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Parallel synthesis of chiral pentaamines and pyrrolidine containing bis-heterocyclic libraries. Multiple scaffolds with multiple building blocks: A double diversity for the identification of new antitubercular compounds

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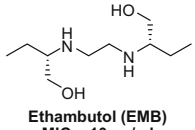
ABSTRACT

Combinatorial chemistry offers a unique opportunity for the synthesis and screening of large numbers of compounds and significantly enhances the prospect of finding new drugs. Collaborative efforts with the Tuberculosis Antimicrobial Acquisition & Coordinating Facility (TAACF), have led to the identification of submicromolar novel antitubercular hits. Chiral pentaamines and bis-heterocyclic compounds with 90–100% inhibition against *Mycobacterium tuberculosis* strain $H_{37}R_v$ were identified. Some of the identified compounds are more active than the existing drug ethambutol.

Tuberculosis (TB) is the biggest reemerging infectious disease in recent history and kills an estimated 3 million people worldwide each year. Although many believe TB to be a scourge of the past, the disease continues to strike people throughout the world at an alarming rate. Almost 2 billion people are infected with *Mycobacterium tuberculosis*, the TB bacterium, and each year, 8 million of them develop active TB.[1–3] Tuberculosis is particularly dangerous to those with weakened immune systems and is the primary cause of death among people infected with HIV.[4] In recent years, drug-resistant strains of TB have emerged, posing a formidable threat to the global population. The discovery and development of new therapeutic anti-TB regimens compounds are urgently needed. Combining the power of combinatorial chemistry and close collaborative interactions with the Tuberculosis Antimicrobial Acquisition & Coordinating Facility (TAACF),[5] a leading laboratory having assays and screening facilities against tuberculosis, a large selection of diversified compounds were tested and led to the identification of potential useful lead compounds. Low molecular weight compounds, especially heterocyclic compounds, offer a high degree of structural diversity and have proven to be broadly and economically useful as therapeutic agents.[6–11] We have proven the inherent strengths of combinatorial chemistry (large numbers of individual compounds and mixture based combinatorial libraries) to accelerate chemical information acquisition for basic research and drug design.[12,13]

Polyamines were reported to have high antitubercular activities.[14] It has been recently reported that active chiral diamines were identified following the screening of a large library of compounds.[14] It has been described that amines which occurred most frequently in active compounds included many with large hydrophobic moieties, suggesting that optimization was perhaps selecting for the isoprenoid binding site of the arabinosyltransferase target of the antitubercular drug ethambutol (EMB) (Fig. 1). Encouraged by the reported antitubercular activities of polyamines, we sent 120 individual chiral pentaamines to TACFF. As



Ethambutol (EMB)
MIC = 10 μg/ml

Figure 1. Chemical structure of ethambutol.

Abbreviations: SPPS, solid phase peptide synthesis; PS-SCL, positional scanning synthetic combinatorial library; TB, tuberculosis; MIC, minimal inhibitory concentration; TAACF, Tuberculosis Antimicrobial Acquisition & Coordinating Facility.

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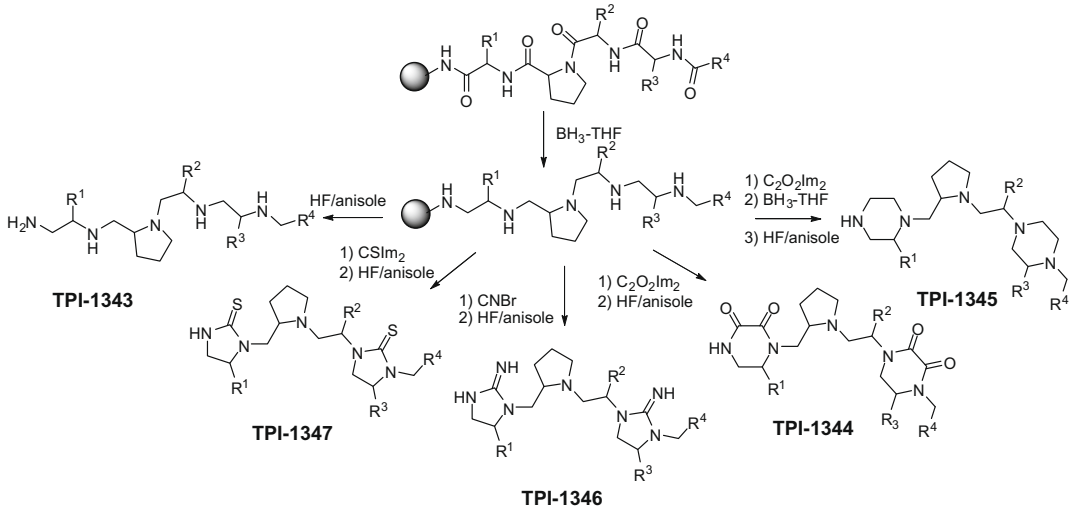


Scheme 1. Parallel synthesis of pentaamine and bis-heterocyclic libraries.

it will be elaborated, different pentaamines, and bis-heterocyclic compounds having hydrophobic groups at R^1, R^2, R^3 and R^4 gave interesting activities (Scheme 1).

Using the tea-bag technology and following the strategy outlined in Scheme 1,[15] we developed an efficient approach for the solid phase synthesis of different pentaamines and pyrrolidine bis-heterocyclic libraries from resin-bound proline-containing acylated tetrapeptides. Starting from resin-bound amino acids (diversity R_1), Boc-proline was coupled using standard solid phase synthesis (SPPS) coupling reagents,[16] followed by Boc deprotection and subsequent coupling of two Boc-amino acids (diversities R_2 and R_3). The N-terminal Boc was cleaved and the generated primary amine was N-acylated with different commercially available carboxylic acids (diversity R_4). The generated resin-bound N-acylated tetrapeptide was exhaustively reduced using borane–THF.[16] Typical reaction conditions for the solid phase reduction of polyamides consists of the treatment of resin-bound peptides with BH_3–THF at 65 °C for 72 h.[17] The generated resin-bound borane-amine complexes are then disproportionate following overnight treatment with neat piperidine at 65 °C. The reduction is free of racemization. Our approach involved the use of proline as a spacer, which, following the exhaustive reduction of the amide groups, yielded resin-bound pentaamine containing two pairs of secondary amines separated by a pyrrolidine ring. One set of compounds were cleaved to afford the corresponding pentaamine library TPI-1343. Applying the concept of 'libraries from libraries',[18] extra sets of tea-bags were prepared, where the resulting pairs of secondary amines were separately treated with different bifunctional reagents such as, thiocarbonyldiimidazole, cyanogen bromide and oxalyldiimidazole to afford following cleavage of the solid support the corresponding libraries, namely pyrrolidine bis-cyclic thiourea TPI-1347, pyrrolidine- bis-cyclic guanidines TPI-1346, and pyrrolidine bis-diketopiperazine TPI-1344, respectively. An extra set of diketopiperazine was prepared and treated prior to cleavage of the solid support with BH_3-THF to afford following reduction of the oxamide and cleavage of the resin the corresponding pyrrolidine bis-piperazine TPI-1345. We used the approach described in Scheme 1, for the preparation of 5 positional scan libraries.[12,19] Twenty six different amino acids were selected for R_1, R_2, and R_3, and 42 carboxylic acids for R_4 (Table 1) to prepare in parallel, a pentaamine library and 4 different mixture based pyrrolidine bis-heterocycles each containing 738,192 individual compounds in positional scanning format.

Along with the synthesis of the mixture based libraries, 120 different individual compounds were synthesized for each library. These individual compounds served as controls to determine whether the individual building blocks used at each of the variable positions could be successfully incorporated into the synthesis of the corresponding libraries. The individual building blocks were varied while the other three positions remained fixed (Scheme 2).

In vitro evaluation of antimycobacterial activity: (description of TAACF assays)

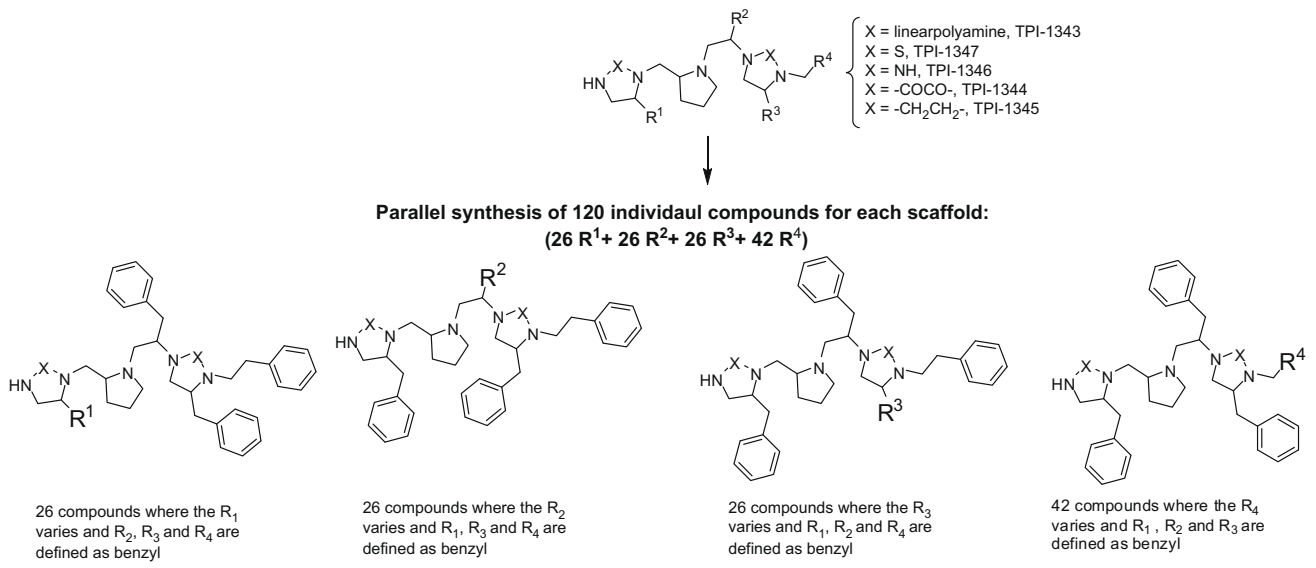
1. Primary screening is conducted at 6.25 μg/mL (or molar equivalent of highest molecular weight compound in a series of congeners) against *M. tuberculosis* $H_{37}Rv$ (ATCC 27294) in BACTEC 12B medium using a broth microdilution assay. The Microplate Alamar Blue Assay (MABA).[20] Compounds exhibiting fluorescence are tested in the BACTEC 460 radiometric system. Compounds affecting <90% inhibition in the primary screen (i.e., MIC >6.25 μg/mL) are not generally evaluated further.
2. Compounds demonstrating at least 90% inhibition in the primary screen are retested at lower concentrations against *M. tuberculosis* $H_{37}Rv$ to determine the actual minimum inhibitory concentration (MIC) using MABA. The MIC is defined as the lowest concentration effecting a reduction in fluorescence of 90% relative to controls.
3. Concurrent with the determination of MICs, compounds are tested for cytotoxicity (IC_{50}) in VERO cells at concentrations $\leqslant$ 62.5 μg/mL or l0 times the MIC for *M. tuberculosis* $H_{37}Rv$ (solubility in media permitting). After 72 h exposure, viability is assessed on the basis of cellular conversion of MTT into a formazan product using the Promega CellTiter 96 non-radioactive cell proliferation assay.

Screening results: Driven by the reported antitubercular activities of polyamines, 120 individual chiral pentaamines (TPI-1343) (Scheme 1) were evaluated in a primary screen against *M. tuberculosis* (Table 2). The individual pentaamines were screened for% inhibition against *M. tuberculosis* strain H37Rv at 6.25 μg/mL. Compounds are considered active with inhibition >90%. Eleven compounds demonstrated higher than 90% inhibition in the primary screen and were tested at lower concentrations to determine the minimum inhibitory concentration (MIC) by serial dilution. As shown in Table 2, pentaamines substituted with different hydrophobic groups provided high inhibition at MIC values ranging from 3 to 6 μg/mL.

Table 1
Building blocks used to synthesize the pentaamine and bis-heterocyclic libraries and resulting functionalities at the four positions of diversity

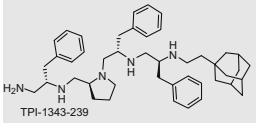
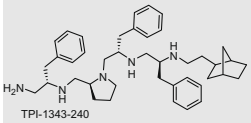
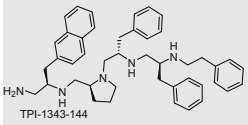
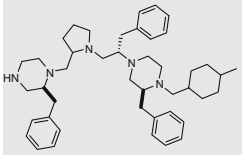
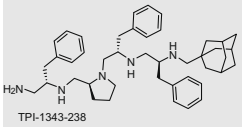
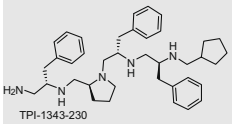
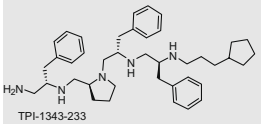
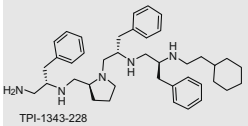
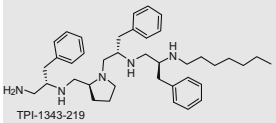
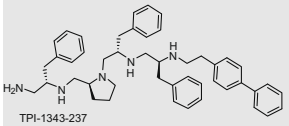
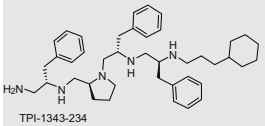
Building block used forR^1, R^2 and R^3	Functionality	Building block used for R^4	Functionality
Boc-L-Ala	*S*-Methyl	1-Phenyl-1-cyclopropanecarboxylic acid	(1-Phenyl-cyclopropyl)-methyl
Boc-L-Phe	*S*-Benzyl	2-Phenylbutyric acid	2-Phenylbutyl
Boc-Gly	Hydrogen	3-Phenylbutyric acid	3-Phenylbutyl
Boc-L-Ile	*S*-2-Butyl	*m*-Tolylacetic acid	*m*-Tolylethyl
Boc-L-Leu	*S*-Isobutyl	3-Fluorophenylacetic acid	2-(3-Fluoro-phenyl)-ethyl
Boc-L-Ser(Bzl)	*R*-Hydroxymethyl	3-Bromophenylacetic acid	2-(3-Bromo-phenyl)-ethyl
Boc-L-Thr(Bzl)	(*R*,*R*)-1-Hydroxyethyl	(Alpha-alpha-alpha-trifluoro-*m*-tolyl) acetic acid	2-(3-Trifluoromethyl-phenyl)-ethyl
Boc-L-Val	*S*-Isopropyl	*p*-Toly lacetic acid	*p*-Tolylethyl
Boc-L-Tyr(BrZ)	*S*-4-Hydroxybenzyl	4-Fluorophenylacetic acid	2-(4-Fluoro-phenyl)-ethyl
Boc-D-Ala	*R*-Methyl	3-Methoxyphenylacetic acid	2-(3-Methoxy-phenyl)-ethyl
Boc-D-Phe	*R*-Benzyl	4-Bromophenylacetic acid	2-(4-Bromo-phenyl)-ethyl
Boc-D-Ile	*R*-2-Butyl	4-Methoxyphenylacetic acid	2-(4-Methoxy-phenyl)-ethyl
Boc-D-Leu	*R*-Isobutyl	4-Ethoxyphenylacetic acid	2-(4-Ethoxy-phenyl)-ethyl
Boc-D-Ser(Bzl)	*S*-Hydroxymethyl	4-Isobutyl-alpha-methylphenylacetic acid	2-(4-Isobutyl-phenyl)-propyl
Boc-D-Thr(Bzl)	(*S*,*S*)-1-Hydroxyethyl	3,4-Dichlorophenylacetic acid	3,4-Dichlor ophe nethyl
Boc-D-Val	*R*-Isopropyl	3,5-Bis(trifluoromethyl)-phenylacetic acid	2-(3,5-Bis-trifluoromethyl-phenyl)-ethyl
Boc-D-Tyr(BrZ)	*R*-4-Hydroxybenzyl	3-(3,4-Dimethoxyphenyl)-propionic acid	3-(3,4-Dimethoxy-phenyl)-propyl
Boc-L-Phenylglycine	*S*-Phenyl	Phenylacetic acid	Phenethyl
Boc-L-Norvaline	*S*-Propyl	3,4,5-Trimethoxybenzoic acid	3,4,5-Trim ethoxy-benzyl
Boc-D-Norvaline	*R*-Propyl	Butyric acid	Butyl
Boc-L-Norleuc ne	*S*-Butyl	Heptanoic acid	Heptyl
Boc-D-Norleucine	*R*-Butyl	Isobutyric acid	Isobutyl
Boc-L-Naphthylalanine	*S*-2-Naphthylmethyl	2-Methylbutyric acid	2-Methylbutyl
Boc-D-Naphthylalanine	*R*-2-Naphthylmethyl	Isovaleric acid	3-Methylbutyl
Boc-L-Cyclohexylalanine	*S*-Cyclohexyl	3-Methyvaleric acid	3-Methylpentyl
Boc-D-Cyclohexylalanine	*R*-Cyclohexyl	4-Methyvaleric acid	4-Methylpentyl
		p-Toluic acid	4-Methyl-benzyl
		Cyclopentanecarboxylic acid	Cyclopently-methyl
		Cyclohexanecarboxylic acid	Cyclohexyl-methyl
		Cyclohexylacetic acid	Cyclohexyl-ethyl
		Cyclohexanebutyric acid	Cyclohexyl-butyl
		Cycloheptanecarboxylic acid	Cycloheptyl-methyl
		2-Methylcyclopropanecarboxylic acid	(2-Methyl-cyclopropyl)-methyl
		Cyclobutanecarboxylic Acid	Cyclobutyl-methyl
		3-Cyclopentylpropionic acid	3-Cyclopentyl-propyl
		Cyclohexanepropionic acid	Cyclohexyl-propyl
		4-Methyl-1-cyclohexanecarboxylic acid	4-Methyl-1-cyclohexyl-m ethyl
		4-*tert*-Butyl-cyclohexanecarboxylic acid	4-*tert*-Butyl-cyclohexyl-methyl
		4-Biphenylacetic acid	2-Biphenyl-4-yl-ethyl
		1-Adamantanecarboxylic acid	Adamantan-1-yl-m ethyl
		1-Adamantaneacetic acid	2-Adamantan-1-yl-ethyl
		2-Norbornaneacetic acid	2-Bicyclo[2.2.1]hept-2-yl-ethyl

Encouraged by these results, we tested different bis-heterocyclic compounds as functionalized and constrained pentaamines analogs, while we maintained the same R groups. One hundred and twenty individual pyrrolidine bis-cyclic thioureas (TPI-1347),

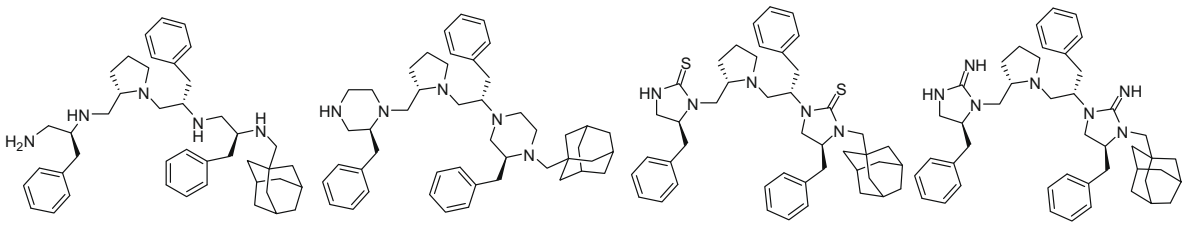


Scheme 2. Synthesis of individual controls.

Table 2
MIC of chiral pentaamines against *Mycobacterium tuberculosis*

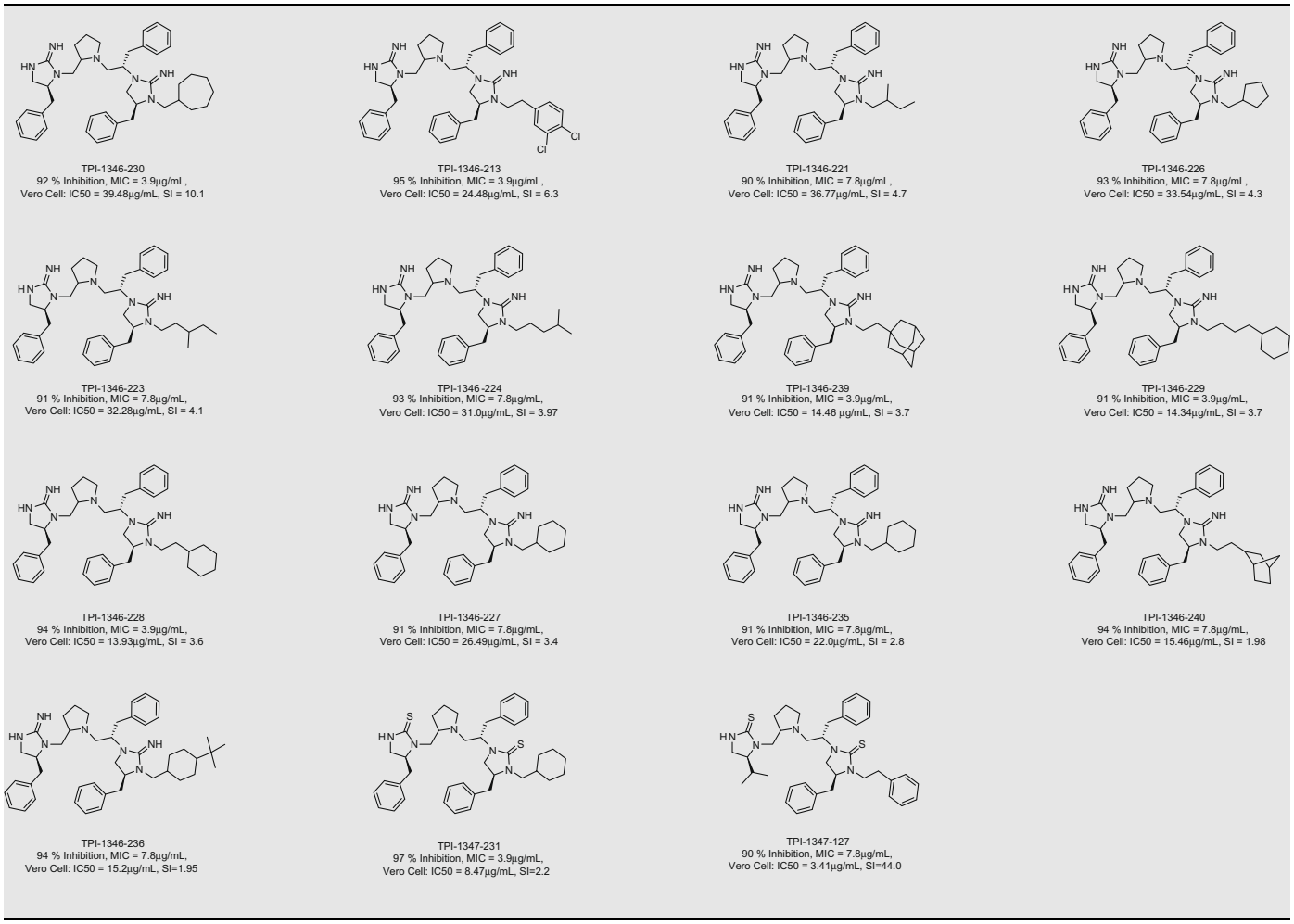
% Inhibition		MIC (μg/mL)	Vero cell IC_{50} (μg mL)
 TPI-1343-239	99	3.13	1.1
 TPI-1343-240	91	3.13	1.03
 TPI-1343-144	98	6.25	4.23
 TPI-1345-235 99 % Inhibition, MIC = 3.9μg/mL, Vero Cell: IC50 = 0.82μg/mL, SI = 0.21	99	6.25	1.39
 TPI-1343-238	99	6.25	n.d.
 TPI-1343-230	97	6.25	n.d.
 TPI-1343-233	92	6.25	n.d.
 TPI-1343-228	90	6.25	1.05
 TPI-1343-219	96	>6.25	n.d.
 TPI-1343-237	94	>6.25	n.d.
 TPI-1343-234	99	n.d.	n.d.

120 individual pyrrolidine bis-cyclic guanidines (TPI-1346, Scheme 3), 120 individual pyrrolidine bis-cyclic piperazines (TPI-1345), and 120 individual pyrrolidine bis-cyclic diketopiperazines (TPI-1344) were evaluated in a primary screen against *M. tuberculosis.* These compounds were prepared according to the strategy described in Scheme 3. They were all derived from the same pentaamines, thus providing a double diversity of compounds, namely a diversity of scaffolds bearing the same substituents, and a diver-



Scheme 3.

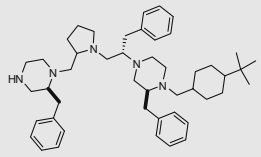
Table 3
MIC of bis-cyclic guanidines and bis-cyclic thioureas against *Mycobacterium tuberculosis*

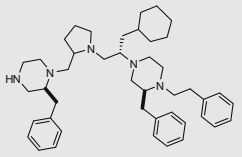


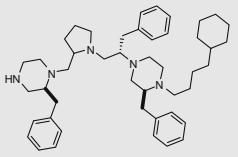
sity of R groups around each scaffold. In a first assay, thirty nine bis-cyclic guanidines, six bis-cyclic thioureas and sixty individual bis-cyclic piperazines demonstrated greater than 90% inhibition against strain H37Rv at less than 6.25 μg/mL. Identified active compounds were tested in a secondary assay. The results for the secondary screening of the active compounds showed inhibitions greater then 97% against strain $H_{37}Rv$ at less than 4 μg/mL for some of these compounds. Concurrent with the determination of MICs, the individual pyrrolidine bis-cyclic thioureas (TPI-1347), individual pyrrolidine bis-cyclic guanidines (TPI-1346) and individual pyrrolidine bis-cyclic piperazines (TPI-1345) were tested for cytotoxicity (IC_{50}) in VERO cells at concentrations $\leqslant$ 62.5 μg/mL or l0 times the MIC for *M. tuberculosis* $H_{37}Rv$. The selectivity index is defined as the ratio of the measured IC50 in VERO cells to the MIC. As shown in Table 3, following the secondary screening, thirteen bis-cyclic guanidines and only 2 bis-cyclic thioureas demonstrated higher than 90% inhibition with MIC values ranging from 3.9 to 7.8 μg/mL. The bis-cyclic guanidine TPI-1346-230 showed the most interesting results with 92% inhibition at 3.9 μg/mL, having a desired selectivity index SI = 10.18 with a high cytotoxicity value in vero cell (IC_{50} = 39.48 μg/mL).

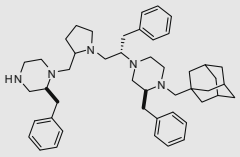
The pyrrolidine bis-cyclic piperazines demonstrated the highest inhibition among all scaffolds. Following the secondary screening, fifty compounds provided higher than 97% inhibition at low MIC

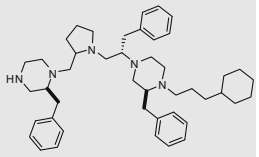
Table 4
MIC of bis-cyclic piperazines against *Mycobacterium tuberculosis*

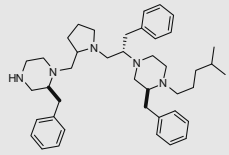

TPI-1345-236
97 % Inhibition, MIC = 2μg/mL,
Vero Cell: IC50 = 1.15μg/mL, SI = 0.58

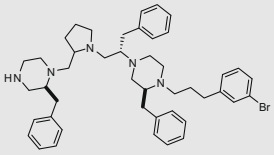

TPI-1345-171
100 % Inhibition, MIC = 2μg/mL,
Vero Cell: IC50 = 0.99μg/mL, SI = 0.50

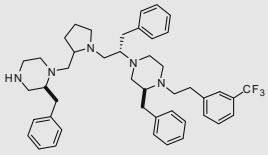

TPI-1345-229
99 % Inhibition, MIC = 2μg/mL,
Vero Cell: IC50 = 1.0μg/mL, SI = 0.50

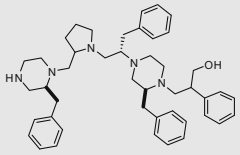

TPI-1345-238
97% Inhibition, MIC= 2μg/mL,
Vero Cell: IC50 = 0.97μg/mL, SI= 0.49

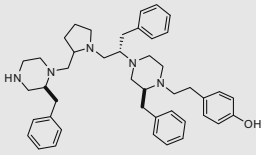

TPI-1345-234
99 % Inhibition, MIC= 2μg/mL,
Vero Cell: IC50= 0.94μg/mL, SI= 0.47

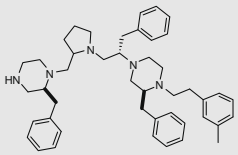

TPI-1345-224
99 % Inhibition, MIC = 2μg/mL
Vero Cell: IC50 = 0.89μg/mL, SI = 0.45

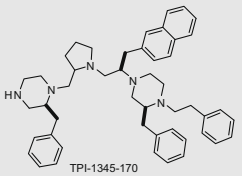

TPI-1345-204
99 % Inhibition, MIC = 3.9μg/mL,
Vero Cell: IC50 = 1.12μg/mL, SI = 0.29

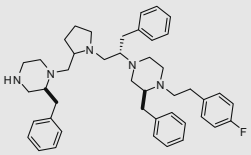

TPI-1345-205
99 % Inhibition, MIC = 3.9μg/mL,
Vero Cell: IC50 = 1.12μg/mL, SI = 0.29

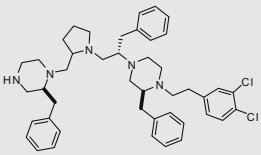

TPI-1345-200
99 % Inhibition, MIC= 3.9μg/mL,
Vero Cell: IC50= 1.08μg/mL, SI= 0.28

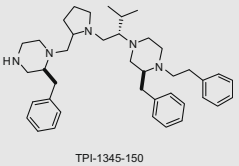

TPI-1345-206
99 % Inhibition, MIC= 3.9μg/mL,
Vero Cell: IC50= 1.11μg/mL, SI= 0.28

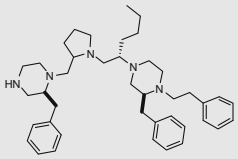

TPI-1345-202
99 % Inhibition, MIC = 3.9μg/mL,
Vero Cell: IC50 = 1.05μg/mL, SI = 0.27

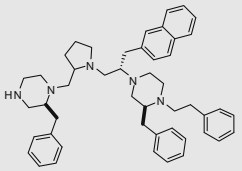

TPI-1345-170
100 % Inhibition, MIC = 3.9μg/mL,
Vero Cell: IC50 = 1.06μg/mL, SI = 0.27

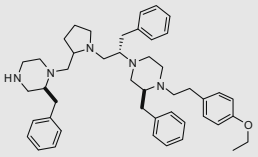

TPI-1345-207
98 % Inhibition, MIC = 3.9μg/mL,
Vero Cell: IC50 = 1.05μg/mL, SI= 0.27

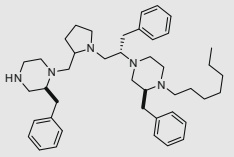

TPI-1345-213
99 % Inhibition, MIC = 3.9μg/mL,
Vero Cell: IC50 = 1.07μg/mL, SI = 0.27

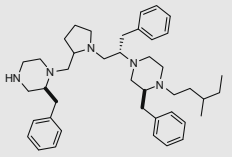

TPI-1345-150
100 % Inhibition, MIC = 3.9μg/mL,
Vero Cell: IC50 = 1.0μg/mL, SI = 0.26

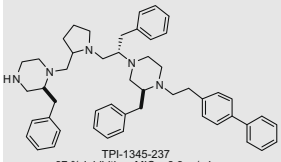

TPI-1345-167
100 % Inhibition, MIC = 3.9μg/mL,
Vero Cell: IC50 = 1.0μg/mL, SI = 0.26

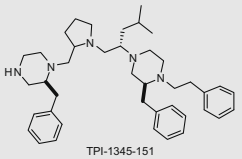

TPI-1345-169
100 % Inhibition, MIC = 3.9μg/mL,
Vero Cell: IC50 = 1.0μg/mL, SI = 0.26

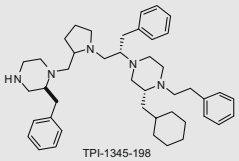

TPI-1345-211
98 % Inhibition, MIC =3 .9μg/mL,
Vero Cell: IC50 = 1.03μg/mL, SI = 0.26

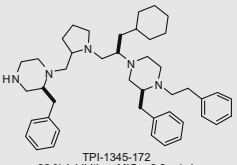

TPI-1345-219
99 % Inhibition, MIC = 3.9μg/mL,
Vero Cell: IC50= 1.03μg/mL, SI = 0.26

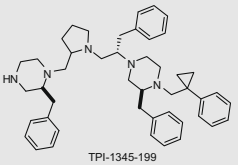

TPI-1345-223
96 % Inhibition, MIC = 3.9μg/mL,
Vero Cell: IC50 = 1.0μg/mL, SI = 0.26

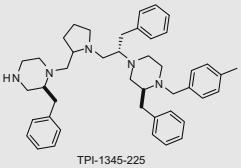

TPI-1345-237
97 % Inhibition, MIC = 3.9μg/mL,
Vero Cell: IC50 = 1.0μg/mL, SI = 0.26

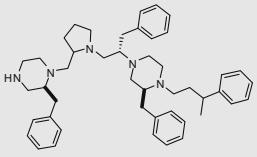

TPI-1345-151
100 % Inhibition, MIC = 3.9μg/mL,
Vero Cell: IC50 = 0.99μg/mL, SI = 0.25

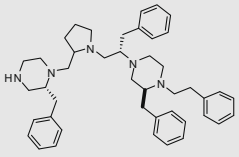

TPI-1345-198
98 % Inhibition, MIC = 3.9μg/mL,
Vero Cell: IC50 = 0.97μg/mL, SI = 0.25

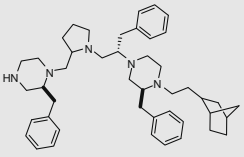

TPI-1345-172
98 % Inhibition, MIC = 3.9μg/mL,
Vero Cell: IC50 = 0.92μg/mL, SI = 0.24

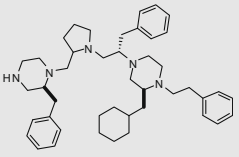

TPI-1345-199
99 % Inhibition, MIC = 3.9μg/mL,
Vero Cell: IC50 = 0.94μg/mL, SI = 0.24

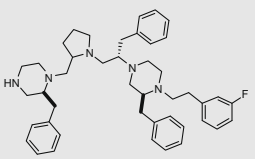

TPI-1345-225
98 % Inhibition, MIC = 3.9μg/mL,
Vero Cell: IC50 = 0.88μg/mL, SI = 0.23

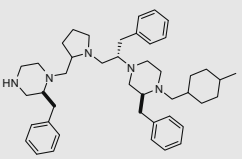

TPI-1345-201
99 % Inhibition, MIC = 3.9μg/mL,
Vero Cell: IC50 = 0.87μg/mL, SI = 0.22

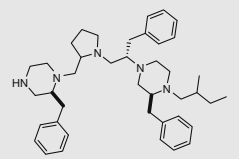

TPI-1345-131
99 % Inhibition, MIC = 3.9μg/mL,
Vero Cell: IC50 = 0.86μg/mL, SI = 0.22

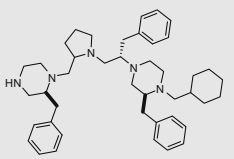

TPI-1345-240
97 % Inhibition, MIC = 3.9μg/mL,
Vero Cell: IC50 = 0.87μg/mL, SI = 0.22


TPI-1345-197
99 % Inhibition, MIC = 3.9μg/mL,
Vero Cell: IC50 = 0.82μg/mL, SI = 0.21


TPI-1345-203
98 % Inhibition, MIC = 3.9μg/mL,
Vero Cell: IC50 = 0.8μg/mL, SI=0.21


TPI-1345-235
99 % Inhibition, MIC = 3.9μg/mL,
Vero Cell: IC50 = 0.82μg/mL, SI = 0.21


TPI-1345-221
97 % Inhibition, MIC = 3.9μg/mL,
Vero Cell: IC50 = 0.7μg/mL, SI = 0.18


TPI-1345-227
100 % Inhibition, MIC = 3.9μg/mL,
Vero Cell: IC50 = 0.71μg/mL, SI=0.18

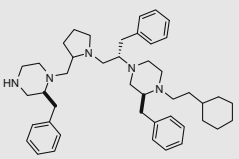
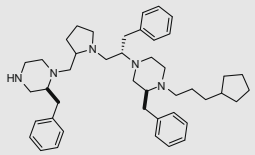
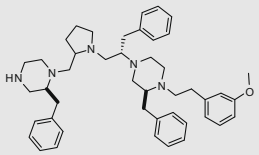

TPI-1345-228
99 % Inhibition, MIC = 3.9μg/mL,
Vero Cell: IC50 = 0.62μg/mL, SI = 0.16

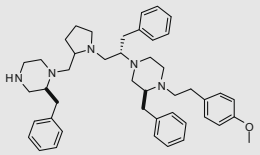
Table 4 (*continued*)



TPI-1345-233
100 % Inhibition, MIC = 3.9μg/mL,
Vero Cell: IC50 = 0.42μg/mL, SI = 0.11



TPI-1345-208
99 % Inhibition, MIC = 3.9μg/mL,
Vero Cell: IC50 = 0.32μg/mL, SI = 0.08

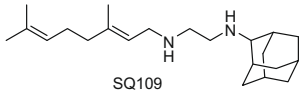


TPI-1345-210
99 % Inhibition, MIC = 3.9μg/mL,
Vero Cell: IC50 = 0.33μg/mL, SI = 0.08

values ranging from 2 to 7 μg/mL, with eight compounds that displayed 100% inhibition at MIC values less than 4 μg/mL (Table 4).

Interestingly, the diketopiperazine analogs (TPI-1344) were not active. They displayed low inhibition at concentrations at MIC higher than 6.25 μg/ml.

Analysis of the results obtained from the screening of the chiral polyamine and bis diazacyclic libraries indicate that all the active identified compounds have hydrophobic moieties at all R^1, R^2, R^3 and R^4 positions. Interestingly, the four scaffolds bearing the same hydrophobic R groups showed good activities (Scheme 3), which strengthen the suggestion that the observed activities are mainly due to the hydrophobicity of the substituents. It is worth noting that the adamantyl is present in all templates, this group exists in SQ109 [*N*-geranyl-*N*'-(2-adamantyl)ethane-1,2-diamine], a novel 1,2-diamine-based EMB analog, which is in advanced clinical trials for the development of new drug for the treatment of pulmonary tuberculosis (TB).[21]



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When taken in total, the results for the polyamines and constrained polyamine analogs as described in Scheme 1 provided a substantial structure–activity relationship (SAR) profile. Analogs which are fragments of the most identified active compounds will be synthesized and tested while keeping the same chemical nature of the R groups.

Acknowledgments

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