

Current Status and Research Strategies in Tuberculosis Drug Development

Miniperspective

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■ INTRODUCTION

In this Miniperspective we broadly cover the recent developments and strategies that are being adopted globally in the battle to urgently discover and develop new drugs to treat tuberculosis (TB). It highlights the impact and outcomes of recent nongovernment organizations (NGO) and academic research consortia that have made a significant impact in recent years in the field, providing the reader with an insight into the overall status of TB drug discovery and development while illustrating the current strategies and directions that are currently being adopted to find new drugs to control the disease.

Specifically, we report an overview of the current status of TB drug development with a focus on recent strategies that are not directed toward “genetic” based efforts. Such genetic strategies have recently dominated the field of TB and antibiotic drug discovery with little effect, arguably, and now the identification of new chemical entities is exploiting other strategies. These programs include phenotypic screening, repurposing of existing antimicrobials and drugs for noninfection indications, and the coadministration of positive regulators of prodrug activation. The Miniperspective will complement other detailed review articles published in recent years that discuss the mechanisms of action of existing drug classes^{1,2} and strategies^{3,4} to elucidate the targets of newly discovered chemical entities which is required for their downstream development and regulatory approval.

New drugs are urgently needed because TB remains a global health priority, as around nine million new cases are estimated each year with almost two million fatalities.^{5,6} An epidemiological synergy exists with HIV; co-infections represent 15% of the global TB burden and account for almost one-quarter of HIV/AIDS-associated deaths.⁷ TB co-infection encourages the progression to AIDS by effectively increasing replication of HIV,⁸ and the viral infection vastly increases the risk of developing TB disease.⁹ The treatment of TB is complicated by the tendency for its etiological agent, predominantly *Mycobacterium tuberculosis*, to adopt a nonreplicating persistent state.^{10–13}

Antibiotics are most effective against actively growing *M. tuberculosis*,¹⁴ as these persistent organisms exhibit a phenotypic drug resistance; i.e., their resistance is not associated with genetic changes but with their extant metabolic state. The structures of the developing tuberculous lesions may effectively define the metabolic status of their bacterial inhabitants, and it has been speculated that at least four significant subpopulations of bacteria

exist for which different drugs could be efficacious. These might include active growers that may be killed by isoniazid (INH), those with sporadic metabolic bursts that could be killed by rifampicin (RIF), a population with low metabolic activity that is considered likely to experience acidic surroundings and hypoxia that may be susceptible to pyrazinamide (PZA), and finally dormant bacilli that are not killed by any current agents.^{15,16} These complex phenomena are poorly understood and add a further barrier to the already formidable challenges associated with drug development and treatment of the disease.

The most common recommended standard chemotherapeutic regime for TB treatment consists of an initial 2-month phase of treatment with INH, RIF, PZA, and ethambutol (EMB) followed by a continuation phase of treatment lasting 4 months with INH and RIF (Table 1).¹⁷ The individual roles of these drugs in combination have been reviewed.¹⁸ Briefly, INH reduces the bacterial load by around 95% over the first 2 days of treatment and thus decreases risk of TB transmission.¹⁸ Despite its superlative early bactericidal activity (EBA), INH is no more effective than other drugs after this period and RIF becomes the most significant bactericidal drug. Its activity against sporadically active *M. tuberculosis* is crucial for preventing relapses, and INH then serves to limit the emergence of RIF resistance.¹⁸ Because of its apparent ability to kill a subset of bacteria not killed by the other drugs, supposed sporadically active organisms subject to an hypoxic and possibly acidic environment,^{16,19,20} PZA represents an important component of combination therapy. Its inclusion has allowed the shortening of the chemotherapeutic regimen to the current 6 months from an initial 9–12 month period.¹⁸

Poor management of chemotherapy has contributed to the emergence of drug resistance, and this is particularly relevant in TB. The complex nature and length of the treatment, side effects, various socioeconomic factors, and the tendency for patients to feel well long before safe completion of the prescribed course promote nonadherence.²¹ An unacceptable degree of nonadherence prompted the development of DOTS (directly observed treatment, short-course)^{22–24} in which therapy is directly monitored. Initially, this acronym described only the intensively managed chemotherapy regime but has since become used to describe a broader public health strategy that has been adopted in over 150 countries.^{22,25}

Received: March 17, 2011

Published: August 08, 2011

Table 1. Agents Used in Current Antituberculosis Regimes

drug		chemical class	cellular target
isoniazid	INH	isonicotinic acid	enoyl-ACP reductase, mycolic acid elongation
rifampicin	RIF	rifamycin	DNA-primed RNA polymerase
pyrazinamide	PZA	pyrazine	fatty acid biosynthesis/membrane depolarization/ribosomal protein S1 (RpsA), protein translation and the ribosome-sparing process of trans-translation
ethambutol	EMB	ethylenediamine	cell wall arabinan deposition

Strains of *M. tuberculosis* resistant to both INH and RIF, regardless of profiles of sensitivity/resistance to other drugs, have been termed multidrug-resistant (MDR). MDR-TB is a major concern due to the associated high risk of death. While resistance to either drug may be managed with other first-line drugs, MDR-TB requires treatment with second-line drugs under DOTS-Plus.¹⁷ These agents often possess limited sterilizing capacity and are not suitable for short-course treatment, necessitating prolonged treatment with drugs that are less effective and more toxic; several require injection.^{26–28} The World Health Organization (WHO) currently recommends the use of a regimen including amikacin (AMK), ethionamide (ETH), a fluoroquinolone (such as moxifloxacin, MXF), and PZA to treat MDR-TB. In a mouse model, 9 months of this therapy are needed to sterilize both lungs and spleen while only 6 months are needed with the RIF + INH + PZA regimen.²⁹ Recently, the emergence of extensively drug-resistant TB (XDR-TB) strains, initially defined by CDC as those MDR-TB strains with resistance to at least three of the six classes of second-line drugs (aminoglycosides, polypeptides, fluoroquinolones, thioamides, cycloserine, and *p*-aminosalicylic acid), has been reported.²⁶ In some regions almost 20% of MDR-TB cases were classified as XDR-TB, raising concerns over a future epidemic of virtually untreatable TB.²⁶ More recently another definition of XDR-TB as MDR-TB resistant to any fluoroquinolone and at least one of the injectable second-line drugs used in TB treatment (capreomycin, kanamycin, and amikacin) has been adopted.³⁰

It is very clear that there is an urgent need for a new generation of TB drugs, but what specific criteria should they satisfy? They must be active against drug-resistant forms of *M. tuberculosis*, which implies that they must act upon different molecular targets from the current drugs. As any new drug will certainly be part of a multidrug regime, they must utilize different metabolic pathways to the other drugs to avoid drug–drug interactions. Importantly, activity against persistent *M. tuberculosis* might afford a further reduction in the treatment duration from months into weeks, a prospect that should improve patient compliance.

As one-quarter of all TB related deaths occur in patients with HIV/AIDS, another important consideration is the effectiveness in coadministration with antiviral agents used to treat AIDS.³¹ Combined treatment is complicated by shared drug toxicities, which may exacerbate immunosuppression and promote adverse reactions and ultimately nonadherence, and pharmacokinetic drug interactions that reduce drug levels.³¹ The most important of these RIF activates cytochrome P450 enzymes that metabolize antivirals, significantly reducing their plasma concentrations.^{32,33} Similarly, new drugs must also be effective for treating pediatric TB, which represents a significant proportion of the global TB burden and is complicated by the widely differing extent of disease caused and the paucity of relevant pharmacokinetic data available.³⁴ Finally, and by no means least, new drugs must be affordable for the

Table 2. Agents in Clinical Evaluation

drug	chemical class	cellular target ^a
gatifloxacin	fluoroquinolone	DNA gyrase, DNA replication and transcription
moxifloxacin	fluoroquinolone	DNA gyrase, DNA replication and transcription
levofloxacin	fluoroquinolone	DNA gyrase, DNA replication and transcription
linezolid	oxazolidinones	protein synthesis ^a
metronidazole	nitroimidazole	cytochrome P450 ^a
TMC207	diarylquinoline	ATP synthesis
PA-824	nitroimidazooxazine	mycolic acid biosynthesis and protein synthesis
OPC-67683	nitroimidazo-oxazole	cell wall biosynthesis
LL-3858	pyrrole	unknown
SQ109	ethylenediamine	fatty acid biosynthesis
SCV-07	dipeptide	none, immunomodulator

^a Supposed from activity in other microorganisms.

developing countries in which the vast majority of all TB cases exist. The challenges for TB drug discovery are, therefore, very different from those for many other infectious diseases, and thus, the global strategies devised to facilitate this work are diverse and complex. Recent effort has focused on the mechanism of product development partnerships (PDPs) to advance compounds through the development pipeline. These typically include not for profit organizations, or NGOs, working in partnership with academic institutions and with a limited, but growing, collaboration with the pharmaceutical industry aided by strategic financial support from the public sector or philanthropy.³⁵

■ AGENTS IN CLINICAL EVALUATION

Development of the current clinical portfolio, in part, is focused on the repurposing of existing antibiotics alongside current TB drugs as part of new multidrug regimes (Table 2). Gatifloxacin (GAT), moxifloxacin (MXF), levofloxacin (LVF), linezolid, and metronidazole are being trialed by multipartnership consortia which include the TB Alliance, The Bill and Melinda Gates Foundation, World Health Organization (WHO), National Institute of Allergy and Infective Disease, National Institutes of Health, USA (NIAID/NIH), Wellcome Trust, Lupin, Bayer Pharmaceuticals, Centers for Disease Control (CDC), Research and Training in Tropical Diseases (TDR), and their partner academic or research institutions.³⁵

Initial studies revealed that MXF, GAT, and high-dose LVF all showed excellent EBA, approaching that for INH.^{36,37} Encouragingly, a more potent extended EBA, i.e., from day 2 to day 7, was observed with these fluoroquinolones than with INH.³⁶ Adding MXF to the standard antituberculosis regimen in the first 2

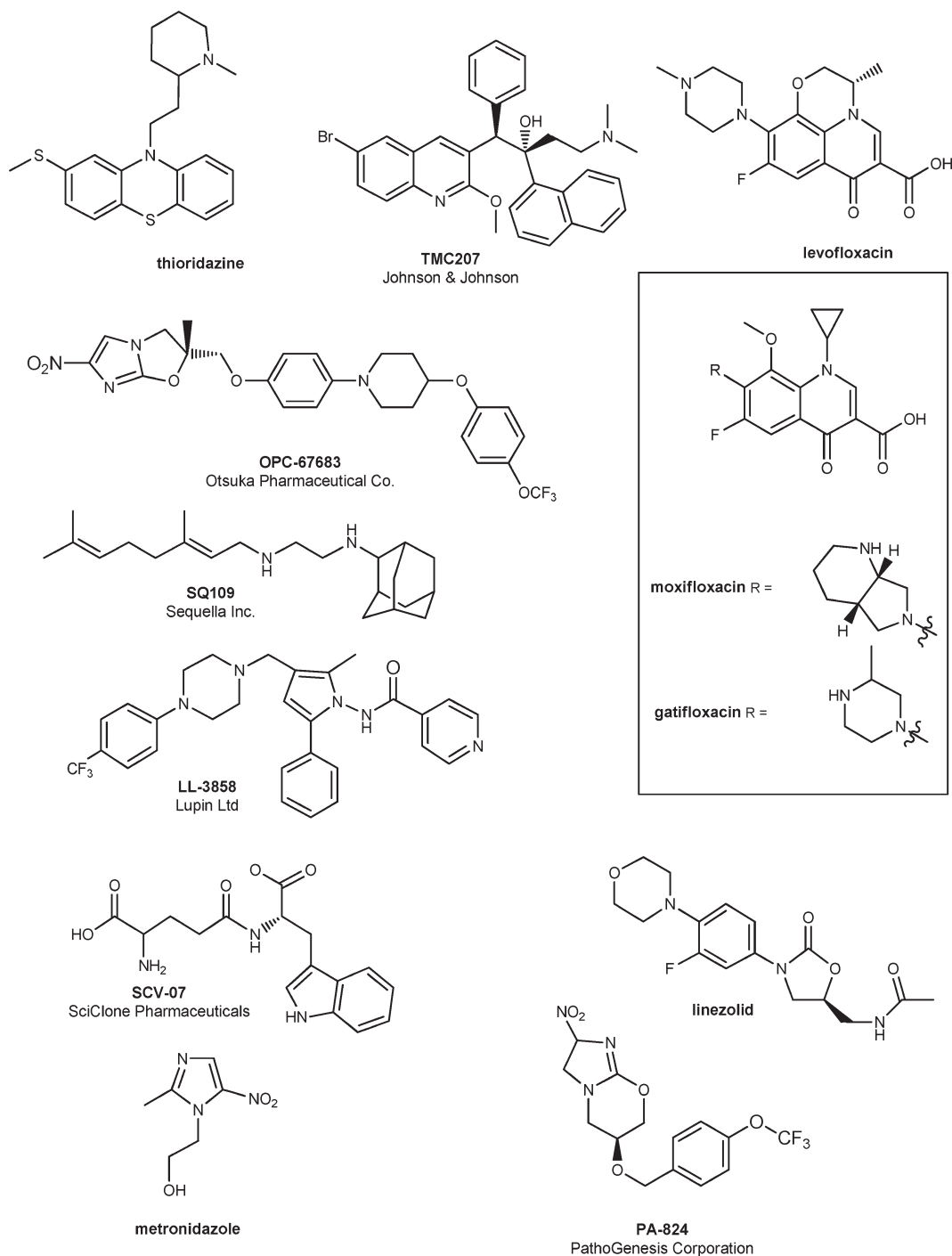


Figure 1. Compounds currently undergoing TB drug clinical evaluation.

months shortened the time to culture conversion (to a negative result for culture), produced a higher 6-week culture conversion rate, and reduced transmission of tuberculosis.³⁸ The 2-month time point coincides with the end of the initial phase of treatment in common regimens, and culture conversion rates at this stage are a well-accepted surrogate marker for the sterilizing activity of antituberculosis drugs. A recent phase II trial to investigate whether MXF could replace EMB in combinations revealed that although the MXF regimes showed more frequent sputum conversion at 4 weeks, the success of the treatments provided identical outcomes after 2 months.³⁹ Likewise, a recent phase II

trial to determine whether substitution of MXF for INH improved rates of sputum conversion at the 2-month stage did not demonstrate a significant improvement while using the fluoroquinolone.⁴⁰ Two separate phase III clinical trials assessing the success of a 4 month regime containing either one of the fluoroquinolones, GAT or MXF, are ongoing.

Encouragingly, the development pipeline now contains new chemical entities under clinical evaluation. Diarylquinoline TMC207⁴¹ (formerly R207910) from Johnson & Johnson and the nitroimidazole PA-824 from PathoGenesis Corporation⁴² lead the way; phase II clinical trials to establish EBA for both compounds have recently

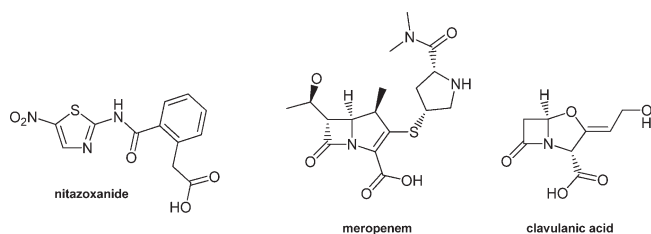


Figure 2. Promising FDA-approved agents in preclinical analysis for TB treatment.

completed. TMC207 is particularly interesting, as it inhibits a novel molecular target in ATP synthase.⁴¹ Importantly, both of these new drugs have demonstrated activity against nonreplicating bacteria, an important factor that might afford shorter treatment regimens.

Clinical evaluation of other new compounds has also begun recently. These include pyrrole LL-3858⁴³ (Sudoterb) from Lupin Ltd., the nitrodihydroimidazole analogue OPC-67683⁴⁴ from Otsuka Pharmaceutical Co, and the ethambutol analogue SQ109⁴⁵ from Sequella Inc., which has recently been granted orphan drug status by the U.S. Food and Drug Administration (USFDA) and European Medicines Agency.

Another approach involves the repurposing of the sedative drug thioridazine which has been shown to cure 10 out of 12 XDR-TB patients in Buenos Aires, Argentina, and is currently being used for the therapy of nonantibiotic responsive terminal XDR-TB patients in Mumbai, India, on the basis of compassionate therapy.⁴⁶ An alternative strategy involves boosting the patient's immune response to promote clearance of the bacteria using the SciClone Pharmaceuticals' immunomodulator γ -glutamyltryptophan (SCV-07, Figure 1). This might represent a useful component of a combination therapy, and as it does not act upon it directly, the bacterium might not develop resistance to it.

PRECLINICAL PROMISE

It is critical that a good supply of new chemical entities is forthcoming in order to overcome the high rates of attrition encountered during the drug discovery process. At present there are still a worryingly low number of these, although a number of promising compounds are now in preclinical development (Figures 3 and 4). These include derivatives of existing compounds under clinical evaluation such as oxazolidinones from Pfizer, the dipiperidine SQ609⁴⁷ from Sequella Inc., the nitroimidazole backup series from Otsuka Pharmaceutical Co., and nonfluorinated quinolones from TaiGen. Other new classes of compounds are also in development, which include translocase I inhibitors from Sequella Inc. and Sankyo, the most active of which is the capuramycin analogue RS-118641.⁴⁸

Encouragingly, there is a rapidly strengthening portfolio of early stage discovery projects underway from both academic and industrial research groups. These efforts have been greatly assisted by partnering with TB Alliance and the emergence of newly formed drug discovery consortia such as the European Union funded New Medicines for TB consortium (NM4TB) and the UK Medical Research Council funded TB Drug Discovery UK (TBD-UK).

REPURPOSING OF EXISTING ANTIMICROBIAL AGENTS FOR TB CONTROL

Antimicrobials used in the treatment of other infections have received some attention recently. The prodrug nitazoxanide

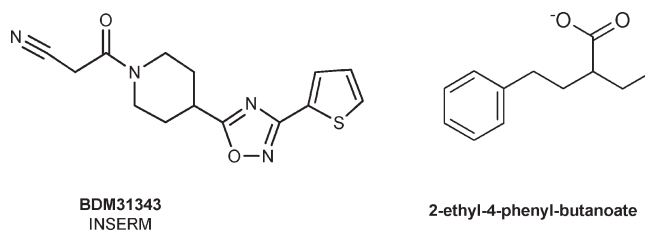


Figure 3. EthR ligands with potential for improving thiocarbamide efficacy.

(NTZ, Figure 2) was approved by USFDA in 2002 for the treatment of protozoal infections and has since entered clinical trials for the treatment of other bacterial and viral infections. NTZ is particularly well tolerated, and remarkably, the emergence of resistant mutants has not been reported. Preliminary investigations suggest that NTZ kills replicating and nonreplicating *M. tuberculosis* at a clinically achievable MIC with an exceptionally low frequency of resistance.⁴⁹

Despite representing some of the most clinically important antibacterial agents, no members of the β -lactam class of antibiotics have yet proven useful for treatment of *M. tuberculosis* infection. A major factor in this lack of efficacy is the bacterium's possession of a single, highly active β -lactamase. The increased sensitivity to β -lactams⁵⁰ displayed by β -lactamase mutants suggested that a chemical intervention might sensitize the organism to existing β -lactam antibiotics. Despite its exceptionally broad substrate specificity, meropenem is an extremely poor substrate for the *M. tuberculosis* β -lactamase. When combined with the β -lactamase inhibitor clavulanic acid (Figure 2), an improvement in MIC was observed. The mixture sterilized aerobically grown organisms in 2 weeks and inhibited the growth of anaerobic organisms and 13 strains of XDR-*M. tuberculosis*. These agents might be combined to treat XDR-TB and are sufficiently free of side effects to allow pediatric use.⁵¹

COADMINISTRATION OF POSITIVE REGULATORS OF PRODRUG ACTIVATION

An interesting approach to improve the tolerability of thiocarbamides used in treatment of MDR-TB has been prompted by research into the process of activation of this class of prodrugs. These are activated by a Baeyer–Villiger monooxygenase, EthA,^{52–54} whose synthesis is controlled by the EthR repressor protein.⁵⁵ The natural ligand for this regulator and physiological role of EthA are unknown but maximizing the synthesis of the enzyme has been shown to increase the sensitivity of mycobacteria to these drugs. The availability of crystal structures of EthR^{56,57} allowed the definition of an activating pharmacophore and its refinement through structural investigation of regulator–activator complexes twinned with DNA binding assays. This process identified BDM31343⁵⁸ (INSERM, Figure 3) as an activating agent that when coadministered allowed the 3-fold reduction of the dose of ethionamide (ETH) without loss of efficacy. A related approach provides the basis for an effective screen of similar agents while also addressing their penetration of human cells and potential cytotoxicity. Here a synthetic mammalian gene circuit senses the important EthR–DNA interaction in human cells and produces quantitative reporter gene expression. Use of this tool to screen compounds of a rationally designed chemical library revealed 2-phenylethyl butyrate (Figure 3) as a nontoxic substance that abolished the repressor

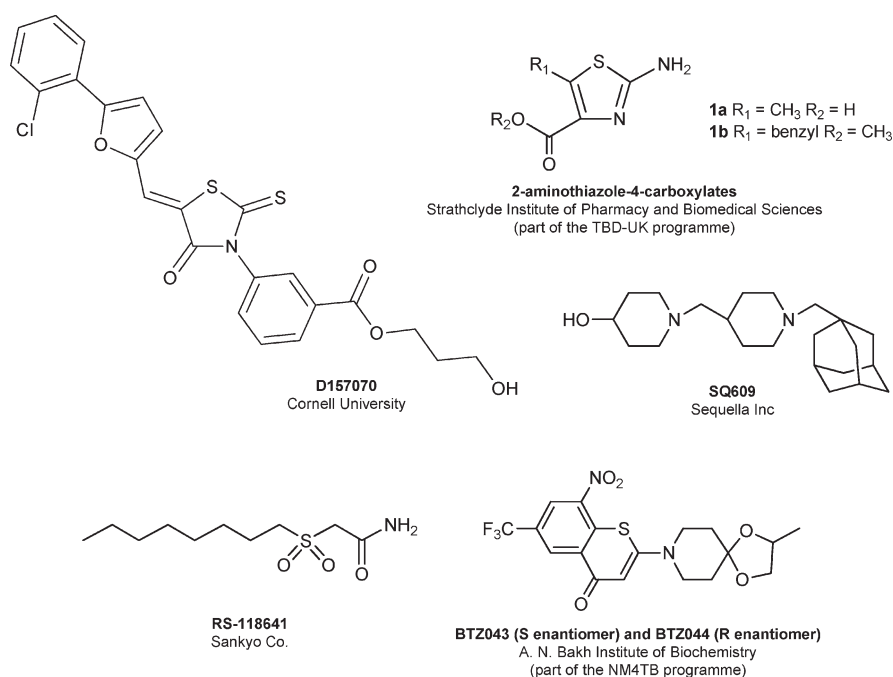


Figure 4. Compounds currently under preclinical TB drug development and recently identified as possessing antitubercular activity in the discovery phase.

function of EthR inside human cells. This function was evident in mice and within the bacterium where it increased its sensitivity to ethionamide.⁵⁹ This approach may eventually improve the tolerability of thiocarbamides by reducing the effective dosage and/or improve the efficacy by improving the MIC obtained from current doses.

■ PHENOTYPIC SCREENING STRATEGIES

Early stage drug discovery projects are focused on finding new chemical entities either by targeting a specific biosynthetic pathway or by phenotypic screening of compound libraries, specific pharmacophores or chemical clusters, and natural products. In the former, and not covered by this review, projects are underway to find inhibitors of the *M. tuberculosis* proteasome, fatty acid biosynthesis, siderophore biosynthesis, dihydrolipoamide acetyltransferase, *N*-acetyltransferase, and the mycobacterial topoisomerase. Of special interest, because of its selective killing of nonreplicating mycobacteria, is the rhodanine dihydrolipoamide acetyltransferase (DlaT) inhibitor D157070⁴⁴ (Cornell University, NY). A structure–activity relationship was defined using hits from a 15 000 small compound library (Chemical Diversity Inc.) that implicated a group of modified rhodanines. More rhodanines were synthesized, and the predecessor to D157070 was selected because of its potency as a DlaT inhibitor. This compound was ester-modified to improve its penetration of macrophages.⁶⁰ Perhaps the most important aspect of the study is the demonstration that it is possible to screen for compounds that selectively inhibit nonreplicating persistors and supports the notion that such screens should be undertaken⁶¹ to provide a means for identifying agents that might shorten the treatment for active disease and an effective prophylactic treatment for latent *M. tuberculosis* infection.

However, a trend toward adoption of phenotypic screening strategies is rapidly gathering momentum. Efforts have centered

on the exploration of a specific compound class in order to find compounds that will exhibit activity against the organism rather than producing a “highly engineered” inhibitor for a specific target.⁶² The active compounds identified from such efforts are then known to penetrate the cell wall and kill the mycobacteria, a trait that has proved very difficult to achieve, having screened only for exquisite activity against a specific target.⁶³ The mechanism of action of these compounds which possess desirable physicochemical properties, toxicity profiles, and efficacy in a number of *M. tuberculosis* models, may then be elucidated using a number of genetic and biochemical techniques.

Recent efforts from the NM4TB program have exploited this strategy effectively with the discovery of the benzothiazinones (BTZ) and in particular the *S* enantiomer BTZ043⁶⁴ and the *R* enantiomer BTZ044⁶⁴ (A. N. Bakh Institute of Biochemistry, Figure 4) which showed bactericidal activity and possessed an MIC against *M. tuberculosis* H₃₇R_v of 1 ng/mL.⁶⁴ This compound was active against MDR and XDR strains and showed activity in macrophages. Similarly from the TBD-UK program, excellent in vitro activity against *M. tuberculosis* H₃₇R_v has also been demonstrated by the 2-aminothiazole-4-carboxylates (ATC) compounds.⁶⁵ These compounds, which possess a thiazole ring system, were found to be active with MICs of 0.06 μg/mL for the 5-methyl analogue **1a**⁶⁵ and the 5-benzyl analogue **1b**⁶⁵ and typically displayed unclear structure–activity relationships, a phenomenon frequently observed during the optimization stages of TB drug discovery programmes. However, these compounds were shown to be nontoxic against human cell lines in vitro and show promise in terms of providing a low cost scaffold for further development.

A number of promising compounds (Figure 5) has emerged from the screening of commercial libraries against *M. tuberculosis* H₃₇R_v. As well as their whole cell activity, this effort evaluated their selectivity over human cell lines to generate a selectivity index in order to further aid the global research

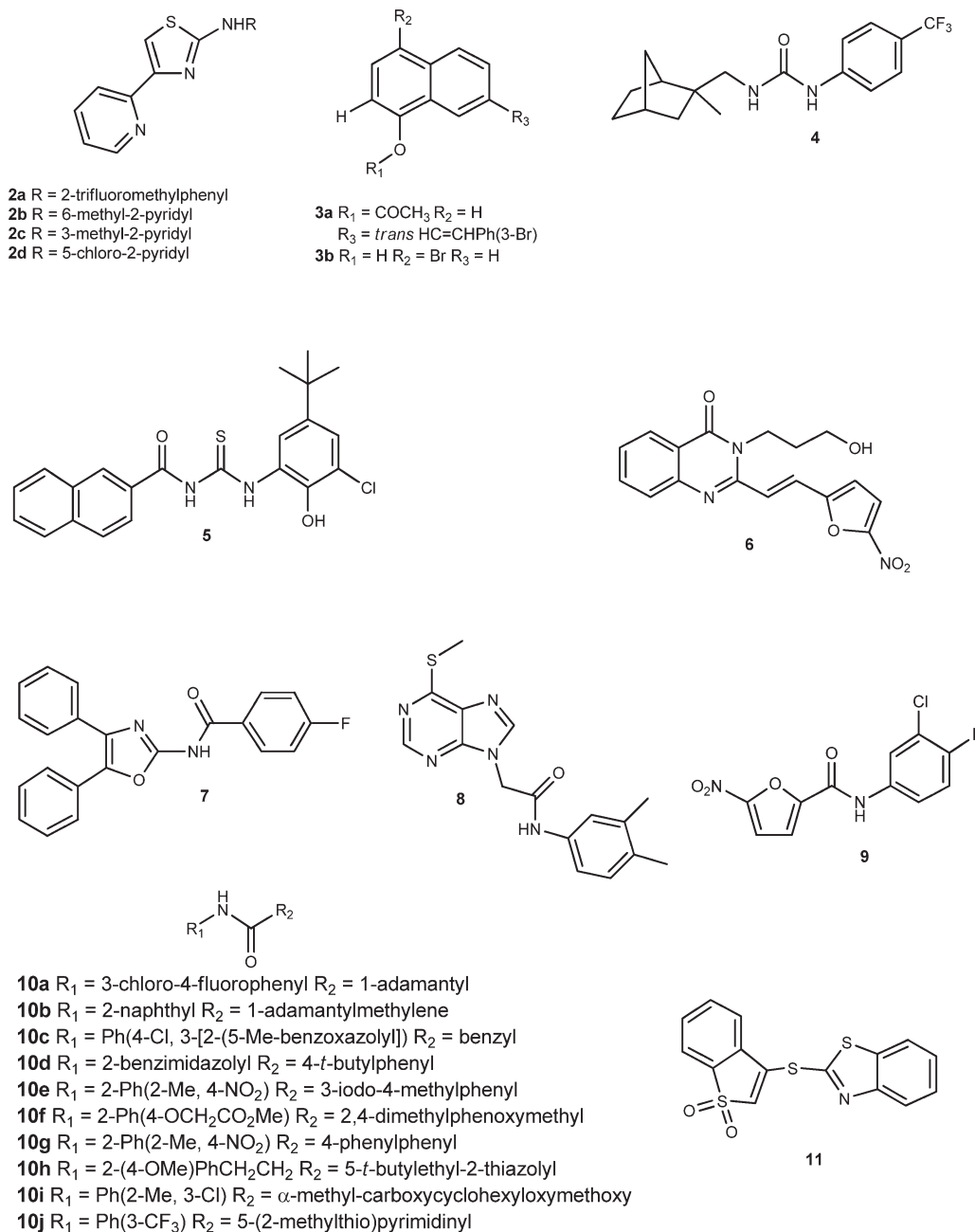


Figure 5. Compounds active at less than 0.1 $\mu\text{g}/\text{mL}$ against *M. tuberculosis* H₃₇R_v identified.

community in their selection of new molecular scaffolds for drug development.^{66,67} In this research effort a number of commercially available libraries were selectively purchased and the compounds screened. While not intended to be a comprehensive review of the NIH/TAACF screening program which looked at a series of chemical libraries, we aim to give an overview here of the chemical classes identified from the screening of a 3200 ChemBridge library and a 1200 Prestwick library which possessed excellent whole cell activity with IC₉₀ values below 0.1 $\mu\text{g}/\text{mL}$.⁶⁶

Interestingly the screening of these libraries identified the 2-aminothiazole scaffold (Figure 5) as a promising new class of anti-TB compound sharing similar chemical space to that of the ATCs and NTZ discussed earlier. As well as being active against

the mycobacteria, compounds **2a–d**⁶⁶ all possessed selectivity indexes in excess of 100. Known for their antimicrobial properties, two compounds based upon the 8-hydroxyquinoline core were also identified as having sub 0.1 $\mu\text{g}/\text{mL}$ IC₉₀ values. Compounds **3a**⁶⁶ and **3b**⁶⁶ possessed selectivity indexes of >150. Similarly thioureas and ureas identified from screening of the ChemBridge and Prestwick compound libraries were found to exhibit activity, with the urea **4**⁶⁶ and thioamide **5**⁶⁶ having potent activity and selectivity factors of >140. Also identified as promising scaffolds were the quinazolin-4(3*H*)-one analogue **6**,⁶⁶ the 2-benzamido-3,4-diphenyloxazole **7**,⁶⁶ the purine analogue **8**,⁶⁶ the 5-nitrofuran-2-carboxamide **9**,⁶⁶ a series of adamantyl and diarylamides **10a–j**,⁶⁶ and finally the benzothiothiazole **11**.⁶⁶

SUMMARY

There is no doubt that the future success in the battle to end the scourge of this debilitating disease relies heavily on the discovery of new drugs. At the moment there are a worryingly low number of potential new chemical entities in the TB drug pipeline. To overcome the high rates of attrition, many more need to be discovered and developed. To ensure this, a growing and sustainable supply of new drug discovery and development programmes must be fostered by highly multidisciplinary collaborative partnerships. This will only be possible by the growing number of academic, pharmaceutical, and not for profit organization collaborations having access to open and available data, compound libraries, and expertise to assist all involved in such research initiatives. Support for clinical trials to evaluate a steady supply of promising compounds is critical as well as funding to sustain biomarker research to provide surrogate end points to accelerate candidate selection during drug discovery and dose selection in early clinical research and ultimately to shorten the time to licensing of new drugs. As combination therapy is unavoidable and treatment of HIV co-infection is of paramount importance, funding must also be made available to address the inherent pharmacokinetic issues raised.

Critical to the success of these strategies is sustained financial and legislative support from the public sector to ensure that TB drug discovery remains a viable and attractive proposition for academia and pharmaceutical companies to engage with as they did in the mid-20th century. This paradigm shift in the way that TB drug discovery research is coordinated and conducted is vital for its success, and the time for its implementation is now!

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BIOGRAPHIES

Lynn G. Dover is Head of Biomedical Sciences at Northumbria University, U.K. After gaining his Ph.D. in Microbial Physiology at the University of Hull, U.K., he carried out postdoctoral research at the Health Protection Agency, Newcastle University, U.K., and at the University of Birmingham, U.K. His research interests are focused on the biosynthesis of the cell wall of pathogenic actinomycete bacteria exemplified by *Mycobacterium tuberculosis*, *Rhodococcus equi*, and *Corynebacterium diphtheriae*. The former is especially interesting, as we face great challenges to find new treatments for multidrug resistant strains causing human tuberculosis. New drugs inhibiting the action of new cellular targets are urgently required.

Geoffrey D. Coxon is a Lecturer in Medicinal Chemistry at the Strathclyde Institute for Pharmacy and Biomedical Sciences (SIPBS), University of Strathclyde, U.K. After receiving his Ph.D. from the University of Newcastle upon Tyne, U.K., and a short term in industry, he moved to SIPBS where he set up his research group in the discovery and development of new agents to treat tuberculosis. He is the cofounder and Deputy Leader of TB Drug Discovery UK (www.tbd-uk.org.uk). In this role he works with fellow scientists and clinicians, U.K. government policy makers, and advocates with the goal of strengthening scientific research across all areas of TB drug development as a key part of the U.K. response in the global eradication of the disease.

ABBREVIATIONS USED

TB, tuberculosis; NGO, nongovernment organizations; HIV, human immunodeficiency virus; AIDS, acquired immunodeficiency syndrome; INH, isoniazid; RIF, rifampicin; PZA, pyrazinamide; EMB, ethambutol; EBA, early bactericidal activity; DOTS, directly observed treatment short-course; MDR, multidrug-resistant; WHO, World Health Organization; AMK, amikacin; ETH, ethionamide; XDR, extensively drug-resistant; GAT, gatifloxacin; MXF, moxifloxacin; LVF, linezolid; NIAID/NIH, National Institute of Allergy and Infective Disease, National Institutes of Health; CDC, Centers for Disease Control; TDR, Research and Training in Tropical Diseases; NM4TB, New Medicines for Tuberculosis; TBD-UK, Tuberculosis Drug Discovery UK; NTZ, nitazoxanide; MIC, minimum inhibitory concentration; BTZ, benzothiazinones; ATC, 2-aminothiazole-4-carboxylates; NIH/TAACF, National Institutes of Health Tuberculosis Antimicrobial Activity and Coordination Facility

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