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2-Phenylindole and Arylsulphonamide: Novel Scaffolds Bactericidal against *Mycobacterium tuberculosis*

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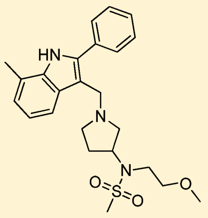
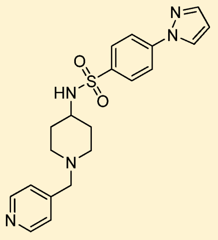
Supporting Information

ABSTRACT: A cellular activity-based screen on *Mycobacterium tuberculosis* (Mtb) H37Rv using a focused library from the AstraZeneca corporate collection led to the identification of 2-phenylindoles and arylsulphonamides, novel antimycobacterial scaffolds. Both the series were bactericidal *in vitro* and in an intracellular macrophage infection model, active against drug sensitive and drug resistant Mtb clinical isolates, and specific to mycobacteria. The scaffolds showed promising structure−activity relationships; compounds with submicromolar cellular potency were identified during the hit to lead exploration. Furthermore, compounds from both scaffolds were tested for inhibition of known target enzymes or pathways of antimycobacterial drugs including InhA, RNA polymerase, DprE1, topoisomerases, protein synthesis, and oxidative-phosphorylation. Compounds did not inhibit any of the targets suggesting the potential of a possible novel mode of action(s). Hence, both scaffolds provide the opportunity to be developed further as leads and tool compounds to uncover novel mechanisms for tuberculosis drug discovery.


MtuMIC H37Rv(uM):0.98


MtuMIC H37Rv(uM):1.56

KEYWORDS: *Tuberculosis, Mycobacterium tuberculosis, 2-phenylindoles, arylsulphonamides*

One of the major factors for tuberculosis (TB) developing into global health emergency is the rise of multi and extensively drug resistant (MDR and XDR) *Mycobacterium tuberculosis* (Mtb) strains. Although a large number of antibiotics are available for TB therapy, both as first and second line treatment, TB continues to have a high mortality rate. WHO reported 1.3 million deaths in the year 2012.[1] TB therapy is a multidrug therapy for a duration of up to 6−24 months for drug sensitive and resistant TB, respectively. The recent emergence of strains that are resistant to nearly all antimycobacterials has left very limited options for TB patients.[2] Moreover, most TB drugs were discovered decades ago and exhibit suboptimal safety profiles in relation to modern anti-infective therapy. Therefore, there is a critical need for antimycobacterials that work via novel mechanisms and have better tolerability. For the first time since the 1960s, novel TB drugs are emerging.[3] Approvals of bedaquiline and delamanid provide hope for MDR-TB patients and for TB research, despite the associated toxicities with these novel agents. The challenge, therefore, is to find new classes of antibiotics that are safe and more efficacious on both MDR and XDR TB.

Mtb exists in multiple physiological phases, e.g., replicating and nonreplicating phase in human lung.[4] It was long realized that multidrug combination is crucial to target all Mtb populations in order to cure patients and reduce relapse rates. The present first line therapy for drug sensitive TB consists of four drugs, i.e., isoniazid (INH), rifampicin (RIF), ethambutol (ETM), and pyrazinamide (PZA).[5,6] While INH and ETM inhibit cell wall biosynthesis, RIF acts by inhibiting transcription. PZA is a prodrug that is active on nonreplicating Mtb and is believed to act via multiple mechanisms, i.e., accumulation of pyrazinoic acid disrupting membrane potential and energy production, inhibition of fatty acid synthesis, and inhibition of trans−translation. Among second line drugs, compounds act by inhibiting cell wall biosynthesis including peptidoglycan synthesis, DNA gyrase, and protein synthesis.[5,6] Interestingly, identification of a novel drug like bedaquiline was instrumental in uncovering the critical nature of oxidative phosphorylation and the ATP synthesis pathway under varied physiological states.[7] Similarly bactericidal compounds, SQ109, led to the identification of MmpL3[8] and benzothiazinones (BTZ043) to DprE1.[9] Therefore, prioritizing whole cell actives that are inactive on known targets/mechanisms could potentially uncover hitherto unknown mechanisms that can be exploited for TB drug discovery.

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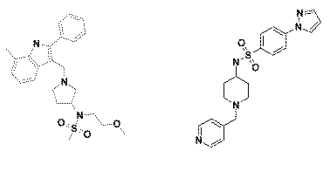
A representative collection of 320,000 compounds from AstraZeneca's corporate library was initially evaluated at 20 μM against Mtb for their growth inhibitory activities. About 1600 compounds exhibited ≥80% inhibition of growth as compared to the culture control in the primary single point screen. These compounds were prioritized for minimum inhibitory concentration (MIC) determination. Compounds with potent MIC were tested for minimum bactericidal concentration (MBC). Hit evaluation and prioritization of chemical scaffolds were carried out based on MIC, MBC, and lead-like properties. Solids of the prioritized scaffolds and their near neighbors were procured from AstraZeneca corporate collection for confirmation and to derive a preliminary structure−activity relationship (SAR). To rule out preliminary safety issues, cytotoxicity was evaluated by measuring the CC_{50} against mammalian cells. Finally, representative compounds were tested for inhibition of known antitubercular mechanisms. Chemical scaffold with potent cellular activity, attractive physicochemical properties, and potentially novel mode(s) of inhibition were prioritized. Here, we report two such novel scaffolds: the 2-phenylindoles (compound **1**) and arylsulphonamides (compound **21**) that possess potent antimycobacterial properties (Figure 1).



Compound **1**
MIC: 0.8-1.6 μM

Compound **21**
MIC: 0.8-3.1 μM

Figure 1. Lead molecules: 2-phenylindole (compound **1**) and arylsulphonamide (compound **21**).

A robust SAR was developed for the 2-phenylindole scaffold, which resulted in lead like structures with good physicochemical properties. Herein, we report the chemical optimization of 2-phenylindoles. The SAR of these modifications is summarized in Supporting Table 1.

The strategy was to identify a key pharmacophore required for cellular activity, by checking the essentiality of different groups in the molecule and building an understanding of a MIC based SAR. Toward this end, the scaffold was broadly divided into ring A, ring B, and ring C as shown in Figure 2. It was observed that methylating the NH of indole (compound **3**) retained cellular potency hence, confirming that the indole NH is not essential for activity. Further, the effects of various substituents on ring A revealed that electron donating substitutions like methyl, methoxy, and isopropyl were tolerated at the C-7 position (compounds **8** and **15**); however, a disubstitution on the indole ring (compounds **12** and **16**) resulted in increased MICs. Saturating the phenyl ring (ring A, compound **20**) compromised potency to a certain extent. The 2-phenyl group (ring B) was essential for the activity as removal of it (compound **13**) made the molecule inactive, suggesting the role of large aromatic group and/or hydrophobic interactions for activity. The benzyl group attached to the indole NH (compound **11**) failed to occupy this hydrophobic space as in the case of 2-phenyl, hence the compound was weakly active. Both electron withdrawing and electron donating groups were tolerated on the ring B; however, the best results were obtained when there was an unsubstituted phenyl ring at 2-position (compound **1**). A pyridine ring was not tolerated at C-2 position of the indole ring (compound **14**). The substitution on the pyrolidine ring at the C-3 position of the indole has limited effect on the cellular potency; MIC was retained even when the side chain was completely removed on pyrrolidine (compound **6**) or one of the side chains was maintained (compounds **2** and **5**). This provided a greater opportunity for structural modifications and also to improve physicochemical properties. The stereochemistry at C-3 position of pyrolidine had no role in defining potency as both the enantiomers (compounds **18** and **19**) and the racemate (compound **2**) had similar MICs.

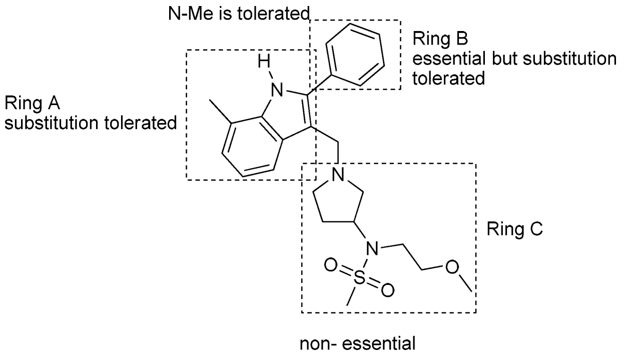
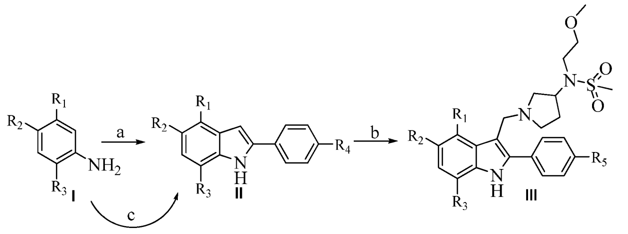


Figure 2. SAR for 2-phenylindoles.

2-Phenylindole Synthesis. Compounds involving ring A and ring B modifications were synthesized starting from their corresponding anilines and bromoacetyl derivatives using the general indole synthesis protocol[11] outlined below (Scheme 1).

Scheme 1. Synthesis of Phenylindoles[a]



[a]Reagents and conditions: (a) phenacyl bromide derivative, *N,N*-dimethylaniline, MW, 140 °C, 20 min; (b) amine, $ZnCl_2$, ethanol, RT, 3 h; (c) phenacyl bromide, xylene, DMA, 150 °C, overnight.

Optimum results for the indole synthesis were obtained when the reactions were performed under microwave conditions using the corresponding anilines (**I**) and acetyl bromide derivatives in minimum amount of dimethylaniline. An alternate procedure was also tried for few compounds (condition **c**) as shown in Scheme 1.[12] The corresponding acetyl bromides were made by bromination of acetyl derivatives using general protocols available in the literature.[13] The Mannich reaction on this indole derivative (**II**) at 3-position with the corresponding amines using $ZnCl_2$ and formaldehyde solution in ethanol provided the final compounds (Supporting Table 1) in very good yield. The intermediate amine was made according to the procedures mentioned in the Supporting Information.

Arylsulphonamide, a low molecular weight scaffold with potent Mtb activity was another promising scaffold that emerged out of this screening.

Similar to 2-phenylindoles, the initial strategy here was also to discern the key pharmacophoric features required for cellular activity. The requirement of different functionalities on the molecule was checked by making targeted analogues. The molecule was broadly divided into four parts as shown in Figure 3. The initial exploration concluded that the pyrazole on the phenyl ring is not essential as replacing pyrazole with oxazole (compound **24**) and phenyl group (compound **29**) retained the potency. This provided opportunities for structural modifications on ring A. The phenyl ring tolerated substitution ortho to the sulphonamide (compound **22**). Methyl substitution on the phenyl ring ortho to the sulphonamide linkage improves the activity (MIC = 0.55 μM), and the corresponding 2-pyridine derivative retained MIC (compound **23**). The pyridine derivative reduced the logD of the molecule (1.7) and improved the solubility to 1000 μM. The sulphonamide was essential for activity, as the corresponding amide derivative (compound **32**) was inactive; however, alkylation of NH of the sulphonamide (compound **25**) was moderately active (12.5 μM). A methoxy substitution on the linker piperidine (ring C, compound **26**) made the compound much weaker compared to the original compound. Replacing the aminopiperidine with piperazine (compound **31**) gave a moderate MIC of 12.5 μM. The potency was lost (MIC > 200 μM) when 4-pyridine (Ring D) was replaced with 3-methoxyphenyl (compound **33**) indicating that phenyl group may not be tolerated at this position. The methylene linker between the piperidine and pyridine rings was converted to carbonyl (compound **30**); the compound showed MIC of 6.25 μM, which opened up an opportunity for modifications at this portion of the molecule. The SAR of these modifications is summarized in Supporting Table 2.

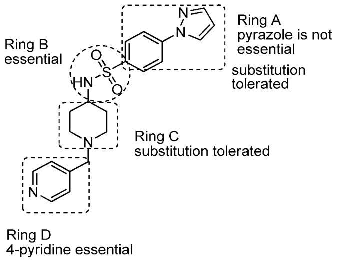
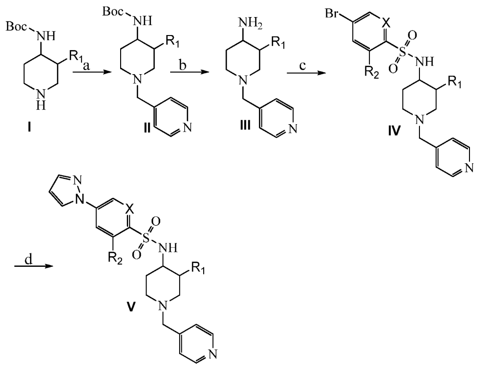


Figure 3. SAR for arylsulphonamides.

Arylsulphonamide Synthesis. The general synthesis involved is shown in Scheme 2. The corresponding BOC protected 4-aminopiperidine (**I**) was treated with pyridinemethyl halides using potassium carbonate in DMF. After removal of the BOC protecting group, compound **III** was treated with corresponding sulphonyl chloride in DMF using potassium carbonate as base. The final conversion to compound **V** was done using (1*R*,2*R*)-(−)-1,2-diaminocyclohexane and copper iodide in dioxane using microwave conditions.

In a few cases the corresponding 4-(1*H*-pyrazol-1-yl)-benzenesulphonyl chloride derivatives were commercially available, so these were converted into the corresponding sulphonamides using the condition mentioned in Scheme 2. Representative compounds from both the scaffolds were profiled for logD (experimental) and aqueous solubility (Table 1). For 2-phenylindoles, the logDs were in the range of 3 to 3.5, with multiple SAR handles to reduce logD, while retaining MIC. The solubility for the compounds were poor in general (as seen for compound **1**); however, replacing methyl with methoxy at C-7 position of indole (compound **8**) improved the solubility significantly (100 μM). The changes in ring C are expected to have maximum impact on solubility without impacting the potency (compound **17**, solubility 752 μM). The logDs for arylsulfonamides were in the range of 1.7 to 2.3 with good solubility (Table 1).

Scheme 2. Synthesis of Arylsulphonamide[a]



R_1=H, OCH_3; R_2=H, CH_3, F, CF_3; X=C, N

[a] Reagents and conditions: (a) 4-pyridinemethyl chloride, potassium carbonate, DMF, RT, 5 h; (b) HCl in dioxane, RT; (c) potassium carbonate, phenyl sulphonyl chloride, RT, 3 h; (d) (1*R*,2*R*)-(−)-1,2-diaminocyclohexane, copper iodide, pyrazole, 1,4-dioxane, MW, 30 min.

Table 1. *In Vitro* Evaluation of logD (Experimentally Determined) and Solubility for Representative Compounds[a]

PI	logD	solubility (μM)	AS	logD	solubility (μM)
1	3	5.4	**21**	2.6	149
8	2.8	103	**22**	2.3	66
17	1.8	752	**23**	1.7	1000

[a] PI: 2-phenylindoles. AS: arylsulphonamides.

The antibacterial properties were assessed in detail for representative compounds from both the scaffolds (Table 2 and Figure 4). 2-Phenylindoles (compounds **1** and **2**) were active and bactericidal against H37Rv with MBC to MIC ratio of ∼5−10, while arylsulphonamides (compounds **21** and **22**) showed MBC to MIC ratio of ∼1−2. Compounds **1** and **21** both were

Table 2. *In Vitro* Microbiology Profile

	1	2	21	22
MIC[a] (μM)	0.8−1.6	3.3−6.2	0.8−3.1	1.6
MBC (μM)	3.8−12.5	50	1.6−3.1	1.6
HBC[b] (μM)	3.1−12.5	25	>200	>200
Clinical isolates MIC (μM)	0.8−6.3	3.3−12.5	0.8−3.1	1.6−6.3
INH^R, RIF^R, EMB^R MIC (μM)	0.8−6.3	3.3−12.5	0.8−3.1	1.6−6.3
G−ve and G+ve MIC (μM)	>200	>200	>200	>200
THP1 $\log_{10}$ CFU reduction	∼1.5	ND	∼1.5	ND
THP1 cytotoxicity (CC_{50}) (μM)	>64	>64	32	32

[a] Four-fold variations are acceptable. [b] Compound concentration, which shows ≥2 $\log_{10}$CFU/mL reduction under hypoxic conditions.

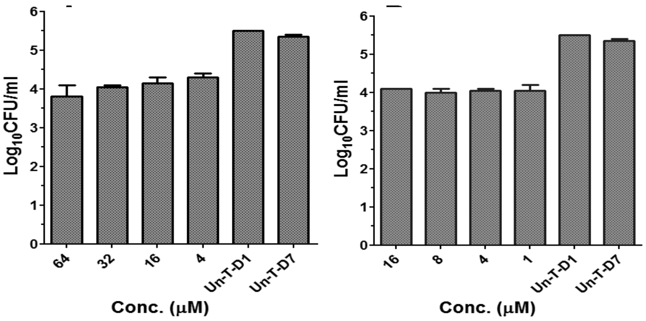


Figure 4. Activity in THP1 infection model.

active in intracellular THP1 model and showed ~1.5 Log_{10}CFU reduction, respectively, at MIC post 7 days treatment (Figure 4). Interestingly, 2-phenylindoles as a series (represented by compounds **1** and **2**) were bactericidal under hypoxic conditions (HBC, Table 2), a nonreplicating *in vitro* Mtb model,[14] whereas arylsulphonamides did not show bactericidality under these conditions (Table 2). Both series did not show activity against a panel of Gram-positive and Gram-negative bacteria, namely, *Escherichia coli*, *Haemophilus influenzae*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Staphylococcus aureus*, and *Streptococcus pneumoniae*; and thereby appear to be specific for Mtb. Moreover, the observed activity against H37Rv was retained on drug sensitive Mtb clinical isolates and on isoniazid, rifampicin, and ethambutol single resistant strains. Compounds were tested for cytotoxicity against mammalian cell line THP1 (human monocytic cell line); compounds **1** and **2** were not cytotoxic at concentrations tested, whereas compounds **21** and **22** (arylsulphonamides) showed cytotoxicity beyond 32 μM.

Table 3. Assessing Inhibition of Various Mtb Strains

compd	H37Rv MIC (μM)	InhA OE MIC (μM)	DprE1 OE MIC (μM)
1	0.8−1.6	0.8−1.6	1.6
21	0.8−3.1	1.6−3.1	1.6
isoniazid	0.5	>7.5	0.5
rifampicin	0.01	0.01	0.01
BTZ043	0.003−0.006	0.003−0.006	12.5−50

Table 4. Inhibition of Known Target Biochemical Assays

IC_{50} (μM)	1	21	control (IC_{50})
InhA	>100	>100	triclosan 0.63 μM isoniazid (prodrug)
DprE1	>10	>10	BTZ043 10 nM
Gyrase	>100	>100	moxifloxacin 10 μM; novobiocin 15 nM
TopoI	>100	>100	camptothecin 500 μM
Oxphos	15.6	>70	bedaquiline 1 nM
RNAP	>00	>100	rifampicin 30 nM

Table 5. Macromolecular Biosynthesis in μg/mL

compd	MIC	adenine (IC_{50})	uracil (IC_{50})	leucine (IC_{50})
1	5	NI*	NI	NI
21	4.25	NI	NI	NI
sparfloxacin	0.25	16.7	7.3	11.4
rifampicin	0.03	NI	2.9	2
chloramphenicol	16	NI	NI	5.6

*NI: no inhibition observed.

Compounds **1** and **21** were also used as representative compounds for understanding the mechanism of action of 2-phenylindoles and arylsulphonamides, respectively. These were screened for known antitubercular mechanisms using varied phenotypic and biochemical assays (Tables 3−5). InhA, target for isoniazid, was ruled out as a target, as compounds did not inhibit InhA biochemical assay and also did not show an upshift of MIC on target overexpression compared to wild-type. Isoniazid in the phenotypic assay showed an 8- to 16-fold increase in MIC for InhA overexpressing strain compared to wild-type H37Rv. On similar lines, compounds were tested for activity in DprE1 biochemical assay and MIC modulation for DprE1 overexpression strain compared to wild-type Mtb. They were inactive in both assays, whereas reference compounds BTZ043,[9] a covalent inhibitor, and 1,4-azaindoles, a noncovalent inhibitor of DprE1,[10] behaved as expected. Inhibition of DNA topoisomerases, i.e., DNA gyrase and DNA topoisomerase I (TopoI), were assessed using gel-based supercoiling and relaxation assays, respectively. Both compounds did not inhibit topoisomerase catalyzed reactions even at 100 μM, ruling them out as targets. Moxifloxacin and novobiocin, known DNA gyrase inhibitors, both inhibited the supercoiling reaction. A potent and specific bacterial TopoI inhibitor has not been identified yet. Therefore, we used camptothecin, an inhibitor of eukaryotic TopoI and poor inhibitor of mycobacterial enzyme, as the tool compound in the DNA relaxation assay. The test compounds also failed to show significant inhibition of mycobacterial oxidative phosphorylation (Oxphos) assay, whereas bedaquiline (TMC207) in the same assay had an IC_{50} of 1 nM. Although, compound **1** did show an IC_{50} of 15 μM in this assay, the potent MIC observed for the molecule did not correlate with the IC_{50}s, hence minimizing the possibility of oxidative phosphorylation as a potential target mechanism. Compounbds **1** and **21** were found to be inactive in *in vitro* transcription assay catalyzed by *Mycobacterium smegmatis* RNA polymerase. Additionally, they did not inhibit incorporation of radioactively labeled [^{3}H]uracil in *Mycobacterium bovis*-BCG (Mbo-BCG), a surrogate readout for transcription ongoing in the cell. Rifampicin, an inhibitor of RNA polymerase (RNAP), shows an IC_{50} of 30 nM under the assay conditions and also inhibited incorporation of labeled [^{3}H]uracil and [^{3}H]leucine (marker for protein synthesis) in the cells. Finally, compounds also did not show inhibition of protein synthesis, while chloramphenicol, a protein synthesis inhibitor, specifically inhibited incorporation of radioactive [^{3}H]leucine in Mbo-BCG. Taken together, we conclude that both chemical series do not act by primary antitubercular mechanisms known and hence are expected to have novel mechanisms of action. Experiments are underway to identify the mode of action for the chemical scaffolds.

In summary, we have identified two novel scaffolds that have potent antimycobacterial activity against extracellular and intracellular bacterium. We also present SAR understandings for the two series with respect to potency. Finally, we have tested the compound against available assays for understanding the mode of action. The compounds do not act by primary known mechanisms and therefore are expected to have a novel mode of action. Moreover, both series retain activity on single drug resistant Mtb strains. Taking all the information together, we believe 2-phenylindoles and arylsulphonamides have the potential to be progressed further and are also valuable as tool compounds for the identification of novel targets for TB drug discovery.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Tables describing the SAR, details of biological assays, and chemical synthesis. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

M.N., S.G., M.P., and P.I. were responsible for medicinal chemistry design and analyses. M.N., L.K.G., G.G., and L.K.N. performed the synthesis of the compounds. A.N., S.G., S.S., N.D., P.K., and V.R. performed whole cell screen and microbiology experiments. R.N., J.B., G.B. and V.H. performed biochemical assays. P.K. was responsible for compound management. M.C. has steered the evaluation of the screen hits based on bactericidality and novel mechanism and driving the overall biology. M.N. and M.C. wrote the manuscript.

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Notes

The authors declare no competing financial interest.

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