberculosis* strains including MDR-TB or XDR-TB, cytotoxicity, in vivo studies, etc. The compounds should then be grouped according to their perceived state of development into discovery research, preclinical development and clinical development.[38]

The benefits of the increased research and development activity have led to approximately 20 new compounds in preclinical and clinical phases and approximately 20 compounds in the discovery phase. This represents a major step of effective TB treatment with the hope that within the next decade an effective anti-TB regimen of shorter duration may be achieved.

TABLE 1. The MICs of various compounds against *M. tuberculosis*.

Compounds	*M. tuberculosis* stains	MICs
3-Alkylsulfanyl-1,2,4-triazole derivatives[4]	H37Rv	6.25 μg/ml
2-Chloro-4(2-furanyl)-9-benzylpurine[5]	H37Rv	0.78 μg/ml
6-Chloro-3-phenyl-4-thioxo-2H-1,3-benzoxazine-2(3H)-ones	H37Rv	0.5 μM
6-Chloro-3-phenyl-2H-1,3-benzoxazine-2,4(3H)-dithiones[6]	H37Rv	0.5 μM
Cloxyquin (5-chloroquinolin-8-ol)[7]	H37Rv, H37Ra, H37Rv-PAS-R,	0.062-0.25 μg/ml

Compounds	*M. tuberculosis* stains	MICs
	H37Rv-CS-R, H37Rv-KM-R, H37Rv-PZA-R, H37Rv-TAC-R, H37Rv-ETA-R, H37Rv-EMB-R, 100 sensitive stains, 20 resistant stains, and 30 MDR-TB	
Compounds obtained from plants:		
• *Alpinia galangal*; 1′-Acetoxychavicol acetate (ACA) (Hongmanee P, et al., unpubl. Data, 2004)	H37Rv, H37Ra, H37Rv-PAS-R, H37Rv-CS-R, H37Rv-KM-R, H37Rv-PZA-R, H37Rv-TAC-R, H37Rv-ETA-R, H37Rv-EMB-R, 100 sensitive stains, 20 resistant stains, and 30 MDR-TB	0.25-2.0 μg/ml
• *Angelica sinensis (Oliv.) Diels (Dang Gui)*; Falcarindiol, 9Z,17-octadecadiene-12,14-diyne-1,11,16-triol,1-acetate[8]	H37Rv, Erdman	1.4-26.7 μg/ml
• *Azorella madreporica Clos*; Mulinane diterpenoid[9]	H37Rv	20 μg/ml
• *Beilschmiedia tsangii;*		
Beilschmin A	MTB 90-221387	2.5 μg/ml
Beilschmin B[10]	MTB 90-221387	7.5 μg/ml
• *Caesalpinia pulcherrima;*		
6Beta-benzoyl-7beta-hydroxyvouacapen-5alpha-ol	H37Rv	25 μg/ml
6Beta-cinnamoyl-7beta-hydroxyvouacapen-5alpha-ol[11]	H37Rv	6.25 μg/ml
• *Chrysanthemum morifolium (Asteraceae)* flowers;		
Maniladiol	H37Rv	4 μg/ml
3-Epilupeol	H37Rv	4 μg/ml
4,5Alpha-epoxyhelianol[12]	H37Rv	6 μg/ml
• *Cinnamomum kotoense*;		
Isoobtusilactone A	MTB 90-221387	22.48 μM
Lincomolide B[13]	MTB 90-221387	10.16 μM
• *Colubrina retusa*;		
Jujubogenin saponin[14]	H37Rv	10 μg/ml
• *Garcinia linii;*		
1,7-Dihydroxy-3-methoxyxanthone	MTB 90-221387	~3.1 μg/ml
1,5-Dihydroxy-3-methoxyxanthone[15]	MTB 90-221387	~6.3 μg/ml
• *Lantana hispida (Verbenaceae)*;		
3-Acetoxy-22-(2′-methyl-2Z-butenyloxy)-12-oleanen-28-oic acid	H37Rv	50 μg/ml
3-Hydroxy-22beta-(2′-methyl-2Z-butenoyloxy) -12-oleanen-28-oic acid	H37Rv	50 μg/ml
Oleanolic acid[16]	H37Rv	25 μg/ml
• *Lessonia nigrescens*;		
Phytosterol saringosterol	H37Rv	0.25 μg/ml
24S epimers	H37Rv	1 μg/ml
24R epimers[17]	H37Rv	0.125 μg/ml
• *Micromelum hirsutum*;		
Micromolide[18]	H37Rv	1.5 μg/ml
• *Piper aff. pedicellatum*;		
(+)-Bornyl piperate[19]	H37Ra	25 μg/ml
• *Ziziphus cambodiana PIERRE (Rhamnaceae)*;		
3-O-(4-hydroxy-3-methoxybenzoyl) ceanothic acid (3-O-vanillylceanothic acid)	H37Ra	25 μg/ml
Betulinaldehyde	H37Ra	25 μg/ml
Betulinic acid	H37Ra	25 μg/ml
2-O-E-p-coumaroyl alphitolic acid	H37Ra	12.5 μg/ml
Alphitolic acid	H37Ra	50 μg/ml
Zizyberanalic acid	H37Ra	50 μg/ml
Zizyberenalic acid[20]	H37Ra	100 μg/ml

Compounds	*M. tuberculosis* stains	MICs
Deazapteridine derivatives[21]	H37Rv	~0.1 μg/ml
Diarylpyrrole derivatives;		
• 1-(4-Fluorophenyl)-2-methyl-3-(thiomorpholin-4-yl) methyl-5-(4-methylphenyl)-1H-pyrrole, 5[22]	H37Rv	0.4 μg/ml
Diarylquinoline (R207910)[23]	drug-sensitive and drug-resistant MTB	0.06 μg/ml
2-(3-(Diethylcarbamoyl)piperidin-1-yl)-)-3-fluoro-5,12-dihydro -5-oxobenzothiazolo[3,2-a]quinoline-6-carboxylic acid[24]	H37Rv MDR-TB	0.18 μM 0.08 μM
1,1-Dioxido-3-oxo-1,2-benzisothiazol-2(3H)-yl)methyl N,N-disubstituted dithiocarbamate/O-alkyldithiocarbonate derivatives[25]	H37Rv	0.78, 1.56 μg/ml
8-[6-[[(1,1-Dimethylethoxy)carbonyl]amino]-3-azabicyclo [3.1.0]hex-3-yl]-1,2-dihydro-7-nitro-5-oxo-5H-thiazolo [3,2-a]quinoline-4-carboxylic acid[26]	H37Rv MDR-TB	0.08 μM <0.08 μM
Imidazo(4,5-c)pyridines[27]	H37Rv and other MTB stains	0.256-2.56 μg/ml
Isatin derivatives;		
• 1-Cyclopropyl-6-fluoro-8-methoxy-1,4-dihydro-4-oxo-7 [[N4-[3′-[(4,6-dimethylpyrimidin-2-yl)benzenesulfonamido -4-yl]imino-1′-(5-fluoroisatinyl)]methyl]-3-methyl N1-piperazinyl]-3-quinoline carboxylic acid[28]	H37Rv	1.22 μg/ml
Ketone and amide derivatives of quinoxaline 1,4-di-N-oxide[29]	H37Rv, resistant stains, MDR-TB	4.0 μg/ml
2-Methyl-6-furyl-9-(p-methoxybenzyl)purine[30]	H37Rv	0.20 μg/ml
Miconazole[31]	H37Ra	2 μg/ml
Naphthalene-1,4-dione derivatives[32]	H37Rv	3.13 μg/ml
Nitro-dihydro-imidazooxazole derivative (OPC-67683)[33]	H37Rv, MDR-TB	0.006-0.024 μg/ml
Oxazolidinone (DA-7867)[34]	67 susceptible and drug-resistant clinical isolates	~0.125 μg/ml
Ring-substituted 4-methylquinolines[35]	H37RV	6.25 μg/ml
9-Sulfonylated/sulfenylated-6-mercaptopurine derivatives[36]	H37Rv, resistant stains	0.39-3.39 μg/ml
Thiazolylhydrazone derivatives[37]	H37Rv	6.25 μg/ml

H37Rv-PAS-R (*p*-aminosalicylic acid resistant), H37Rv-CS-R (cycloserine resistant), H37Rv-KM-R (kanamycin resistant), H37Rv-PZA-R (pyrazinamide resistant), H37Rv-TAC-R (thiacetazone resistant), H37Rv-ETA-R (ethionamide resistant), H37Rv-EMB-R (ethambutol resistant), MTB *(M. tuberculosis)*

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