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Synthesis and anti-tubercular activity of a series of 2-sulfonamido/trifluoromethyl-6-substituted imidazo-[2,1-*b*]-1,3,4-thiadiazole derivatives

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This paper is dedicated to Professor C. S. Mahajanshetti on the occasion of his 73rd birthday

Abstract—A series of 2-sulfonamido/trifluoromethyl-6-(4′-substituted aryl/heteroaryl)imidazo[2,1-*b*]-1,3,4-thiadiazole derivatives (**II**) have been synthesized by reaction of 2-amino-5-sulfonamido/trifluoromethyl-1,3,4-thiadiazoles and an appropriate α-haloaryl/heteroaryl ketones. Further 5-bromo (**III**), 5-thiocyanato (**IV**), 5-gaunylhydrazone (**V**) derivatives were synthesized in order to study the effect of these substituents on biological activity. Structures of these compounds were established by IR, ^{1}H NMR, ^{13}C NMR, Mass and HRMS. The selected compounds were evaluated for their preliminary in vitro anti-tuberculosis activity against *Mycobacterium tuberculosis* H37Rv strain using radiometric BACTEC and broth dilution assay methods. The results show that compounds **5**, **7**, **8**, **10** and **12** exhibited moderate to good anti-tubercular activity with percentage inhibition of 29, 43, 58, 31 and 41, respectively, at a MIC of > 6.25 μg/mL. Compound **18** showed a MIC of 20 μg/mL.

1. Introduction

Tuberculosis (TB) is a chronic necrotizing bacterial infection with wide variety of manifestations caused by *Mycobacterium tuberculosis*, which has been a scourge of humanity for thousands of years and remains one of the prevalent health tribulations in the world.[1] Today, TB is among the top five causes of global mortality. The history of TB highlights man's struggle for existence against a disease that dates from antiquity and is the story of failures and successes of disaster and hope.[2]

It has been estimated that approximately one third of the world's population is infected with the bacillus, and that each year 8 million people develop active disease and 2 million die of the disease. In developing countries where rates of both infection and active disease have always been high, the number of cases skyrocketed, so dramatic was the increase that the World Health Organization (WHO) declared TB a global health emergency in 1993, for the first time an infectious disease achieved that dubious distinction.[3–5] Approximately, 80% of TB cases are found in 23 countries; the highest rates of incidence being found in South-East Asia and Africa.[6]

This saddle is further augmented by HIV infection, which impairs the immune system and allows large number of people already infected with TB to progress to active disease. The exponential increase in TB cases has been greatest in areas with high prevalence of HIV infections.[7] The active TB is currently treated with a four-drug regimen comprising isoniazid, rifampicin, pyrazinamide and ethambutol for a period of at least six months.[8–10] The long treatment regimen can be difficult to fully complete, fueling the development of more infectious and virulent multidrug resistant (MDR) strains of TB, which shows very high mortality.[11] Such MDR-TB is difficult and expensive to treat and is not always curable, alternative combination treatment of five-drug regimen is recommended initially, including both ethambutol and rifampicin. Later, the treatment will be modified on the basis of results of susceptibility tests. In such patients, other anti-tubercular drugs so called second line drugs (ethionamide, cycloserine, capreomycin, kanamycin, *p*-aminosalicylic acid and some time

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clofazimine) are variably combined with each other and with first line drugs with the aim to overcome resistance. MDR-TB often requires prolonged treatment sometimes up to 24 months[12] and thus poses a major challenge to the control of the disease worldwide.

There is now recognition that innovative drugs to combat TB are urgently required. With the completion of the genome of *M. tuberculosis* comes the promise of a new generation of potent drugs to combat the emerging epidemic of TB. The emphasis of mycobacterial research now has shifted from gene hunting to interpretation of the biology of the whole organism in an effort to better define which activities is likely to be critical to survival and thus amenable to the development of new drugs.[13] In this regard, however, there have been few additions of some promising new anti-tuberculosis agents, such as the long acting rifamycins,[14,15] fluoroquinolones,[16–18] oxazolidinones[19,20] and nitroimidazopyrans[21] to the existing main-line drugs.

The development of sulfonamides is one of the most fascinating and useful areas in medicinal chemistry. The discovery of sulfonamides as antibacterial agents in early 1930's was the beginning of the present chemotherapeutic agents. The sulfonamides have a relatively broad antibacterial spectrum with high activity profile against pneumococci, streptococci, staphylococci, meningococci and shigelle.[22] The sulfonamido group ($-SO_2NH_2$) is a common pharmacophore found in various biologically active molecules, enzyme inhibitors and receptor antagonists.[23,24]

Fluorinated compounds in general and fluorinated heterocyclic compounds in particular are the focus of much interest in modern medicinal chemistry. The trifluoromethyl group ($-CF_3$) is an important structural moiety in diverse classes of bioactive organic molecules, which exhibited wide ranging biological properties.[25–27] Many efficient methods for the introduction of a trifluoromethyl group into organic molecules have been developed. The electronegativity of fluorine can have a significant effect on the basicity or acidity of neighbouring groups and on the electron distribution, and can change the overall reactivity and stability of a molecule.[28] The CF_3 group has a larger van der Waals radius than that of a CH_3 group and the same electronegativity as oxygen. The CF_3 substituted compounds have been reported to possess biological activities such as herbicides, fungicides, analgesic agents, antipyretic agents and anticancer agents.[29–32]

In view of the above facts and in continuation of our search for various biologically active molecules[33,34] and encouraging antibacterial activity of some imidazo[2,1-*b*]-1,3,4-thiadiazole derivatives[35] has prompted us to synthesize some novel molecules of fused imidazo[2,1-*b*]-1,3,4-thiadiazole and carry out their preliminary anti-tubercular activity. In this paper we report the synthesis and spectral studies of a novel series of 2-sulfonamido/trifluoromethyl-6-(4′-substituted aryl/heteroaryl)imidazo[2,1-*b*]-1,3,4-thiadiazole derivatives and evaluation of in vitro anti-tuberculosis activity.

2. Chemistry

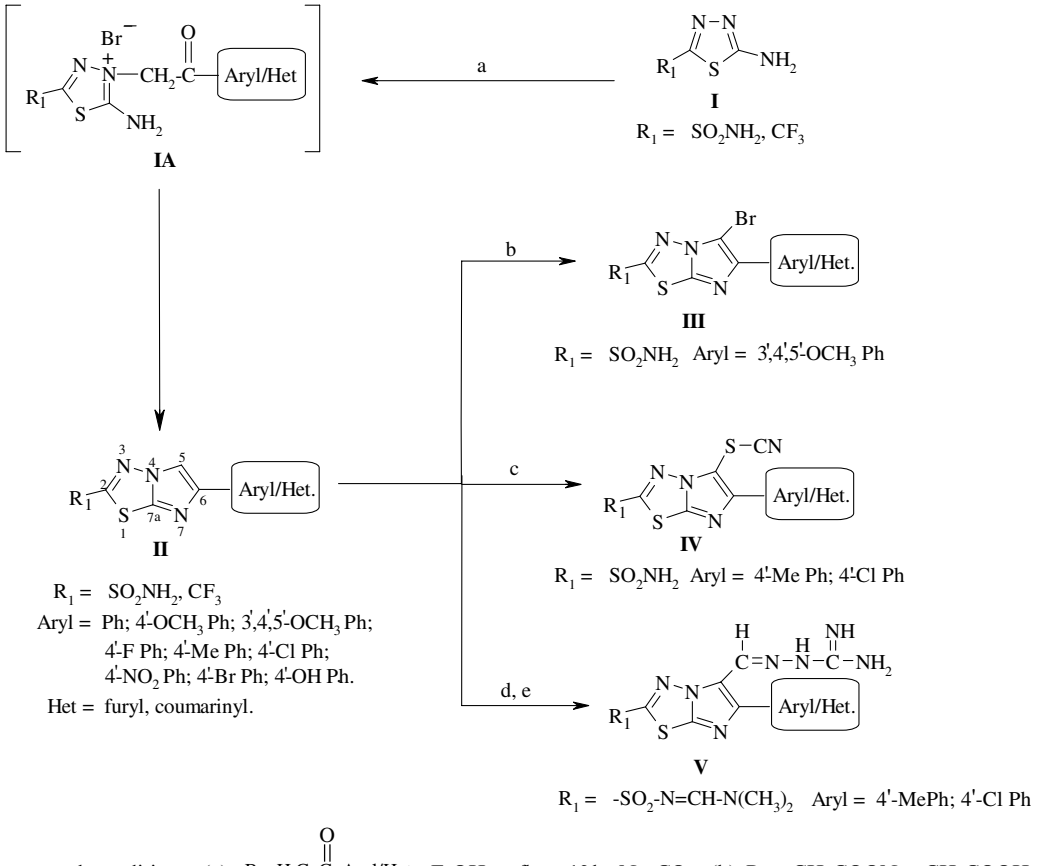
The synthesis of the imidazo[2,1-*b*]-1,3,4-thiadiazoles (II, Scheme 1) was carried out by the condensation of (I) with a α-haloaryl/heteroaryl ketone under reflux in ethanol. It is well established[35] that this reaction proceeds via the intermediate iminothiadiazole (IA), which under reflux temperature spontaneously underwent ring closer to form the desired fused heterocycle (II) with good yields. The electronic and steric factors at 5th position of 2-amino-5-substituted-1,3,4-thiadiazole are crucial in determining the course of its reaction with substituted α-haloaryl/heteroaryl ketones.[36] The sulfonamido and trifluoromethyl groups are strongly electronegative and consequently its inductive effects impart less nucleophilic character to the nitrogen at 4th position of the 1,3,4-thiadiazole. Thus the alkylation of this thiadiazole occurs at 3rd nitrogen with subsequent ring closer to form the corresponding bridgehead nitrogen heterocyclic system. The various α-haloaryl/heteroaryl ketones were prepared by the bromination of corresponding ketones using well-established Friedel–Craft's reaction.[37] Thus obtained 2-sulfonamido/trifluoromethyl-6-aryl/heteroaryl-imidazo[2,1-*b*]-1,3,4-thiadiazole derivatives were subjected to electrophilic substitution reaction[38] at the fifth position with bromine in the presence of sodium acetate in acetic acid to obtain 5-bromo derivative (III). 5-Thiocyanato (IV), 5-guanylhydrazone (V) derivatives were prepared by earlier reported methods.[33–35]

3. Biological activity

In vitro evaluation of the anti-tuberculosis activity was carried out at NIH within the Tuberculosis Acquisition Antimicrobial Coordinating Facility (TAACF) screening program, Alabama, USA and Haffkine Institute for Training, Research and Testing, Mumbai, India. Minimum Inhibitory Concentration (MIC) was determined against *M. tuberculosis* strain H37Rv by using the radiometric BACTEC[39,40] and broth dilution[41,42] assay methods, respectively. The purpose of the screening program is to provide a resource whereby new experimental compounds can be tested for their capacity to inhibit the growth of virulent *M. tuberculosis.*

4. Results and discussion

We have synthesized a series of nineteen derivatives of imidazo[2,1-*b*]-1,3,4-thiadiazole **1–19** containing sulfonamido/trifluoromethyl groups at 2nd position by reacting 2-amino-5-substituted-1,3,4-thiadiazole of general formula (**I**) with substituted α-haloaryl/heteroarylketones as depicted in Scheme 1. Further, compounds **4–8** were obtained by bromination, thiocyanation and guanylation. Structures of the synthesized compounds were established on the basis of IR, ^{1}H NMR, ^{13}C NMR and mass spectral data. HRMS data provided additional proof in order to substantiate the structures of the compounds.



Scheme 1. Reagents and conditions: (a) $Br–H_2C–\overset{O}{\overset{\|}{C}}–Aryl/Het$, EtOH, reflux, 12 h, Na_2CO_3; (b) Br_2, CH_3COONa, CH_3COOH; (c) KSCN, Br_2, CH_3COOH, 0–5 °C; (d) Vilsmeier reagent, 80–90 °C, 4 h; (e) aminoguanidine·HCl, EtOH, reflux, 0.5 h.

Compounds **1**–**6** showed, absorption bands ranging from 3300 to 3400 cm^{-1} for NH_2, compounds **5** and **6** showed peaks at 2150 to 2195 cm^{-1} for SCN, compound **16** showed broad absorption band at 3422 cm^{-1} for OH, compound **19** showed strong absorption band at 1728 cm^{-1} for C=O group of coumarin, in their respective IR spectra.

In particular, it must be pointed out that in ^1H NMR the presence of a singlet between δ 8.0 and 8.9 ppm indicates the formation of bridgehead nitrogen heterocycle (**II**) by cyclodehydration process via **IA**. Further the absence of this singlet in compounds **4**–**8** confirms that 5-substituted derivatives have been formed. Compounds **1**–**6** showed a singlet around δ 8.8 ppm indicating the presence of $–SO_2NH_2$ and the characteristic peaks at δ 5.01, 3.8–3.9, 2.3 ppm indicated the presence of OH, OMe and Me groups in their respective structures. The compounds **1**–**17** showed prominent signals for aromatic protons around δ 8.27–6.89 ppm and in case of compound **18** and **19** heterocyclic protons appeared between δ 8.79–6.49 ppm.

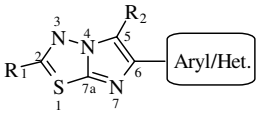
In ^{13}C NMR spectrum we have observed most characteristic signals appeared at around δ 21.0, 42.0, 56.0–60.0, 120.0 and 148.0 ppm, for CH_3, $N(CH_3)_2$, OCH_3, CF_3, SCN, respectively. The signals appeared at around δ 102.0, 110.0, 140.0, 165.0 ppm for C-5, C-6, C-7a, C-2 and carbons of Ph group at δ 128.0–132.0 ppm, respectively. Electron impact mass spectra showed an accurate molecular ion peaks at *m/z* 310.2, 370.95, 298.1, 448.1, 351.1, 371.1, 433.3, 453.2, 299.2, 314.9, 303.8, 349.8, 283.1, 259.1 and 337.2 for compounds **1**–**8**, **10**, **12**, **14**, **15** and **17**–**19**, respectively.

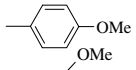
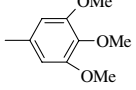
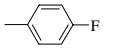
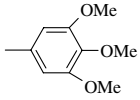
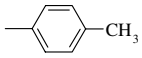
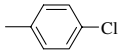
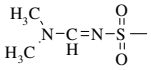
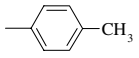
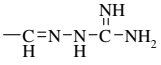
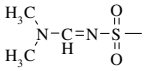
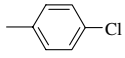
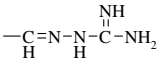
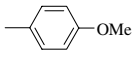
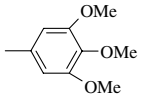
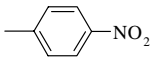
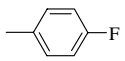
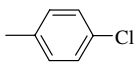
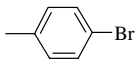
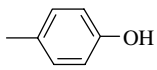
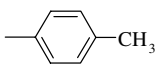
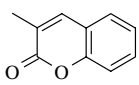
Imidazo[2,1-*b*]-1,3,4-thiadiazoles are planar and rigid aromatic system with two condensed heterocycle, which have different π conjugation. The mesomorphic properties of new mesogens are strictly dependent not only on the nature of substituents but also on their position in the thiadiazolic or imidiazolic part of the molecule, consequently, which influences the biological activity.[43]

The synthesized compounds were evaluated for their in vitro anti-tuberculosis activity against *M. tuberculosis* strain H37Rv by using radiometric BACTEC and broth dilution assays. The result of anti-mycobacterial activity is presented in Table 1. We studied the effects of various substituents at 4′ position of the aromatic ring. Amongst them 4′-nitro, 4′-methyl, 4′-chloro substituted derivatives showed encouraging activity. The results showed that compounds **5**, **10** and **12** exhibited moderate antitubercular activity with percentage inhibition of 29, 31 and 41, respectively, at a MIC of > 6.25 μg/mL.

The activity is considerably affected by substituents at position-5 on the imidazo[2,1-*b*]-1,3,4-thiadiazole nucleus. It has been observed that compounds **7** and **8**

Table 1. The in vitro anti-tuberculosis activity of compounds **1**–**19** against *M. tuberculosis* H37Rv



Sl. no.	R_1	Aryl/Het	R_2	MIC in μg/mL
1	SO_2NH_2		H	>6.25
2	SO_2NH_2		H	>6.25 (5)
3	SO_2NH_2		H	50
4	SO_2NH_2		Br	ND[a]
5[b]	SO_2NH_2		SCN	>6.25 (29)
6[b]	SO_2NH_2		SCN	>6.25 (3)
7[b]				>6.25 (43)
8[b]				>6.25 (58)
9	CF_3		H	ND[a]
10	CF_3		H	>6.25 (31)
11	CF_3		H	40
12	CF_3		H	>6.25 (41)
13	CF_3		H	50
14	CF_3		H	40
15	CF_3		H	50
16	CF_3		H	50
17	CF_3		H	40
18	CF_3		H	20
19	CF_3		H	40
INH	—	—	—	0.044

Values in bracket indicate % inhibition.

[a] Not determined.

[b] Prepared by the method given in literature.[35]

having a gaunylhydrazone group at 5th position, showed a better anti-mycobacterial activity with percentage inhibition of 43 and 58, respectively, at a MIC of >6.25 μg/mL. We have also studied the effect of sulfonamido group in compounds **1**–**6** and trifluoromethyl group in compounds **9**–**19** on the biological activity, we observed that replacement of trifluoromethyl for sulfonamido group at 2nd position did not alter the anti-tuberculosis activity to a greater extent.

When the 6-substituted phenyl group is replaced by a heterocyclic group, the moderate anti-tuberculosis activity was observed. In two cases we have replaced the aromatic ring with furan **18** and coumarin **19** ring systems, furan-substituted derivative showed better activity with a MIC of 20 μg/mL.

5. Conclusion

In the present paper, we report the synthesis, spectral studies and anti-tuberculosis activity of novel series of imidazo[2,1-*b*]-1,3,4-thiadiazoles. These fused hetrocyclic compounds were prepared by the cyclodehydration process between 2-amino-5-sulfonamido/trifluoromethyl-1,3,4-thiadiazole derivatives and α-haloaryl/heteroaryl ketones. The preliminary in vitro anti-tuberculosis screening of these novel series of 2-sulfonamido/trifluoromethyl-6-(4′-substituted phenyl)imidazo-[2,1-*b*]-1,3,4-thiadiazoles has evidenced that phenyl substitution at 6th position and gaunylhydrazone group at 5th position, have emerged as potential compounds endowed with moderate to good anti-tuberculosis activity. On the contrary, the replacement of sulfonamido by trifluoromethyl group at 2nd position showed no greater change in the anti-tuberculosis activity. The possible improvement of anti-tuberculosis activity of this basic imidazo[2,1-*b*]-1,3,4-thiadiazole structure through modulation of ring substituents and/or additional functionation warrants further investigations. In summary, we have identified a novel series of imidazo[2,1-*b*]-1,3,4-thiadiazoles, which may develop into the potential class of anti-tubercular agents.

6. Experimental

6.1. Chemistry protocols

All research chemicals were purchased from Sigma-Aldrich or Lancaster Co. and used as such for the reactions. Solvents except LR grade were dried and purified according to the literature when necessary. Reactions were monitored by thin layer chromatography (TLC) on silica gel G plates and compounds visualized by exposure to iodine vapours.

Melting points were determined using open capillary tube method and are uncorrected. Spectra were obtained as follows: UV spectra were recorded using Jasco V-530 spectrophotometer; Infra red (IR) spectra were recorded using KBr disk on a Nicolet MX-1 FTIR spectrometer; ^{1}H NMR spectra were recorded at 300 MHz and ^{13}C NMR spectra were recorded at 75.5 MHz on a Bruker AM spectrometer and their chemical shifts are reported in δ ppm units with respect to TMS as internal standard; Mass spectra were recorded on a VG-Quattro II, Micromark Mass Spectrometer under the electron impact at 70 eV.

6.2. General procedure for the synthesis of substituted imidazo[2,1-*b*]-1,3,4-thiadiazoles (Scheme 1)

A mixture of **I** (30 mmol) and an appropriate quantity of α-halo aryl/heteroaryl ketones (30 mmol) in ethanol (150 mL) was heated to reflux on a water bath for 10–12 h. Excess of solvent was removed under reduced pressure and the solid hydrobromide separated was filtered, washed with cold ethanol and dried. Neutralization of hydrobromide salts with cold aqueous solution of Na_2CO_3 yielded the corresponding free bases II, which was purified by recrystallisation from ethanol.

6.2.1. 2-Sulfonamido-6-(4′-methoxyphenyl)imidazo[2,1-*b*]-1,3,4-thaidiazole (1). This was obtained by reacting 2-amino-5-sulfonamido-1,3,4-thiadiazole (5.41 g, 30 mmol) and 4′-methoxy phenacyl bromide (6.87 g, 30 mmol) as described above and isolated as pale yellow solid crystals: yield 6.1 g (65 %); mp 235–238 °C; λ_{max} (ethanol) 316, 264, 232 nm; IR (KBr) ν_{max} 3334, 3141, 2924, 2853, 1549, 1496, 1286, 1196, 1050, 784 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 8.72 (s, 1H, 5H)), 8.68 (d, J = 4 Hz, 2H, SO_2NH_2), 7.85 (d, J = 9 Hz, 2H, aryl-H), 7.0 (d, J = 8 Hz, 2H, aryl-H), 3.80 (s, 3H, 4′-OCH_3) ppm; ^{13}C NMR (DMSO-d_6) δ 164.3, 159.9, 147.6, 145.7, 127.1, 126.7, 115.0, 110.6, 56.0 ppm; EIMS *m*/*z* (relative intensity) 310.2 (M^+, 60%), 284.4 (52%), 272.4 (61%), 257.3 (97%), 243.3 (96%), 161.2 (50%), 147.2 (65%), 135.2 (80%), 119.1 (90%), 107.1 (91%), 91.1 (92%), 81.2 (94%), 79.2(92%), 53.2 (93%), 41.3 (100%); HRMS (EI) *m*/*z* calcd for $C_{11}H_{10}O_3N_4S_2$: 310.0189; found: 310.0186.

6.2.2. 2-Sulfonamido-6-(3′,4′,5′-trimethoxyphenyl)imidazo[2,1-*b*]-1,3,4-thaidiazole (2). This was obtained by reacting 2-amino-5-sulfonamido-1,3,4-thiadiazole (5.41 g, 30 mmol) and 3′,4′,5′-trimethoxy phenacyl bromide (8.67 g, 30 mmol) as described above and isolated as pale yellow solid crystals: yield 5.8 g (52%); mp 240–242 °C; λ_{max} (ethanol) 326, 268, 232 nm; IR (KBr) ν_{max} 3325, 3154, 2944, 2838, 1591, 1494, 1286, 1196, 1048, 784 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 8.9 (s, 1H, 5H), 8.77 (d, J = 4 Hz, 2H, SO_2 NH_2), 7.24 (s, 2H, aryl-H), 3.86 (s, 6H, 3′-, 5-OCH_3), 3.69 (s, 3H, 4′-OCH_3) ppm; ^{13}C NMR (DMSO-d_6) δ 164.7, 154.0, 153.8, 147.5, 145.3, 143.2, 138.4, 128.6, 111.8, 104.5, 60.9, 56.7 ppm; EIMS *m*/*z* (relative intensity); 370.95 (M^+, 100%), 292.0 (5%), 217.01 (6%), 196.91 (5%), 139.98 (12%), 99.0 (12%), 74.06 (27%).

6.2.3. 2-Sulfonamido-6-(4′-fluorophenyl)imidazo[2,1-*b*]-1,3,4-thaidiazole (3). This was obtained by reacting 2-amino-5-sulfonamido-1,3,4-thiadiazole (5.41 g, 30 mmol) and 4′-fluoro phenacyl bromide (6.51 g, 30 mmol) as described above and isolated as pale yellow solid crystals; yield 4.2 g (47%); mp 264–265 °C; λ_{max} (ethanol)

316, 254, 232 nm; IR (KBr) ν_{max} 3361, 3141, 2923, 2855, 1584, 1496, 1360, 1285, 1195, 1040, 859 cm^{-1}; ^1H NMR (DMSO-d_6) δ 8.86 (s, 1H, 5H), 8.73 (d, $J = 4$ Hz, 2H, SO_2NH_2), 7.9 (d, $J = 8$ Hz, 2H, aryl-H), 7.3 (d, $J = 9$ Hz, 2H, aryl-H) ppm; ^{13}C NMR (DMSO-d_6) δ 164.9, 161.0, 146.5, 146.0, 130.7, 127.8, 116.7, 111.7 ppm; EIMS *m/z* (relative intensity) 298.1 (M^+, 100%), 121.1 (16%), 94.2 (8%), 80.1 (95%), 70.1 (21%), 64.2 (20%), 48.2 (44%); HRMS (EI) *m/z* calcd for $C_{10}H_7O_2N_4FS_2$: 297.9989; found: 297.9985.

6.2.4. 2-Sulfonamido-5-bromo-6-(3′,4′,5′-trimethoxyphenyl)imidazo[2,1-*b*]-1,3,4-thaidiazole (4). To 1.85 g (5.0 mmol) of compound **2**, 0.82 g (10 mmol) of sodium acetate and 10 mL of acetic acid stirred together at room temperature was added drop wise 0.96 g (6.0 mmol) of bromine. After the addition, stirring was continued for 30 min. The mixture was poured into 100 mL of water from which a solid separated. The solid was collected, washed with water and dried. Recrystallisation from acetonitrile gave colourless crystals of compound **4**: yield 0.8 g (36%); mp 200–202 °C; λ_{max} (ethanol) 314, 270, 232 nm; IR (KBr) ν_{max} 3350, 3153, 2941, 2840, 1591, 1495, 1286, 1196, 1050, 784 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.75 (br, 2H, SO_2NH_2), 7.24 (s, 2H, Ar–H), 3.86 (s, 6H, 3′-, 5′-OCH_3), 3.73 (s, 3H, 4′-OCH_3) ppm; ^{13}C NMR (DMSO-d_6) δ 165.9, 153.8, 145.3, 143.2, 138.4, 128.5, 110.8, 104.5, 93.9, 60.9, 56.7 ppm; EIMS *m/z* (relative intensity) 450.1 (M + 2,100), 448.1 (M^+, 95%), 370.1 (94%), 355.1 (93%), 327.1 (61%), 297.1 (38%), 290.1 (42%), 193.1 (54%), 178.1 (58%), 135.1 (50%), 120.1 (52%), 79.9 (96%), 64.1 (93%), 48.2 (63%); HRMS (EI) *m/z* calcd for $C_{13}H_{13}O_5N_4BrS_2$: 447.9505; found: 447.9498.

6.2.5. 2-Sulfonamido-5-thiocyanato-6-(4′-methylphenyl)imidazo[2,1-*b*]-1,3,4-thaidiazole (5). This was obtained by following the procedure described in the literature.[35] 2-sulfonamido-6-(4′-methyl phenyl)imidazo[2,1-*b*]-1,3,4-thaidiazole was prepared in 51% yield as yellow needles by reacting 2-amino-5-sulfonamido-1,3,4-thiadiazole (5.41 g, 30 mmol) and 4′-methyl phenacyl bromide (6.39 g, 30 mmol) in presence of ethanol (150 mL) under reflux for 12 h. Then to a mixture of 2-sulfonamido-6-(4′-methyl phenyl)imidazo[2,1-*b*]-1,3,4-thaidiazole (2.94 g, 10 mmol) and potassium thiocyanate (1.56 g, 16 mmol) in glacial acetic acid (50 mL) was added (at 0–5 °C) bromine (1.6 g, 10 mmol) in glacial acetic acid (20 mL) dropwise with stirring. Then stirring was continued for 30 min at 15–18 °C and then at room temperature for 30 min. The reaction mixture was poured into ice water, filtered and recrystallised from ethanol and isolated as colourless solid crystals of compound **5**; yield 2.52 g (72%); mp 220–222 °C; λ_{max} (ethanol) 322, 266, 234; IR (KBr) ν_{max} 3363, 3147, 2924, 2166, 1610, 1554, 1486, 1369, 1171, 1054, 832 cm^{-1}; ^1H NMR ($CDCl_3$), δ 8.80 (s, 2H, SO_2NH_2), 7.23 (d, $J = 8$ Hz, 2H, aryl-H), 7.71 (d, $J =$ Hz, 2H, aryl-H),2.13 (s, 3H, 4′-CH_3) ppm; ^{13}C NMR ($CDCl_3$) δ 166.6, 152.0, 148.7, 139.6, 130.0, 129.5, 127.9, 110.9, 102.4, 21.4 ppm; EIMS *m/z* (relative intensity) 351.1 (M^+, 100%), 116.2 (12%), 102 (29%), 80.1 (95%), 70.2 (18%), 64.2 (15%); HRMS (EI) *m/z* calcd for $C_{12}H_9O_2N_5S_3$: 350.9913; found: 350.9917.

6.2.6. 2-Sulfonamido-5-thiocyanato-6-(4′-chlorophenyl)imidazo[2,1-*b*]-1,3,4-thaidiazole (6). This was obtained by following the procedure as described for compound **5**, by reacting 2-amino-5-sulfonamido-1,3,4-thiadiazole (5.41 g, 30 mmol) and 4′-chloro phenacyl bromide (7.36 g, 30 mmol), as colourless needles; yield 2.48 g (65%); mp 211–213 °C; λ_{max} (ethanol) 314, 256, 232; IR (KBr) ν_{max} 3332, 3153, 2925, 2196, 1634, 1578, 1481, 1368, 1164, 1089, 829 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.80 (s, 2H, SO_2NH_2), 7.37 (d, $J = 8$ Hz, 2H, aryl-H), 7.75 (d, $J = 9$ Hz, 2H, aryl-H) ppm; ^{13}C NMR (DMSO-d_6) δ 167.4, 152.5, 149.2, 134.9, 131.5, 130.0, 129.9, 129.7, 110.9 ppm; EIMS *m/z* (relative intensity) 371.1 (M^+, 100%), 102 (10%), 80.1 (94%), 64.2 (15%), 48.2 (15%); HRMS (EI) *m/z* calcd for $C_{11}H_6O_2N_5ClS_3$: 370.9367; found: 370.9370.

6.2.7. 2-[N-(Dimethylaminomethino)]sulfonamido-5-guanylhydrazone-6-(4′-methylphenyl)imidazo[2,1-*b*]-1,3,4-thaidiazole (7). This was obtained by following the procedure described in the literatures.[33,35] 2-Sulfonamido-6-(4′-methylphenyl)imidazo[2,1-*b*]-1,3,4-thaidiazole was prepared in 51% yield as yellow needles by reacting 2-amino-5-sulfonamido-1,3,4-thiadiazole (5.41 g, 30 mmol) and 4′-methylphenacyl bromide (6.39 g, 30 mmol) in presence of ethanol (150 mL) under reflux for 12 h. Then 2-sulfonamido-5-formyl-6-(4′-methylphenyl)imidazo[2,1-*b*]-1,3,4-thaidiazole was prepared in 81% yield as yellow needles by slow addition of 2-sulfonamido-6-(4′-methylphenyl)imidazo[2,1-*b*]-1,3,4-thaidiazole (2.94 g, 10 mmol) to the freshly prepared Vilsmeier reagent. Further the 2-sulfonamido-5-formyl-6-(4′-methyl phenyl)imidazo[2,1-*b*]-1,3,4-thaidiazole (3.78 g, 10 mmol) and aminoguanidine hydrochloride (1.1 g, 10 mmol) was refluxed for 30 min in presence of ethanol (150 mL). The resultant precipitate was collected by filtration, followed by basification with aqueous ammonia, title compound **7** was isolated as yellow needles; yield 3.13 g (70%); mp 215–220 °C; λ_{max} (ethanol) 294, 248, 226; IR (KBr) ν_{max} 3425 (b), 3129, 2913, 1678, 1641, 1511, 1418, 1326, 1147, 1091, 918, 850 cm^{-1}; ^1H NMR (DMSO-d_6) δ 12.10 (s, 1H, =N–NH–), 8.55 (s, 1H, 5-CH=N), 8.40 (s, 1H, –CH=N–SO_2), 7.71 (d, $J =$ Hz, 2H, aryl-H), 7.23 (d, $J = 8$ Hz, 2H, aryl-H), 3.00, 3.25 (s, 6H, –$N(CH_3)_2$), 2.30 (s, 3H, Ar CH_3) ppm; ^{13}C NMR (DMSO-d_6) δ 165.5, 152.2, 145.4, 139.7, 131.4, 130.3, 128.9, 110.3, 102.3, 74.7, 42.4, 36.6, 21.7 ppm; EIMS *m/z* (relative intensity) 434.3 (M + 1, 30%), 433.3 (M^+, 100%), 374.2 (5%), 215.1 (12%), 161.1 (13%), 135.1 (58%), 117.2 (34%), 99.2 (60%), 84.2 (84%), 72.2 (72%), 64.0 (95%); HRMS (EI) *m/z* calcd for $C_{16}H_{19}O_2N_9S_2$: 433.1098; found: 433.1097.

6.2.8. 2-[N-(Dimethylaminomethino)]sulfonamido-5-guanylhydrazone-6-(4′-chlorophenyl)imidazo[2,1-*b*]-1,3,4-thaidiazole (8). This was obtained by following the procedure as described for compound **7**, by reacting 2-amino-5-sulfonamido-1,3,4-thiadiazole (5.41 g, 30 mmol) and 4′-chloro phenacyl bromide (7.36 g, 30 mmol), as yellow needles; yield 2.94 g (65%); mp 228–232 °C dec; λ_{max} (ethanol) 289, 257, 225; IR (KBr) ν_{max} 3443 (b), 2923, 1677, 1634, 1498, 1405, 1313, 1152, 1084,

917, 846 cm^{-1}; ^1H NMR (DMSO-d_6) δ 12.10 (s, 1H, =N–NH–), 8.55 (s, 1H, 5-CH=N), 8.40 (s, 1H, –CH=N–SO_2), 7.75 (d, J = 9 Hz, 2H, aryl-H), 7.37 (d, J = 8 Hz, 2H, aryl-H), 3.00, 3.25 (s, 6H, –$N(CH_3)_2$) ppm; ^{13}C NMR (DMSO-d_6) δ 163.9, 152.3, 145.6, 139.1, 131.8, 130.3, 128.9, 110.2, 102.2, 75.1, 42.4, 36.6 ppm; EIMS *m/z* (relative intensity) 455.2 (M + 2, 46%), 453.2 (M^+, 100%), 411.2 (15%), 235.1 (6%), 181.1 (8%), 135.1 (37%), 99.2 (45%), 84.2 (58%), 72.2 (43%), 64.1 (95%), 44.3 (92%); HRMS (EI) *m/z* calcd for $C_{15}H_{16}O_2N_9ClS_2$: 453.0551; found: 453.0545.

6.2.9. 2-Trifluoromethyl-6-(phenyl)imidazo[2,1-*b*]-1,3,4-thaidiazole (9). This was obtained by reacting 2-amino-5-trifluoromethyl-1,3,4-thiadiazole (5.07 g, 30 mmol) and phenacyl bromide (5.97 g, 30 mmol) as described in the general procedure and isolated as colourless solid crystals; yield 4.43 g (55%); mp 160–161 °C; λ_{max} (ethanol) 310, 270, 232 nm; IR (KBr) ν_{max} 3138, 2933, 2854, 1511, 1444, 1311, 1286, 1144, 1020, 831 cm^{-1}; ^1H NMR ($CDCl_3$) δ 78.12 (s, 1H, 5H), 7.84 (d, J = 7 Hz, 2H, aryl-H), 5–7.3 (m, 3H, aryl-H), ppm.

6.2.10. 2-Trifluoromethyl-6-(4′-methoxyphenyl)imidazo-[2,1-*b*]-1,3,4-thaidiazole (10). This was obtained by reacting 2-amino-5-trifluoromethyl-1,3,4-thiadiazole (5.07 g, 30 mmol) and 4′-methoxy phenacyl bromide (6.87 g, 30 mmol) as described in the general procedure and isolated as pale red solid crystals; yield 5.56 g (62%); mp 155–156 °C; λ_{max} (ethanol) 314, 268, 240 nm; IR (KBr) ν_{max} 3121, 2924, 2854, 1514, 1436, 1305, 1286, 1196, 1050, 784 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.03 (s, 1H, 5H), 7.75 (d, J = 9 Hz, 2H, aryl-H), 6.96 (d, J = 9 Hz, 2H, aryl-H), 3.85 (s, 3H, 4′-OCH_3) ppm; ^{13}C NMR ($CDCl_3$) δ 160.2, 148.9, 144.8, 130.9, 127.1, 126.0, 120.8, 117.2, 114.6, 109.2, 55.7 ppm; EIMS *m/z* (relative intensity) 300.2 (M + 1, 28%), 299.2 (M^+, 100%), 284.1 (45%), 256.1 (43%), 177.1 (67%), 146.1 (44%), 133.1 (81%), 103.3 (35%), 90.2 (52%), 76.2 (43%), 63.2 (50%) 44.2 (20%); HRMS (EI) *m/z* calcd for $C_{12}H_8ON_3F_3S$: 299.0335; found: 299.0334.

6.2.11. 2-Trifluoromethyl-6-(3′,4′,5′-trimethoxyphenyl)-imidazo[2,1-*b*]-1,3,4-thaidiazole (11). This was obtained by reacting 2-amino-5-trifluoromethyl-1,3,4-thiadiazole (5.07 g, 30 mmol) and 3′,4′,5′-trimethoxy phenacyl bromide (8.67 g, 30 mmol) as described in the general procedure and isolated as pale orange solid crystals; yield 3.33 g (31%); mp 135–137 °C; λ_{max} (ethanol) 304, 264, 232 nm; IR (KBr) ν_{max} 3121, 2935, 2847, 1590, 1519, 1495, 1275, 1188, 1011, 784 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.08 (s, 1H, 5H), 7.06 (s, 2H, aryl-H), 3.91 (s, 6H, 3′-, 5′- OCH_3), 3.88 (s, 3H, 4′-OCH_3) ppm.

6.2.12. 2-Trifluoromethyl-6-(4′-nitrophenyl)imidazo[2,1-*b*]-1,3,4-thaidiazole (12). This was obtained by reacting 2-amino-5-trifluoromethyl-1,3,4-thiadiazole (5.07 g, 30 mmol) and 4′-nitro phenacyl bromide (7.32 g, 30 mmol) as described in the general procedure and isolated as pale yellow solid crystals; yield 4.71 g (50%); mp 192–193 °C; λ_{max} (ethanol) 330, 266, 234 nm; IR (KBr) ν_{max} 3138, 2923, 2854, 1602, 1519, 1342, 1295, 1157, 1011, 855 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.27 (d, J = 9 Hz, 2H, aryl-H), 8.1 (s, 1H, 5H), 7.98 (d, J = 8 Hz, 2H, aryl-H) ppm; ^{13}C NMR ($CDCl_3$) δ 153.4, 147.8, 146.5, 143.1, 139.4, 130.2, 126.3, 124.7, 112.1 ppm; EIMS *m/z* (relative intensity) 315.94 (M + 1, 45%), 314.98 (M^+, 100%), 256.14 (10%), 217.01 (10%), 102.6 (6%), 74.06 (23%).

6.2.13. 2-Trifluoromethyl-6-(4′-fluorophenyl)imidazo[2,1-*b*]-1,3,4-thaidiazole (13). This was obtained by reacting 2-amino-5-trifluoromethyl-1,3,4-thiadiazole (5.07 g, 30 mmol) and 4′-fluoro phenacyl bromide (6.51 g, 30 mmol) as described in the general procedure and isolated as colourless solid crystals; yield 4.64 g (54%); mp 153–154 °C; λ_{max} (ethanol) 312, 250, 232 nm; IR (KBr) ν_{max} 3138, 2925, 2854, 1609, 1517, 1486, 1335, 1287, 1165, 1016, 839 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.07 (s, 1H, 5H), 7.8 (m, 2H, J = 5, 4 Hz, aryl-H), 7.1 (m, 2H, J = 9, 8 Hz, aryl-H) ppm.

6.2.14. 2-Trifluoromethyl-6-(4′-chlorophenyl)imidazo[2,1-*b*]-1,3,4-thaidiazole (14). This was obtained by reacting 2-amino-5-trifluoromethyl-1,3,4-thiadiazole (5.07 g, 30 mmol) and 4′-chloro phenacyl bromide (7.36 g, 30 mmol) as described in the general procedure and isolated as a colourless solid crystals; yield 4.64 g (51%); mp 155–156 °C; λ_{max} (ethanol) 314, 256, 232 nm; IR (KBr) ν_{max} 3126, 2924, 2854, 1518, 1480, 1296, 1171, 1014, 831 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.08 (s, 1H, 5H), 7.75 (d, J = 9 Hz, 2H, aryl-H), 7.37 (d, J = 8 Hz, 2H, aryl-H) ppm; ^{13}C NMR ($CDCl_3$) δ 150.2, 147.8, 145.2, 134.5, 131.8, 129.4, 127.0, 120.7, 110.3 ppm; EIMS *m/z* (relative intensity), 305.89 (M + 2, 70%), 303.89 (M^+, 100%), 256.1 (5%), 217.01 (6%), 148.85 (3%), 86.06 (4%), 74.07 (33%).

6.2.15. 2-Trifluoromethyl-6-(4′-bromophenyl)imidazo[2,1-*b*]-1,3,4-thaidiazole (15). This was obtained by reacting 2-amino-5-trifluoromethyl-1,3,4-thiadiazole (5.07 g, 30 mmol) and 4′-bromo phenacyl bromide (8.34 g, 30 mmol) as described in the general procedure and isolated as colourless solid crystals; yield 5.53 g (53%); mp 188–190 °C; λ_{max} (ethanol) 304, 262, 232 nm; IR (KBr) ν_{max} 3125, 2924, 2853, 1516, 1480, 1295, 1171, 1011, 826 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.1 (s, 1H, 5H), 7.68 (d, J = 9 Hz, 2H, aryl-H), 7.53 (d, J = 9 Hz, 2H, aryl-H) ppm; ^{13}C NMR ($CDCl_3$) δ 150.8, 147.9, 145.2, 132.4, 132.2, 127.3, 122.7, 120.7, 117.1, 110.3 ppm; EIMS *m/z* (relative intensity), 305.82 (M + 1, 20%), 349.82 (M^+, 100%), 284.12 (6%), 256.14 (41%), 217.01 (7.5%), 148.94 (4%), 102.07 (4%), 74.07 (27%).

6.2.16. 2-Trifluoromethyl-6-(4′-hydroxyphenyl)imidazo[2,1-*b*]-1,3,4-thaidiazole (16). This was obtained by reacting 2-amino-5-trifluoromethyl-1,3,4-thiadiazole (5.07 g, 30 mmol) and 4′-hydroxy phenacyl bromide (6.45 g, 30 mmol) as described in the general procedure and isolated as colourless solid crystals; yield 4.18 g (49%); mp 152–153 °C; λ_{max} (ethanol) 310, 260, 232 nm; IR (KBr) ν_{max} 3422 (b), 3125, 2924, 1517, 1480, 1295, 1171, 1012, 827 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.02 (s, 1H, 5H), 7.70 (d, J = 9 Hz, 2H, aryl-H), 6.89 (d, J = 9 Hz, 2H, aryl-H), 5.01 (broad, 1H, 4′-OH) ppm.

6.2.17. 2-Trifluoromethyl-6-(4′-methylphenyl)imidazo-[2,1-*b*]-1,3,4-thaidiazole (17). This was obtained by reacting 2-amino-5-trifluoromethyl-1,3,4-thiadiazole (5.07 g, 30 mmol) and 4′-methyl phenacyl bromide (6.39 g, 30 mmol) as described in the general procedure and isolated as colourless solid crystals; yield 3.9 g (46%); mp 134–135 °C; λ_{max} (ethanol) 322, 266, 234 nm; IR (KBr) ν_{max} 3166, 2937, 2840, 1600, 1512, 1483, 1270, 1171, 1047, 829 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.08 (s, 1H, 5H), 7.71 (d, J = Hz, 2H, aryl-H), 7.23 (d, J = 8 Hz, 2H, aryl-H), 2.39 (s, 3H, 4′-CH_3) ppm; ^{13}C NMR ($CDCl_3$) δ 149.1, 144.9, 138.7, 130.4, 129.9, 125.7, 120.8, 109.8, 102.6, 21.7 ppm; EIMS *m/z* (relative intensity) 283.1 (M^+, 82%), 264.2 (15%), 188.1 (52%), 161.0 (91%), 117.2 (100%), 89.2 (72%), 69.1 (68%), 44.2 (51%), 39.3 (55%); HRMS (EI) *m/z* calcd for $C_{12}H_8N_3F_3S$: 283.0386; found: 283.0388.

6.2.18. 2-Trifluoromethyl-6-(furoyl)imidazo[2,1-*b*]-1,3,4-thaidiazole (18). This was obtained by reacting 2-amino-5-trifluoromethyl-1,3,4-thiadiazole (5.07 g, 30 mmol) and α-bromoacetyl furan (5.67 g, 30 mmol) as described in the general procedure and isolated as brown solid crystals; yield 3.88 g (50%); mp 165–166 °C; λ_{max} (ethanol) 320, 258 228 nm; IR (KBr) ν_{max} 3159, 2924, 1522, 1482, 1308, 1174, 1017, 888, 774 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.04 (s, 1H, 5H), 7.45 (d, J = 3 Hz, 1H, furan), 6.78 (d, J = 3 Hz, 1H, furan), 6.49 (q, J = 5 Hz, J = 3 Hz, 1H, furan) ppm; ^{13}C NMR ($CDCl_3$) δ 148.5, 145.3, 142.7, 140.7, 112.0, 109.8, 107.4 ppm; EIMS *m/z* (relative intensity) 259.1 (M^+, 78%), 240.1 (16%), 136.9 (100%), 109.1 (96%), 93.1 (74%), 64.2 (75%), 44.2 (36%), 39.3 (68%); HRMS (EI) *m/z* calcd for $C_9H_4ON_3F_3S$: 259.0022; found: 259.0023.

6.2.19. 2-Trifluoromethyl-6-(coumarinyl)imidazo[2,1-*b*]-1,3,4-thaidiazole (19). This was obtained by reacting 2-amino-5-trifluoromethyl-1,3,4-thiadiazole (5.07 g, 30 mmol) and α-bromoacetyl coumarin (8.01 g, 30 mmol) as described in the general procedure and isolated as pale yellow solid crystals; yield 4.54 g (45%); mp 192–193 °C; λ_{max} (ethanol) 340, 288, 234 nm; IR (KBr) ν_{max} 3176, 3072, 2922, 2847, 1728, 1516, 1299, 1191, 1108, 1016, 763 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.79 (s, 1H, 5H), 8.59 (s, 1H, coumarin), 7.59 (d, J = 7 Hz, 1H, coumarin), 7.54 (t, J = 7 Hz, 1H, coumarin), 7.36 (d, J = 8 Hz, 1H, coumarin), 7.31 (t, J = 7 Hz,1H, coumarin) ppm; ^{13}C NMR ($CDCl_3$) δ 159.5, 153.3, 151.7, 150.4, 145.2, 138.1, 132.0, 128.7, 125.1, 120.4, 117.5, 115.8 ppm; EIMS *m/z* (relative intensity) 337.2 (M^+, 50%), 242.1 (5%), 215.1 (4%), 187.1 (35%), 155.1(31%), 143.1 (100%), 115.2 (25%), 88.2 (12%), 69.1 (20%), 44.2 (13%), 39.3 (16%); HRMS (EI) *m/z* calcd for $C_{14}H_6O_2N_3F_3S$: 337.0127; found: 337.0125.

6.3. Biological evaluation

6.3.1. In vitro evaluation of anti-tuberculosis activity. The preliminary anti-tuberculosis screening for test compounds (**1**–**2**, **5**–**8**, **10**, and **12**) was obtained for *M. tuberculosis* H37Rv in BACTEC 12B medium using a broth microdilution assay, the microplate Alamar Blue Assay (MABA).[39] Compounds exhibiting fluorescence were tested in the BACTEC 460 radiometric system.[40] The MIC of each drug was determined and is defined as the lowest concentration of drug, which inhibits ⩾99% of bacterial population present at the beginning of the assay. Percent inhibition was calculated as 1−(growth index of test sample/growth index of control) × 100.

For the remaining test compounds (**3**, **11** and **13**–**19**) MIC of each drug was determined by broth dilution assay[41,42] for *M. tuberculosis* strain H37Rv. A frozen culture in Middlebrook 7H9 broth supplemented with 10% Albumin–Dextrose–Catalase and 0.2% glycerol was thawed and diluted in broth to 2×10^5 cfu/mL for *M. tuberculosis* and used as the inoculum. In the assay U-tubes were used to accommodate ten compounds in 200–10 μg/mL dilutions. Each test compound was dissolved in dimethylsulfoxide (DMSO) then diluted in broth at twice the desired concentration. The final concentration of DMSO in the assay medium was 1.3%. Each U-tube was then inoculated with 0.05 mL of standardized culture and then incubated at 37 °C for 21 days. The growth in the U-tubes was compared with visibility against positive control (without drug), negative control (without drug and inoculum) and with standard Isonaizid.

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