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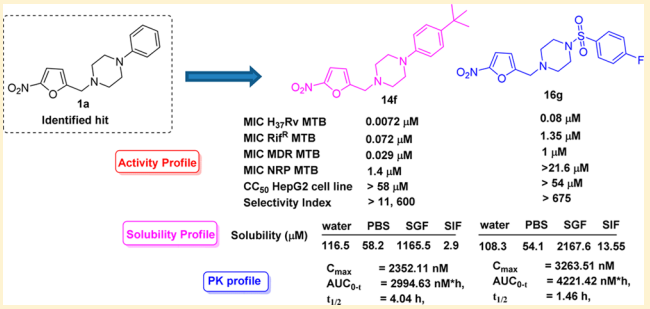
# Nitrofuranyl Methyl Piperazines as New Anti-TB Agents: Identification, Validation, Medicinal Chemistry, and PK Studies

Kushalava Reddy Yempalla,[†,⊥,#] Gurunadham Munagala,[†,⊥,#] Samsher Singh,[‡,⊥,#] Asmita Magotra,[§,⊥] Sunil Kumar,[‡,⊥] Vikrant Singh Rajput,[‡,⊥] Sonali S. Bharate,[∥] Manoj Tikoo,[§] G. D. Singh,[§] Inshad Ali Khan,[*,‡,⊥] Ram A. Vishwakarma,[*,†,⊥] and Parvinder Pal Singh[*,†,⊥]

[†]Medicinal Chemistry Division, [‡]Clinical Microbiology Division, [§]PK–PD and Toxicology Division, [∥]Pre-formulation Laboratory, [⊥]Academy of Scientific and Innovative Research, CSIR-Indian Institute of Integrative Medicine, Canal Road, Jammu 180 001, India

Supporting Information

**ABSTRACT:** Whole-cell screening of 20,000 drug-like small molecules led to the identification of nitrofuranyl methylpiperazines as potent anti-TB agents. In the present study, validation followed by medicinal chemistry has been used to explore the structure–activity relationship. Ten compounds demonstrated potent MIC in the range of 0.17–0.0072 $\mu$M against $H_{37}Rv$ *Mycobacterium tuberculosis* (MTB) and were further investigated against nonreplicating and resistant ($Rif^R$ and MDR) strains of MTB. These compounds were also tested for cytotoxicity. Among the 10 tested compounds, five showed submicromolar to nanomolar potency against nonreplicating and resistant ($Rif^R$ and MDR) strains of MTB along with a good safety index. Based on their overall *in vitro* profiles, the solubility and pharmacokinetic properties of five potent compounds were studied, and two analogues, **14f** and **16g**, were found to have comparatively better solubility than others tested and acceptable pharmacokinetic properties. This study presents the rediscovery of a nitrofuranyl class of compounds with improved aqueous solubility and acceptable oral PK properties, opening a new direction for further development.




**KEYWORDS:** *Mycobacterium tuberculosis, MTB $H_{37}Rv$, multidrug resistant-TB, 6-nitro-2,3-dihydroimidazooxazole, structure–activity relationship*

The emergence of resistant tuberculosis has been a serious concern worldwide that has reinvigorated drug discovery efforts in search of novel candidates that are effective against both susceptible and resistant strains as well as safe and potentially faster-acting, with the aim of shortening lengthy TB treatments.[1−3] Whole cell screening is an attractive approach to the fast identification of novel compounds active against TB.[4] The success of the whole cell screening-driven approach to tuberculosis is best illustrated by the discovery of bedaquiline (TMC207, diarylquinoline derivative).[5,6] Similar success has been shown by the discovery of other preclinical candidates such as benzothiazoles TCA-1[7] and imidazopyridine amides Q-203.[8] Considering the high attrition rate in clinical trials, further enrichment of the clinical pipeline is greatly needed.

To discover novel and potent anti-TB agents, a whole-cell screening approach was adapted, and 20,000 small drug-like compounds were procured and screened.[9] The aim of this approach was to find drug-like compounds in this collection and then to chemically modify these compounds to improve their PK/PD behaviors. The library was initially screened against sensitive ($H_{37}Rv$) and rifampicin resistant ($Rif^R$) strains of MTB at the concentration of 16 $\mu$g/mL, and 707 molecules demonstrated >90% growth inhibition. A minimum inhibitory concentration (MIC) determination for these compounds yielded 233 molecules with ≤8 $\mu$g/mL MIC against sensitive and resistant strains of MTB. The chemical clustering of these hits revealed nitrofuranyl methylpiperazine as one of the most potent scaffold (Figure 1). The identified nitrofuranyl methylpiperazine cluster included six compounds **1a–f** with a MIC in the range of 0.2–25.3 $\mu$M against $H_{37}Rv$ and $Rif^R$ strains of MTB (Figure 1).

A literature survey revealed that nitrofuran containing compounds are known to possess anti-TB potential. Lee and co-workers[10−16] have extensively studied nitrofuranylamides **2** and also generated several leads {**3** (Lee-562), **4** (Lee-878), and **5** (Lee-1106)} as shown in Figure 2. Despite excellent *in vitro* profiles, these molecules possessed poor *in vivo* efficacy because of their low oral bioavailability and aqueous solubility, indicating that further effort is needed to utilize these compounds effectively. Our whole-cell screening program resulted in the identification of nitrofuranyl methyl piperazine **1**, wherein a nitrofuranyl ring is directly attached to a piperizine ring through a methylene instead of an amide linkage. The high

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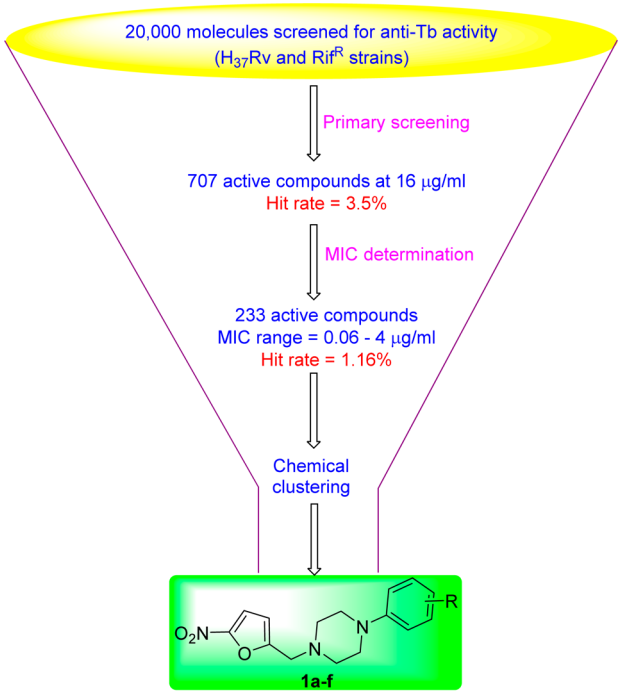



| Compound | R | MIC ($H_{37}R_v$) μM | MIC ($Rif^R$) μM |
|---|---|---|---|
| **1a** | H | 0.20 | 13.93 |
| **1b** | 3-Cl | 0.37 | 0.37 |
| **1c** | 2-F | 6.55 | 13.11 |
| **1d** | 4-F | 3.27 | 6.55 |
| **1e** | 3-$CF_3$ | 0.33 | 5.63 |
| **1f** | 2, 3-dimethyl | 12.69 | 25.3 |

**Figure 1.** Schematic representation of whole-cell screening of 20,000 molecules.

potency of these compounds, along with their comparatively simpler structure and likeliness of increased aqueous solubility indicated the need for further investigation. A medicinal chemistry program was initiated on nitrofuranyl methyl piperazine **1** using the strategy shown in Figure 3.

**Results and Discussion.** *Chemistry.* Initially, the potent hit **1a** was prepared by the reductive amination of 5-nitrofuraldehyde **6** with 4-phenyl piperazine **7** (Scheme 1). Next, to ascertain the role of the nitro group, the des-nitro derivative **13** was prepared using the synthetic strategy shown in Scheme 2.[17] The role of the furan ring was also investigated by synthesizing analogues **14a−c**, in which the furan ring was replaced with a thiophene ring using the same synthetic strategy. The effect of ring C was also studied, and analogues **14d−l** were synthesized with varying substituents. Through further modification, analogues **16a−h** were prepared by replacing the phenyl ring (ring C) with alkyl/aryl sulfonyl groups as per the synthetic strategy shown in Scheme 3. In another modification, the piperazine ring (ring B) was replaced

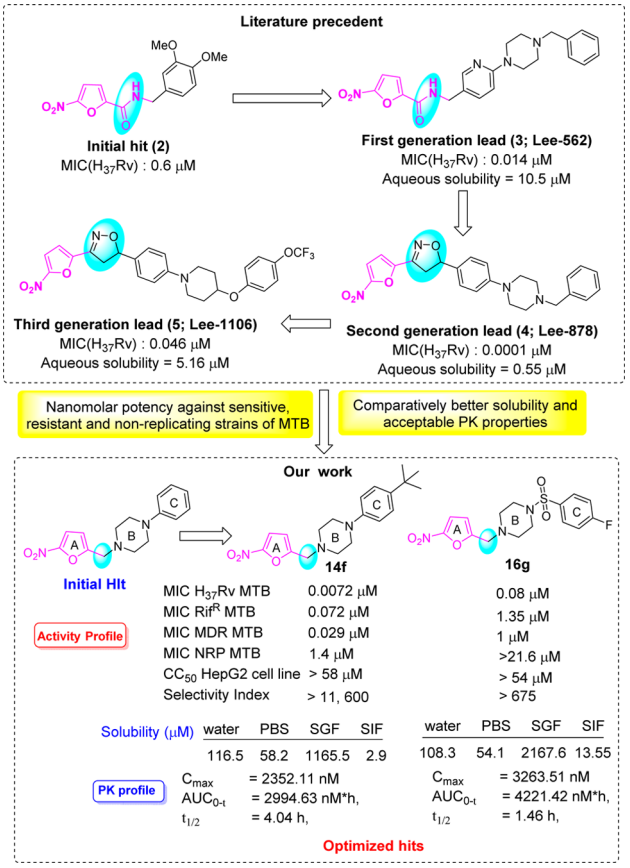



**Figure 2.** Nitrofuranyl containing anti-TB molecules.

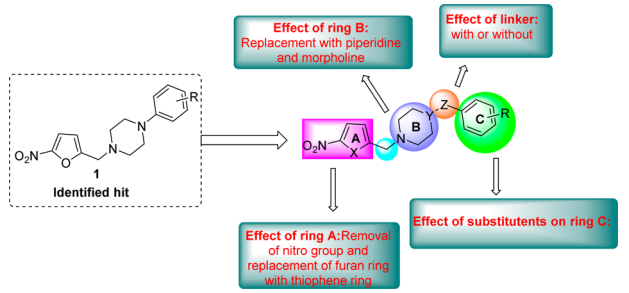
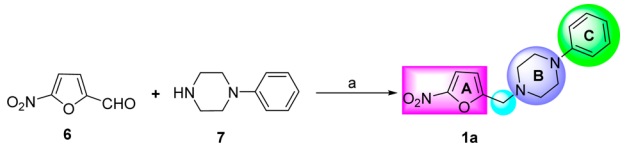



**Figure 3.** Medicinal chemistry approach.

**Scheme 1. Synthesis of Identified Hit 1a**[a]




[a]Reagents and conditions: (a) $Na(OAc)_3BH$, AcOH, DCM, rt, 12 h, 85%.

with piperidine and morpholine rings using the synthetic scheme shown in Scheme 4.

*Biological Evaluation.* The synthesized analogues **1a**, **13**, **14a−l**, **15**, **16a−g**, and **18a−b** were screened for *in vitro* activity against MTB $H_{37}Rv$ (ATCC27294 strain) using the microbroth dilution method. The MIC was determined as the minimum concentration of the compound required to inhibit 90% of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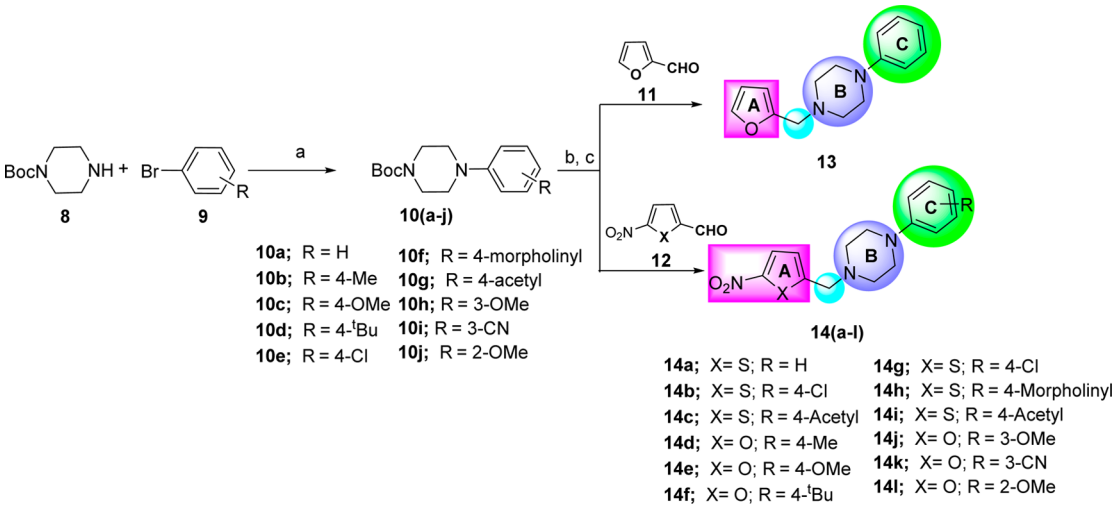
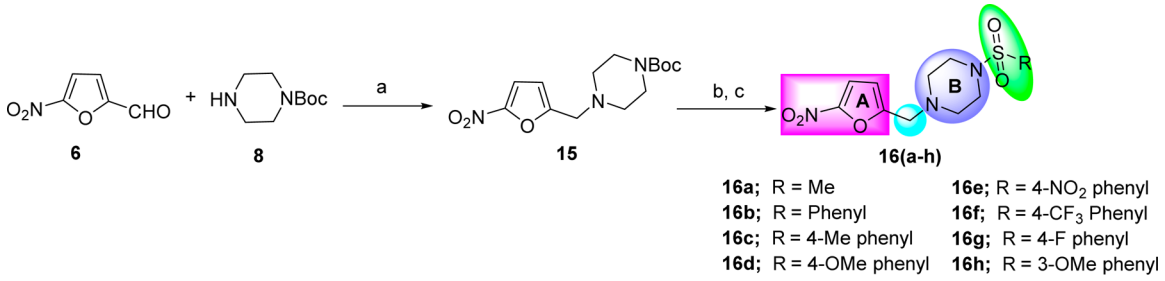
**Scheme 2. Synthesis of Rings A and C Modified Nitrofuranyl Methyl Piperazines**[a]



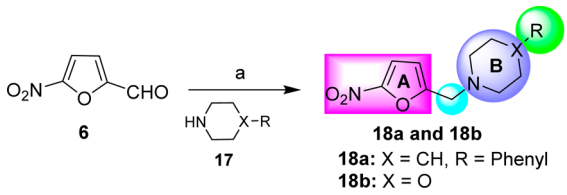

[a]Reagents and conditions: (a) $Pd(OAc)_2$,$Cs_2(CO)_3$, rac-BINAP, toluene, reflux, 4 h, 60−65%;[17] (b) TFA, DCM, rt, 2 h; (c) $Na(OAc)_3BH$, AcOH, DCM, rt, 12 h, 80−90%.

**Scheme 3. Synthesis of Alkyl/Aryl Sulfonyl Groups Containing Nitrofuranyl Methyl Piperazines**[a]




[a]Reagents and conditions: (a) $Na(OAc)_3BH$, AcOH, DCM, rt, 12 h, 80%; (b) TFA, DCM, rt, 15 min; (c) R-$SO_2$CI, TEA, DMAP, DCM, rt, 12 h, 90−95%.

**Scheme 4. Synthesis of Nitrofuranyl Analogues**[a]




[a]Reagents and conditions: (a) $Na(OAc)_3BH$, AcOH, DCM, rt, 12 h, 75−80%.

bacterial growth. The MIC values of all of the synthesized compounds are summarized in Table 1.

Synthesized compound **1a** exhibited an MIC value of 0.2 $\mu$M against the $H_{37}Rv$ strain of MTB, similar to that observed during the library screen. The removal of nitro group destroyed the activity of the compound **13**, which revealed that the presence of the nitro group is essential. The replacement of furan with a thiophene ring was also unfavorable, and none of the thiophene ring-containing analogues **14a−c** demonstrated any inhibition at concentrations up to 10 $\mu$M. The results suggested that the nitro-furan moiety is essential for activity.

The effect of ring C and its substituents were also investigated. The nature and position of the substituents greatly influenced activity. The presence of substituents at *para*- and *meta*-positions on ring C was found to be favorable. Among

**Table 1. *In Vitro* Activity of All Synthesized Compounds**[a]

| compd | MIC ($H_{37}Rv$) ($\mu$M) | compd | MIC ($H_{37}Rv$) ($\mu$M) |
|---|---|---|---|
| **13** | >16.5 | **15** | 0.048 ± 0 |
| **14a** | >13.1 | **16a** | 23.07 ± 7.9 |
| **14b** | >11.8 | **16b** | 0.17 ± 0 |
| **14c** | >11.5 | **16c** | 0.16 ± 0 |
| **14d** | 13.2 ± 6.8 | **16d** | 0.31 ± 0 |
| **14e** | 0.12 ± 0.4 | **16e** | 0.15 ± 0 |
| **14f** | 0.0072 ± 0.03 | **16f** | 0.5 ± 0.1 |
| **14g** | 0.37 ± 0.18 | **16g** | 0.08 ± 0 |
| **14h** | 0.02 ± 0 | **16h** | 1.3 ± 0 |
| **14i** | 0.3 ± 0.1 | **18a** | 0.59 ± 0.2 |
| **14j** | 0.047 ± 0 | **18b** | 31.4 ± 10.8 |
| **14k** | 0.019 ± 0.006 | Rifampicin | 0.07 ± 0.03 |
| **14l** | 25.2 ± 7.6 | | |

[a]Values reported are the average of three individual measurements ± SD.

the different *para*-groups, compounds with bulkier groups, **14f** (4-*tert*-butyl) and **14h** (4-morpholinyl), demonstrated comparatively better MIC values of 0.0072 and 0.02 $\mu$M against $H_{37}Rv$ strain of MTB, respectively. Among the *meta*-groups, compounds with methoxy group **14j** and cyano group **14k** demonstrated the most potent MIC values of 0.047 and 0.019 $\mu$M, respectively (Table 1). The activity results suggested that



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both the nature and position of substituents influenced activity, and the presence of bulkier groups at the *para*-position and smaller groups at the *meta*-position led to enhanced potency.

In further modifications, the phenyl ring (ring C) was replaced by alkyl/aryl sulfonyl groups. Compound **16a**, with a methane sulfonyl group on the piperazine ring, demonstrated decreased activity. However, nitrofuranyl methyl piperazines with un/substituted phenyl sulfonyl groups **16b−h** showed good to excellent activity (Table 1). Moreover, due to the presence of a sulfonyl group between ring B and ring C, analogues with an even smaller group at the *para*-position of ring C exhibited good activity. Overall, these results suggest that replacement of the phenyl ring with an arylsulfonyl moiety is acceptable. The replacement of the piperazine ring with piperidine in compound **18a** led to a MIC of 0.59 $\mu$M, but replacement with morpholine in compound **18b** led to a complete loss of activity. These results indicate that the piperazine ring is preferred over piperidine or morpholine rings. A brief summary of SAR is shown in Figure 4.

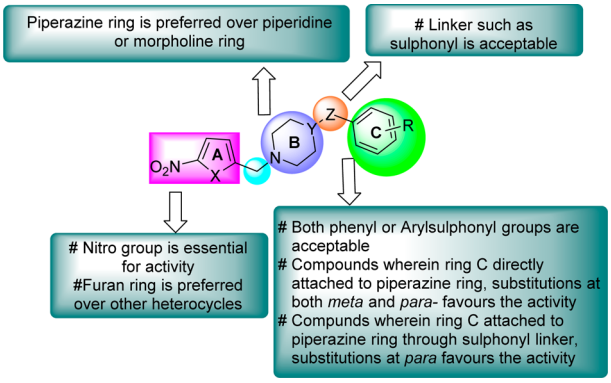


**Figure 4.** Brief SAR of nitrofuranyl methylpiperzine series.

Among all of the tested compounds, the 10 most active nitrofuranyl methyl piperazine analogues with activities of ≤0.2 $\mu$M (Table 1) were further screened against nonreplicating (streptomycin starved *M. tuberculosis* 18b) and resistant ($Rif^R$ and MDR) strains of MTB. The cytotoxic potential of these compounds was also investigated in a HepG2 cell line. The results are shown in Table 2. Five analogues *viz.*, **14f**, **14h**, **14k**, **15** and **16g** demonstrated potent MIC values against nonreplicating and resistant strains of MTB. None of the tested compounds were toxic in HepG2 cell lines, and all have acceptable safety indices.

Based on the measured activity levels against all of the tested strains, the five most active compounds, **14f**, **14h**, **14k**, **15**, and **16g**, were further tested for solubility and pharmacokinetic activity. Previous studies have reported that nitrofuran based compounds suffer from poor absorption, which might be caused by their poor aqueous solubility. We studied the solubility of potent compounds in water and in other media (basic and acidic), and all of the tested compounds except **14h** possess good to excellent aqueous solubility. The oral *in vivo* pharmacokinetic properties of these compounds were also studied in mice at a dose of 10 mg/kg, and the results are summarized in Table 3 (detail given in SI).

Among the five tested compounds, three compounds **14f**, **15**, and **16g** possess promising PK properties, with $C_{max}$ values of 2352.11, 3806.90, and 3263.51 nM, respectively, and $AUC_{0\text{-}t}$ values of 2994.63, 2709.06, and 4221.42 nM·h, respectively. The half-lives of **14f**, **15**, and **16g** were calculated to be 4.04, 1.69, and 1.46 h, respectively. Compound **14h** had a high $C_{max}$ of 5342.18 and an $AUC_{0\text{-}t}$ of 4512.72, but a comparatively short elimination half-life. Although compound **14k** demonstrated good aqueous solubility, it was not detected in an *in vivo* oral PK experiment. This result might be due to the position and nature of the substituents present on ring C. The presence of substituents at the *para*-position provides stability and prevents the compound from being metabolized quickly.[18] In **14k**, a cyano group is present at the *meta*-position, while in the other four compounds (**14f**, **14h**, **15**, and **16g**), substituents are present at the *para*-position. Thus, compound **14k** may undergo fast metabolism, preventing its detection. The PK results obtained suggest that compounds **14f** and **16g** demonstrate good *in vivo* exposure and half-lives.

In conclusion, we have rediscovered nitrofuranyl methyl piperazine as a potent scaffold for compounds effective against sensitive and resistant strains of MTB. The present study demonstrates the promise of the nitrofuranyl-based class of compounds against sensitive, resistant, and nonreplicating strains of MTB. The reported compounds have optimal PK properties and comparatively better aqueous solubility than other reported analogues in this class. Studies to determine the *in vivo* efficacy of these compounds are currently underway.

**Table 2. Activity against Nonreplicating and Resistant Strains of MTB and Cytotoxicity Studies**[a]

| compd | NRP[b] $\mu$M | MIC ($Rif^R$) $\mu$M | MIC (MDR) $\mu$M | $CC_{50}$[c] $\mu$M | selectivity index (SI)[d] |
|---|---|---|---|---|---|
| **14e** | 12.6 ± 0 | 1.32 ± 0.45 | >25.2 | >63 | >700 |
| **14f** | 1.4 ± 0 | 0.072 ± 0.02 | 0.029 ± 0.01 | >58 | >11600 |
| **14h** | 0.56 ± 0.2 | 0.08 ± 0 | 0.08 ± 0 | >53 | >2650 |
| **14j** | 2.11 ± 0.9 | 0.37 ± 0 | 0.09 ± 0 | >63 | >1575 |
| **14k** | 1.34 ± 0.4 | 0.19 ± 0 | 0.06 ± 0.02 | >64 | >3200 |
| **15** | 1.6 ± 0 | 0.32 ± 0.1 | 0.12 ± 0.05 | >64 | >1600 |
| **16b** | >22.7 | 2.13 ± 0.8 | >22.7 | >56 | >329.4 |
| **16c** | >21.9 | 0.68 ± 0 | 14.59 ± 6.32 | >54 | >337.5 |
| **16e** | 20.1 ± 0 | 0.63 ± 0 | 4.19 ± 1.46 | >50 | >333.3 |
| **16g** | >21.6 | 1.35 ± 0 | 1 ± 0.47 | >54 | >675 |
| Rifampicin | 2.4 ± 1.4 | 311.07 ± 0 | 155.5 ± 0 | | |
| Gatifloxacin | 2.66 ± 0 | 2.66 ± 1.5 | 1.33 ± 1.5 | | |

[a]Values reported are the average of three individual measurements ± SD. [b]Nonreplicating phase of *M.tb*. [c]Cytotoxicity (concentration causing death of 50% of cells; $CC_{50}$) to HepG2 cells. [d]Selectivity index ($CC_{50}$(nM)/MIC(nM)).



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**Table 3. Solubility and PK Profiles of Potent Compounds**

| | solubility ($\mu$M)[a] | | | | PK[b] | | | |
|---|---|---|---|---|---|---|---|---|
| compd | water | PBS | SGF | SIF | $C_{max}$ (nM) | $T_{max}$ (h) | $AUC_{0\text{-}t}$ (nM·h) | $t_{1/2}$(h) |
| **14f** | 116.5 | 58.2 | 1165.5 | 2.9 | 2352.11 | 0.25 | 2994.63 | 4.04 |
| **14h** | 2.68 | | | | 5342.18 | 0.25 | 4512.72 | 0.88 |
| **14k** | 256.3 | 256.3 | 2563.1 | 32 | nd[c] | nd[c] | nd[c] | nd[c] |
| **15** | 1285.5 | 2571.1 | 2571.1 | 2571.1 | 3806.90 | 0.25 | 2709.06 | 1.69 |
| **16g** | 108.3 | 54.1 | 2167.6 | 13.5 | 3263.51 | 0.25 | 4221.42 | 1.46 |

[a]Solubility data were the average of three determinations (SD values < 1%). [b]Oral dose at 10 mg/kg, and the data were average of five determinations. [c]nd: not detected.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsmedchemlett.5b00141.

Full experimental details for the compounds synthesized, along with NMR and MS spectra and descriptions of biological assays (PDF)

## ■ AUTHOR INFORMATION


### Corresponding Authors

*Tel: +91-191-2569111. Fax: +91-191-2569333. E-mail: ppsingh@iiim.res.in.
*E-mail: ram@iiim.res.in.
*E-mail: iakhan@iiim.res.in.


### Author Contributions

#K.R.Y., G.M., and S.S. have equally contributed to this work. K.R.Y. and G.M. performed the chemical syntheses. S.S., S.K., and V.S.R. performed biological screening. A.M., M.T., and G.D.S. performed *in vivo* PK. S.S.B. performed the solubility study. P.P.S., I.A.K., and R.A.V. participated in the design and execution of this study.


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### Notes

The authors declare no competing financial interest.

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