

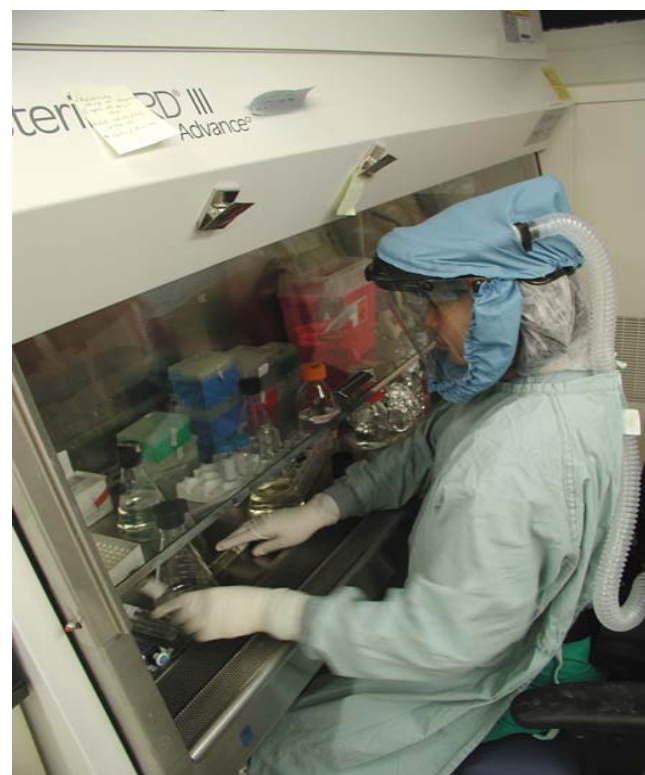
Chemistry-limited TB drug discovery in academia

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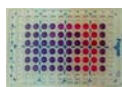
<http://itr.pharm.uic.edu>



ITR Drug Discovery

biological targeting

Assay Development



- Activity against non-replicating *M. tuberculosis*
 - Low Oxygen Recovery Assay (LORA)
 - In vitro Regimen Assessment (IRA)

Persistence Drug Target ID



- Metabolome
- Function of CHPs

hit identification

HTS Cell-based

- diversity libraries
- focused libraries



Target-based

- In silico, In vitro
 - shikimate kinase*
 - dxs*
 - malate synthase*
 - panC*



Natural Products

- plants
- marine invertebrates
- microbes



lead ID/optimization

Med Chem

- macrolides
- aminoquinolines
- fatty acids

Anti-TB Activity

- nitroaromatics
- oxazolidinones
- mycobactins
- carbazoles
- diamidines
- manzamines

Mode of Action

- Mutation mapping
- Spectrum of activity

ADMET

* Medicinal chemistry is performed with collaborators outside of UIC.

Slide 2

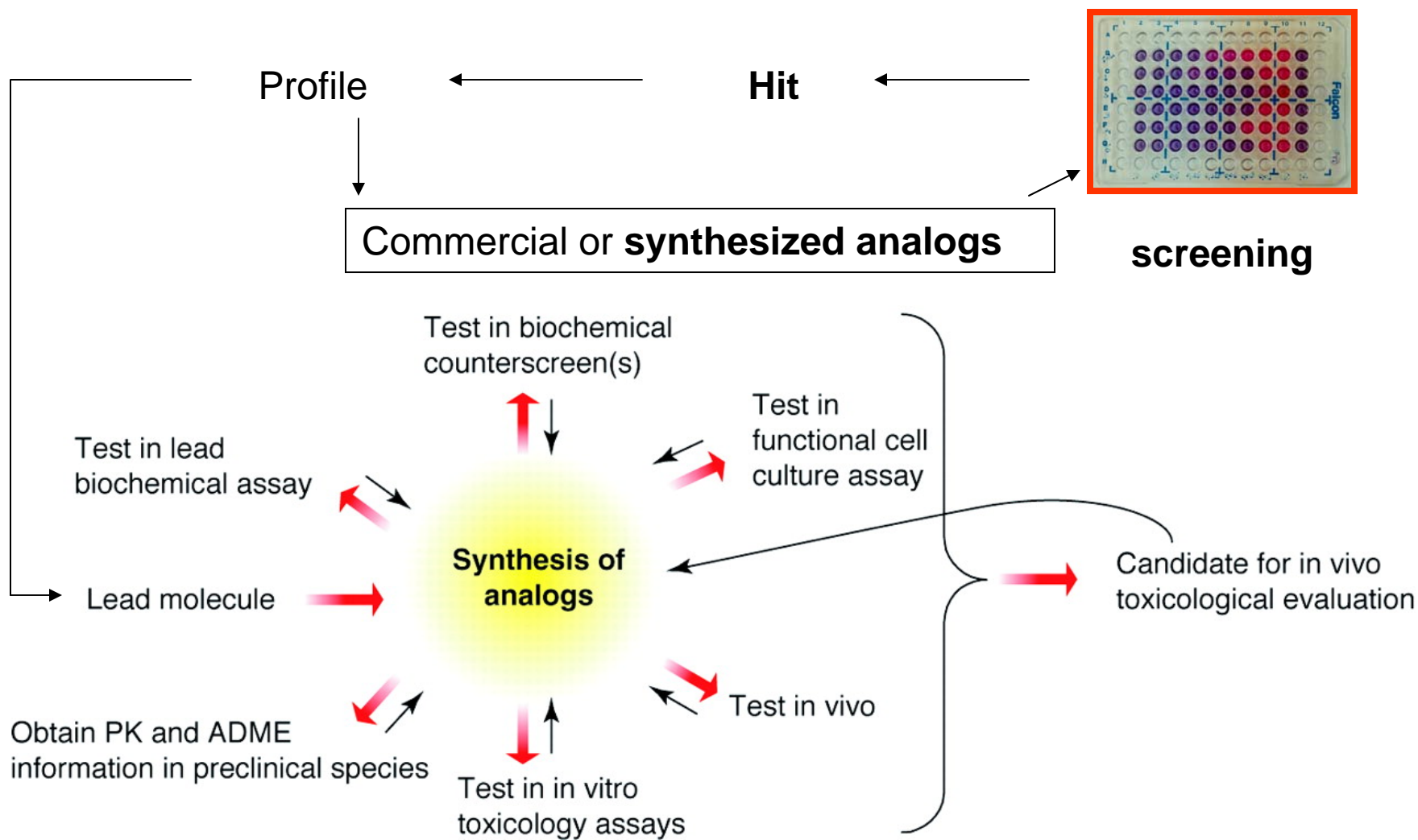
SGF1

Variety of activities related to TB drug discovery

Not unique to our lab - several academic and government labs conduct a variety of TB drug discovery activities. Also, like ours, these labs often collaborate with academic medicinal chemists either within their own institutes or outside. We do both.

Scott Franzblau, 1/10/2007

Med chem bottleneck in compound advancement

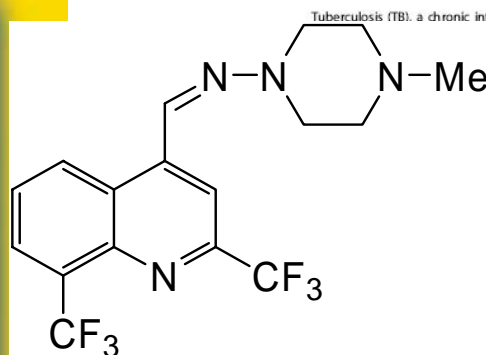


Anti-TB natural products without follow up chemistry

Year/Author	Source	Cmpd / class	MIC (ug/ml)
99 Cantrell	<i>Melia volkensii</i>	triterpenes	4
99 Cantrell	<i>Ajuga remota</i>	Ergosterol ndoperoxide	1-2
00 Mangalindan	<i>Agelas sp.</i>	Agelasine F	3
00 Konig	sponges	(ax)isonitriles	2
01 Wachter	<i>Lessonia nigrescens</i>	Saringosterol	0.25
03 Woldenmichel	<i>R. triflora</i>	Diterpenes	4
	<i>S.hematospermum</i>	Lecherenol A	4
05 Ma	Micromelium	micromolide	1.5
05 Lall	<i>E. natalensis</i>	7-methyl juglone	0.5
05 Gutierrez-Lugo	<i>T. multiflora</i>	Sterols	1.0

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Design, Synthesis, and SAR Studies of Mefloquine-Based Ligands as Potential Antituberculosis Agents

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Tuberculosis (TB), a chronic infectious disease caused by *Mycobacterium tuberculosis* (WHO), is currently the leading cause of death in the world. It is currently infected with 1.75 million deaths resulted from the increase in the incidence of TB. The increase in the incidence of TB is attributed to its co-infection with HIV, which weakens the immune system and facilitates the development of drug-resistant TB (MDR-TB).^[2-6] It has been estimated that 1 billion people have been infected with TB. It is an urgent need to identify new drugs to combat MDR-TB and to improve the current treatment protocol that is ineffective. To achieve this goal, we need

to identify novel drug targets and drug phenotypes; elucidating the mechanism of action of the latter is implicated as a necessity for shortening treatment. As part of our drug-discovery efforts aimed at developing novel anti-tuberculosis agents, we report herein the design, synthesis, and structure-activity studies of mefloquine analogues.

Mefloquine is a well-known antimalarial drug still used today in spite of its neuropsychiatric side-effects that include dizziness, headache, insomnia, and

vivid dreams.^[6] Mefloquine and several of its analogues have been reported to have antibacterial activity.^[7-16] From a screening program carried out at the Walter Reed Army Institute of Research, a series of mefloquine-related compounds with various substitutions on the quinoline ring were found to be more active than mefloquine itself against gram-positive bacteria.^[7] Although mefloquine derivatives are also known to act as purine receptor antagonists,^[11] the only prokaryotic target of mefloquine identified to date is an $F_0F_1H^+$ ATPase in *Streptococcus pneumoniae*.^[12] The crystal structures of the rotor of the V-type and F-type Na^+ ATPases were disclosed recently.^[13,14] In this context, it is important to note that the recently described diarylquinoline R207910, a potent antituberculosis agent, is also believed to owe its activity to interaction with a proton pump of the ATP synthase of *M. tuberculosis*.^[15] From our own in-house screening of the Gen-Plus 960 compound library (MicroSource), mefloquine was found to have relatively potent activity against NRP-TB, which prompted us to choose it as a lead candidate for TB drug discovery.

The results of biological assays performed on the (+) and (-) forms of the erythro and threo isomers of mefloquine are shown in Table 1. The mefloquine isomers were tested against NRP-TB in the luciferase-based low oxygen recovery assay (LORA),^[16] and these data were confirmed by the quantification of colony-forming units (cfu) immediately following the hypox-

Table 1. Anti-TB activity of mefloquine isomers.

Compound	MIC (μM) ^[a]		LORA ^[b]		K ₅₀ (μM) ^[c]		S ^[d]	
	MABA ^[e]	GFP ^[f]	LORA ^[g]	CFU	MABA	GFP	LORA	
(+)-threo-mefloquine-HCl	21.3	14.4	19.2	32	25.1	1.2	1.7	1.3
(-)-threo-mefloquine-HCl	12.8	11.7	17.3	32	30.1	2.3	2.6	1.7
(-)-erythro-mefloquine-HCl	7.8	11.2	7.2	8	17.2	2.2	1.5	2.4
(+)-erythro-mefloquine-HCl	6.7	3.8	7.3	4	38.1	5.6	9.9	5.2
moxifloxacin			42.3	2				
PA-824			7.6	4				
rifampin (RMP)	0.08	0.04	6.5	2	99.7	1266.4	2492.8	15.4

[a] MIC = minimum inhibitory concentration. [b] SI = selectivity index = K₅₀/MIC. [c] MBC = minimal bactericidal concentration determined by quantification of colony forming units. [d] MABA = microplate Alamar Blue assay. [e] GFP = green fluorescent protein microplate assay. [f] LORA = low oxygen recovery assay (luciferase readout). [g] cytotoxicity towards Vero cells.

ic incubation period. As expected through findings made in the malaria field, the erythro isomers were more active against *M. tuberculosis*, and the (+)-erythro isomer appeared to be less cytotoxic than the (-)-erythro isomer. The LORA-based MIC and MBC values are in the same range as those of rifampin, PA-824 (and for MBC, moxifloxacin), compounds that have previously demonstrated activity against NRP-TB. (The fluoroquinolones are the only class for which we have found the luciferase signal to significantly underestimate the activity relative to cfu.)

Mefloquine appears unique in that the MIC values against NRP-TB are similar to those against R-TB. In contrast, compounds such as isoniazid and ethambutol are inactive in the LORA, while only weak activity is observed with streptomycin.^[16]

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Supporting information for this article is available on the WWW under <http://www.chemmedchem.org> or from the author. (Experimental procedures and characterization data for compounds 6a-h, 8a-i, 10a-c, and 11a-j)

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CHEMISTRY ENABLING DRUG DISCOVERY

Fighting
Tuberculosis

6/2006

Mini-review: channel proteins of pathogenic protozoa
Original Contributions: cytotoxic platinum(II) complexes,
enzyme isolective inhibitors, catalytic center of thrombin,
antituberculous agents, MDR inhibitors, and more

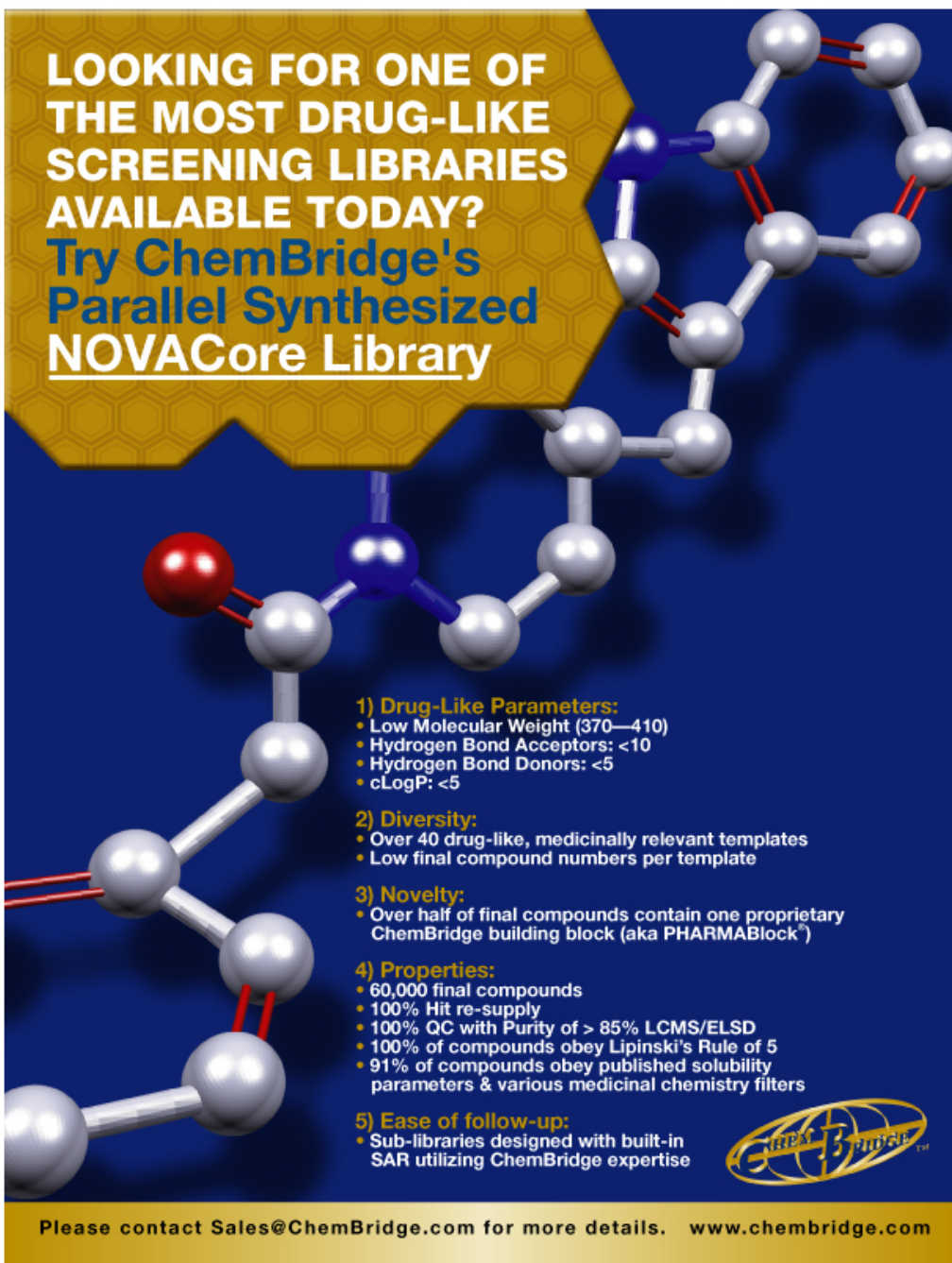


WILEY-VCH

10-fold less cytotoxic vs. mefloquine
5-fold less toxic in mice,
10-100 fold less binding to adenosine A1 and A2A receptors

Diversity Library Screening in ITR

- **NovaCore**
 - 50,000 compounds
 - 47 templates
 - 100% Lipinski-compliant
- **TB screening**
 - 18 days
 - @ 30 μM , ~4.5%
 - @ 10 μM ~ 0.4%
 - Most non-cytotoxic
 - 4 series prioritized for hit-to-lead studies



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