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FULL PAPER

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Design, synthesis, and antitubercular activity of 3-amidophenols with 5-heteroatomic substitutions

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Abstract

A series of novel 3-amidophenols with 5-heteroatomic substitutions were designed and synthesized. Several compounds showed potent antitubercular activity against *Mycobacterium tuberculosis* H37Ra (MIC = 0.25–5 μg/mL). Compounds **12j** and **14i** also displayed good inhibitory activity against *M. tuberculosis* H37Rv and two clinically isolated multidrug-resistant *M. tuberculosis* strains (MIC = 0.39–3.12 μg/mL). The privileged compound **14i** showed certain oral efficacy on a mouse infection model. The compounds are non-cytotoxic against L-O2 hepatocytes and RAW264.7 macrophagocytes. They did not exert inhibitory activity against representative Gram-positive and Gram-negative bacteria.

KEYWORDS
3-amidophenol derivative, antitubercular activity, *Mycobacterium tuberculosis*

1 | INTRODUCTION

Tuberculosis (TB), caused by *Mycobacterium tuberculosis* (*Mtb*), still poses a huge threat to the human health. According to the report of the World Health Organization (WHO), in 2016 there were 10.4 million new cases and 1.7 million deaths caused by TB.[1] The current standard therapy for the drug-susceptible TB requires a combination of several first-line antitubercular agents such as isoniazid (INH), rifampicin (RIF), pyrazinamide (PZA), and ethambutol (EMB) for 6–9 months. Moreover, the treatment period is extended up to 24 months for multidrug-resistant (MDR) and extensive drug-resistant (XDR) TB. In addition, rather limited drugs are applicable for these patients.[2] The cure rates are less than 50%. In the past four decades, only two new anti-TB drugs, delamanide[3] and bedaquiline,[4] were added to clinical practice for the treatment of MDR-TB and XDR-TB as second-line drugs. A number of drug candidates with good potentials including PA-824,[5] SQ109,[6] Q203[7] are still under the investigation. However, the *Mtb* strains resistant to these new candidates have been reported.[8] Therefore the discovery of anti-TB drugs with new chemical structures and mechanisms of action is still an urgent task.[9]

Recently, we identified 3-amidophenol derivatives as a new class of anti-TB agents.[10] The compounds **YZ-6** and **YZ-7** showed potent *in vitro* inhibitory activity against *Mtb* H37Ra, *Mtb* H37Rv and several clinically isolated MDR-TB strains (MIC = 0.39–5 μg/mL). However, the compounds did not show *in vivo* efficacy in a mouse infection

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model, probably due to poor solubility and ADME properties. The 5-benzyl group in the compounds was suspected to be the metabolically liable moiety. The quick oxidization was expected to occur at the diphenylmethylene position. We speculated that the replacement of the methylene group with heteroatoms (O, S, N) can improve the pharmacokinetic properties and exhibit *in vivo* antitubercular activity (Scheme 1). In this paper, we report the synthesis and antitubercular evaluation of 3-amidophenols with 5-heteroatomic substitutions.

2 | RESULTS AND DISCUSSION

2.1 | Chemistry

The synthesis of 3-amidophenol derivatives **3**, **5a**–**h**, **7** with 5-alkoxyl or 5-phenoxyl substitutions is illustrated in Scheme 2. Firstly, 3,5-dimethoxyaniline **1** reacted with benzoyl chloride to give *N*-(3,5-dimethoxyphenyl)benzamide **2**. The double-demethylation of **2** with BBr_3 afforded the compound **4**. The alkylation of **4** with iodoalkanes gave compounds **5a**–**h**. On the other hand, the mono-demethylation of **2** with BBr_3 afforded the compound **3**. The phenylation of **3** with diphenyliodonium triflate afforded the compound **6**. The demethylation of **6** with BBr_3 provided the compound **7**.

The synthesis of compounds **12a–o** is shown in Scheme 3. The Buchwald–Hartwig cross-coupling of 1-bromo-3-methoxy-5-nitrobenzene **8** with amines or thiophenol provided compounds **9a–o**.[11,12] The reduction of the nitro group via the catalytic hydrogenation gave compounds **10a–o**. The subsequent acylation and the demethylation provided compounds **12a–o**.

The synthesis of compounds **14a–j** is illustrated in Scheme 4. The acylation of **10k** with acyl chlorides provided compounds **13a–j**. The demethylation with BBr_3 afforded the compounds **14a–j**.

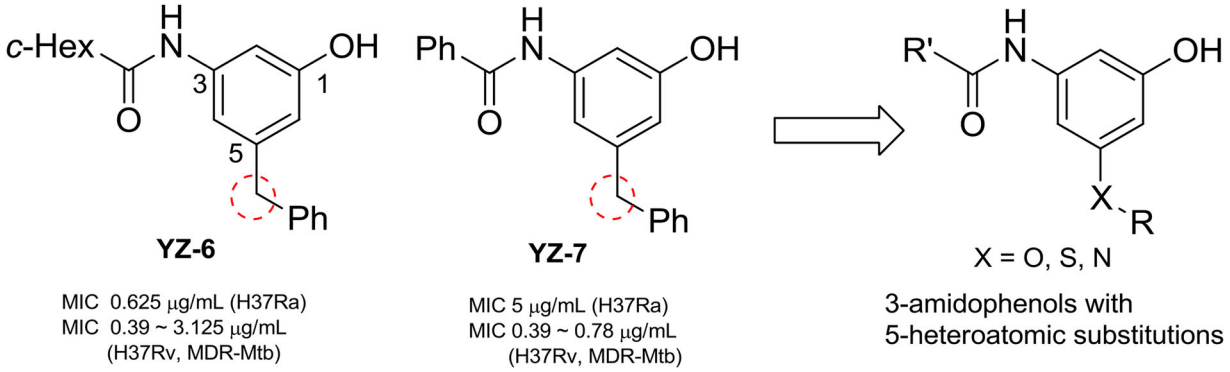
2.2 | Biological evaluation

2.2.1 | *In vitro* inhibitory activity against *Mtb* H37Ra

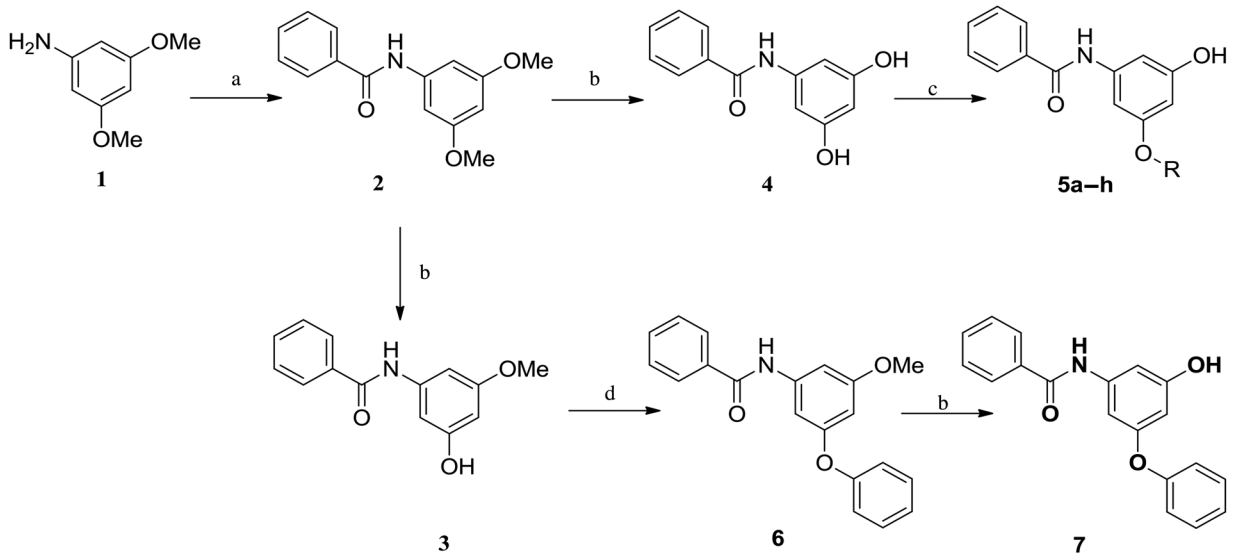
In vitro antitubercular activities of the compounds were evaluated against an unmarked autoluminescent *Mtb* H37Ra strain.[13] The bacteria growth was determined using relative light unit (RLU) by a luminometer.[14] The minimal inhibitory concentration (MIC) was defined as the lowest concentration that can inhibit 90% growth compared with the drug-free control. Isoniazid (INH) was used as the positive control and DMSO was used as the negative control. The results are listed in Tables 1–3.

Firstly, antitubercular activities of 3-amidophenols **3**, **5a–h**, and **7** with 5-alkoxyl and 5-phenoxyl groups were investigated (Table 1**)**. The compounds **3**, **5a–c** with short 5-alkoxyl groups did not show antitubercular activity (Table 1, entries 1–4). The extension of 5-alkoxyl chain (such as 5-butoxyl and 5-pentoxyl) increased antitubercular activity (MIC = 10 μg/mL), however, the introduction of longer alkoxyl chain (hexoxyl) resulted in the decreased inhibitory activity (MIC = 25 μg/mL) (Table 1, entries 5–7). In addition, the substitution with bulkier alkoxyls (*c*-pentoxyl or benzyloxyl) also led to the loss of the antitubercular activity (Table 1, entries 8–9). 5-Phenoxyl-3-amidophenol **7** showed good antitubercular activity (MIC = 5 μg/mL), which is comparable with that of 5-benzyl-3-amidophenol (**YZ-7**). The LogP value of compound **7** is lower than that of **YZ-7** (4.06 vs. 4.54). The result confirmed that the introduction of oxygen atom helps to improve the hydrophilicity.

Furthermore, 3-amidophenols **12a–o** with 5-*N*- or *S*-substituents were evaluated and the results are listed in Table 2. 5-Phenylthio-3-benzamidophenol **12a** showed good antitubercular activity (MIC = 6.25 μg/mL). Lower activity was observed for 5-phenylamino-3-benzamidophenol **12b** (MIC = 10 μg/mL). The substitution at the phenylamino group with methyl or fluoro decreased the activity (Table 2, entries 3–7). The introduction of *t*-butyl or CF_3 resulted in the loss of the antitubercular activity (Table 2, entries 8–9). The results demonstrated that the increase of steric hindrance on the phenyl ring has a detrimental impact on the activity. Furthermore, the substitutions at the 5-nitrogen were examined. 5-*N*-Methylphenylamino-3-benzamidophenol (**12j**) is fourfold more active (MIC = 2.5 μg/mL) than **12b**. However, the introduction of bulkier alkyl group such as ethyl, benzyl led to the loss of the activity (Table 2, entries 11–12). The fact indicated again the existence of a small binding pocket for the 5-substituent. The replacement of *N*-phenyl with *N*-2-pyridinyl resulted in the loss of activity, but 2-pyrimidiyl and 2-pyrazinyl analogs showed good activity (MIC = 6.25 and 12.5 μg/mL,



SCHEME 1 Design of 3-amidophenols with 5-heteroatomic substitutions



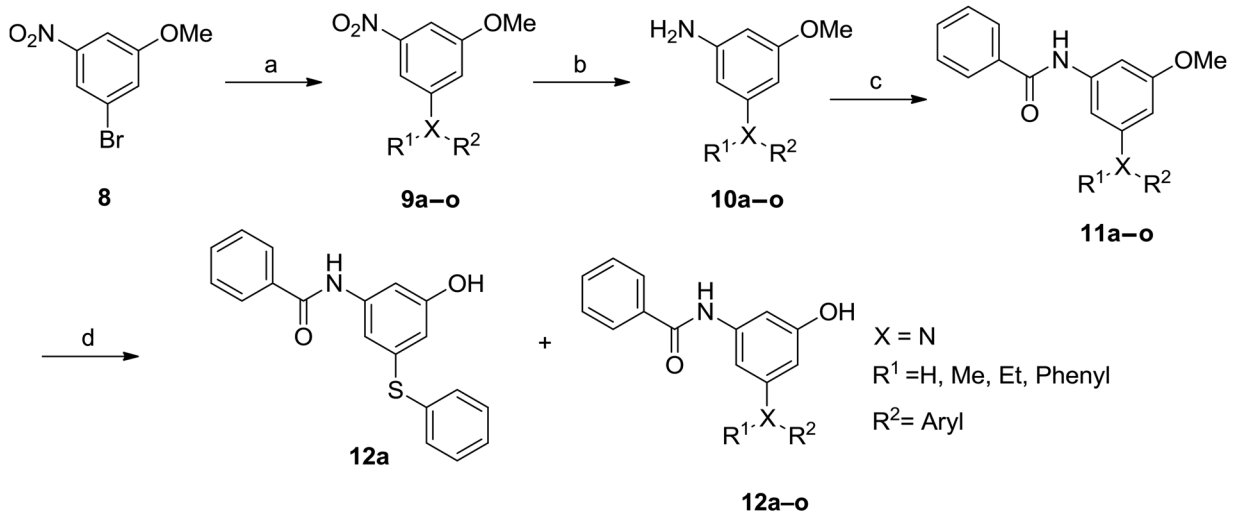
SCHEME 2 Synthesis of products **3**, **5a–h**, **7**. Reagents and conditions: (a) benzoyl chloride, Et_3N, THF, 0°C to rt, 1 h, 92%; (b) BBr_3, CH_2Cl_2, −40 to 0°C, 12 h, 21–68%; (c) R-I, K_2CO_3, Me_2CO, reflux, 6 h, 30–50%; (d) diphenyliodonium triflate, *t*-BuOK, THF, 0°C to rt, 1 h, 63%

respectively) (Table 2, entries 13–15). Based on the results, *N*-methylphenylamino was identified as the best 5-substituent.

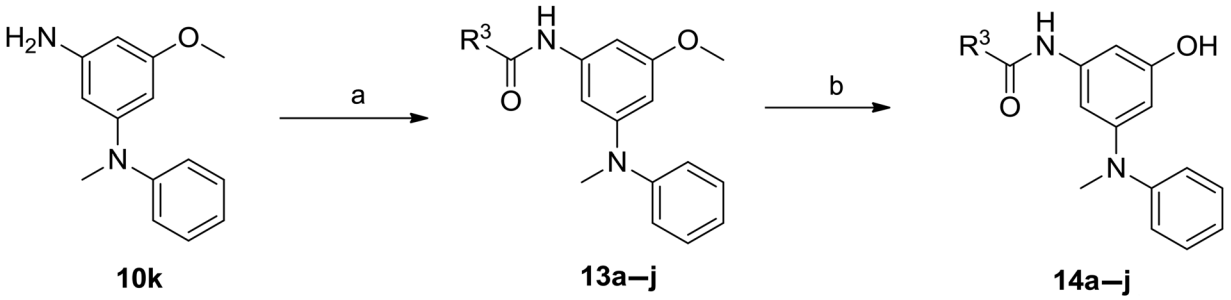
Keeping 5-methylphenylamino substitution, the different 3-amido groups were examined and the results are summarized in Table 3. In general, the size and lipophilicity of R^3 group have strong effect on the antitubercular activity. The replacements of phenyl with furanyl (**14a**), thiophenyl (**14b**), and 2-chloronicotinyl (**14c**) are applicable. Good inhibitory activities (MIC = 1.25–5 μg/mL) were observed (Table 3, entries 1–3). The replacements of phenyl with alkyl groups are also acceptable. 3-Isobutyramido derivative **14d** showed comparable activity (MIC = 2.5 μg/mL) with **12j**. Further increase of antitubercular activity was observed for more lipophilic 3-*tert*-valeramido derivative **14e** (MIC = 0.5 μg/mL). Several cycloalkylcarboxamido derivatives were examined and good inhibitory activities were observed (Table 3, entries 6–9). Among them, 3-cyclohexanecarboxamido derivative **14i** is most potent (MIC = 0.25 μg/mL). The introduction of oxygen atom to the cyclohexyl ring exerted the detrimental effect on the activity (Table 3, entry 10).

2.2.2 | *In vitro* inhibitory activity against *Mtb* H37Rv and MDR-TB strains

Compounds **12j** and **14i** were selected for the further evaluation of the inhibitory activity against *Mtb* H37Rv and five clinically isolated MDR-



SCHEME 3 Synthesis of products **12a–o**. Reagents and conditions: (a) $Pd(OAc)_2$, BINAP, Cs_2CO_3, toluene, 120°C, 6 h, 60–90%; (b) H_2, 10% Pd/C, CH_3OH, 4 h, 45–87%; (c) benzoyl chloride, Et_3N, THF, 0°C – rt, 1 h, 73–95%; (d) BBr_3, CH_2Cl_2, −40 to 0°C, 12 h, 65–88%



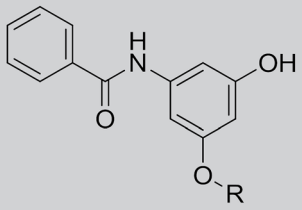
SCHEME 4 Synthesis of products **14a–j**. Reagents and conditions: (a) R^3COCl, Et_3N, THF, 0°C to rt, 1 h, 73–95%; (b) BBr_3, CH_2Cl_2, −40 to 0°C, 12 h, 65–88%

TB strains. The results are summarized in Table 4. Two compounds showed the similar activity against H37Rv (MIC = 1.56 μg/mL). They were also effective against MDR-TB strains P105 and P136 (MIC = 0.39–3.12 μg/mL). Low inhibitory activities were observed against MDR-TB strains P76 and Z23. The compounds **12j** and **14i** were almost inactive against MDR-TB strain L18.

2.2.3 | Evaluation of antibacterial activity

The antibacterial activity of several selected compounds was examined against Gram-positive bacteria *Staphylococcus aureus*, *Enterococcus faecalis*, and Gram-negative bacteria *Escherichia coli*. Amoxicillin and ofloxacin were used as the positive controls. The results are summarized in Table 5. All compounds did not show antibacterial activity (MIC_{90} > 50 μg/mL). The results indicated that 3-amidophenol derivatives can exclusively inhibit *Mtb*.

TABLE 1 Inhibitory activities of 3-amidophenols **3**, **5a–h**, **7** with 5-alkoxyl and 5-phenoxyl groups



3, 5a—h, 7

Entry	Comp.	R	LogP[a]	MIC_{lux} (μg/mL)
1	**3**	Me	2.32	>100
2	**5a**	Et	2.66	>50
3	**5b**	*n*-Pr	3.15	>50
4	**5c**	Allyl	3.02	>50
5	**5d**	*n*-Bu	3.57	10
6	**5e**	*n*-Pent	3.98	10
7	**5f**	*n*-Hex	4.40	25
8	**5g**	*c*-Pent	3.45	>50
9	**5h**	Bn	4.06	>50
10	**7**	Ph	3.99	5
11	**YZ-7**	–	4.54	5
12	INH	–	–	0.1

[a]LogP was calculated with ChemBioDraw Ultra 12.0.

2.2.4 | Evaluation of cytotoxicity

The cytotoxicity of six 3-amidophenol derivatives was evaluated against hepatocyte L-O2 and macrophagocyte RAW264.7. The IC_{50} values are listed in Table 6. All compounds showed low cytotoxicity against RAW264.7, but most of them showed moderate cytotoxicity against L-O_2. To our delight, the privileged compound **14i** was non-cytotoxic against both two cell lines.

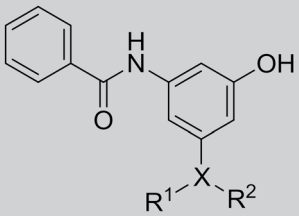
2.2.5 | Evaluation of solubility and metabolic stability

The solubility and metabolic stability of compounds **14i** and **YZ-6** were examined and the results are listed in Table 7. Lower solubility of **14i** in Tris/BSA (0.1%) solution was observed in comparison with **YZ-6**. The half-life of compounds **14i** and **YZ-6** in mouse liver microsome were determined as 5.43 and 6.60 min (CL_{int} = 387 and 318 mL/min/gprot, respectively). The result implicated a faster clearance of compound **14i** than **YZ-6** in the liver. The reason remains to be investigated.

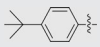
2.2.6 | *In vivo* inhibitory activity against *Mtb* H37a

In vivo efficacy of compound **14i** was investigated on a mouse model infected with *Mtb* H37Ra. Treatment was initiated 1 day after infection: the compound **14i** at 200 mg/kg as treatment group, 0.5% CMC-Na as an untreated control group, and RIF at 10 mg/kg as a positive control group. The treatment was administrated once daily by oral gavage. After 5 days treatment, mice were sacrificed by cervical dislocation. The lungs and spleens were removed and homogenized under sterile conditions. Finally RLU was detected from each homogenate. The results are summarized in Figure 1. The certain reduction of RLU (0.3–0.4 log) was achieved in the lung and the spleen compared with the untreated control group. However,

TABLE 2 Inhibitory activities of 3-amidophenols with 5-*S*- and 5-*N*-substituents



12a–o

Entry	Comp.	X	R^1	R^2	LogP[a]	MIC_{lux} (μg/mL)
1	**12a**	S	–		4.55	6.25
2	**12b**	N	H		3.91	10
3	**12c**	N	H		4.40	25
4	**12d**	N	H		4.40	25
5	**12e**	N	H		4.07	12.5
6	**12f**	N	H		4.07	25
7	**12g**	N	H		4.23	25
8	**12h**	N	H		5.62	>50
9	**12i**	N	H		4.84	>50
10	**12j**	N	Me		4.15	2.5
11	**12k**	N	Ethyl		4.49	>50
12	**12l**	N	Benzyl		5.81	>50
13	**12m**	N	Me		3.53	>100
14	**12n**	N	Me		2.73	6.25
15	**12o**	N	Me		2.19	12.5
16	INH	–	–	–		0.1

[a]LogP was calculated with ChemBioDraw Ultra 12.0.

the inhibitory activity is weak and the further improvement is required.

3 | CONCLUSION

In summary, we designed and synthetized a series of 3-amidophenols with 5-heteroatomic substitutions. Their antitubercular activities were evaluated against *Mtb* H37Ra, H37Rv and clinically isolated MDR-TB strains. A number of compounds with 5-methylphenylamino group showed potent inhibitory activity against H37Ra. The selected compounds **12j** and **14i** also displayed good inhibitory activity against H37Rv and two MDR-TB strains. The privileged compound **14i** was non-cytotoxic against tested cell lines. In addition, the compound **14i** showed *in vivo* antitubercular activity on the mouse infection model via the oral administration. The further improvement of *in vivo* efficacy via the structural modifications is currently underway.

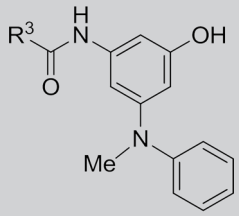
4 | EXPERIMENTAL

4.1 | Chemistry

4.1.1 | General

^{1}H and ^{13}C NMR spectra were recorded on Bruker AVANCE 400 or 500 MHz spectrometers with TMS as the internal standard. Chemical shifts are expressed in parts per million (δ ppm). The coupling constants

TABLE 3 Inhibitory activities of 3-amidophenols **14a–j**



14a–j

Entry	Comp.	R^3	LogP[a]	MIC_{lux} (μg/mL)
1	**14a**		2.77	5
2	**14b**		4.13	2.5
3	**14c**		3.71	1.25
4	**14d**		3.47	2.5
5	**14e**		4.18	0.5
6	**14f**		2.97	5
7	**14g**		3.39	10
8	**14h**		3.81	2.5
9	**14i**		4.23	0.25
10	**14j**		2.54	2.5
11	INH	–		0.1

[a]LogP was calculated with ChemBioDraw Ultra 12.0.

(*J*) are given in Hz. Peaks are labeled as single (s), broad singlet (br), doublet (d), triplet (t), double doublet (dd), doublet of triplets (dt), multiplet (m). The products were purified by column chromatography on silica gel (60–120 mesh) using petroleum ether/ethyl acetate as the eluent. The high-resolution mass spectra were analyzed on a Shimadzu LCMS-IT-TOF mass spectrometer. Melting points were determined in open capillary tubes on a MPA100 Optimelt automated melting point system. The chemicals were purchased from the Energy chemical company and were used without further purification.

The original spectra of the investigated compounds are provided as Supporting Information, as are their InChI codes together with some biological activity data.

TABLE 4 Inhibitory activities of **12j** and **14i** against H37Rv and clinical isolated MDR-TB strains

	MIC_{90} μg/mL)			
***Mtb* strain**	**12j**	**14i**	**INH**	**RIF**
H37Rv	1.56	1.56	0.41	0.003
P105[a]	1.56	0.39	/	/
P136[a]	3.12	3.12	/	/
P76[b]	12.5	25	/	/
Z23[b]	25	50	/	/
L18[b]	>100	50	/	/

[a]Resistant to rifampicin (RIF), isoniazid (INH), and pyrazinamide.
[b]Resistant to RIF and INH.

4.1.2 | Synthesis of compounds 3 and 4

To a solution of compound **1** (306 mg, 2 mmol) and triethylamine (0.554 mL, 4 mmol) in THF (20 mL) was added slowly benzoyl chloride (0.253 mL, 2.2 mmol) at 0°C. After the reaction mixture was stirred for 3 h at room temperature, the reaction was quenched with water (10 mL). The mixture was extracted with EtOAc (15 mL × 2). The combined organic layer was dried over anhydrous Na_2SO_4 and filtered. After the solvent was removed in vacuum, the crude product was purified by column chromatography (petroleum ether/EtOAc = 5:1) to afford **2** as a white solid (473 mg, 92% yield).

To a solution of compound **2** (257 mg, 1 mmol) in dichloromethane (10 mL) was added slowly a solution of BBr_3 in dichloromethane (2 mL, 1.0 M in CH_2Cl_2, 2 mmol) at −40°C. The resulting solution was warmed to 0°C and stirred for 12 h. Saturated aqueous sodium bicarbonate (10 mL) was added at 0°C. The solution was extracted with dichloromethane (10 mL × 3). The combined organic layer was dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuum. The residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc = 2:1) to afford **3** (44 mg, 18% yield) and **4** (119 mg, 52% yield) as white solids.

N-(3-Hydroxy-5-methoxyphenyl)benzamide (3)

Yield 18%, white solid, mp 188.4–189.8°C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.07 (s, 1H), 9.44 (s, 1H), 7.92 (d, *J* = 7.4 Hz, 2H), 7.60–7.56 (m, 1H), 7.52 (t, *J* = 7.3 Hz, 2H), 6.99 (s, 1H), 6.89 (s, 1H), 6.10 (s, 1H), 3.69 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 165.98, 160.75, 158.86, 141.17, 135.58, 131.95, 128.81, 128.10, 100.59, 97.64, 97.31, 55.35. HRMS (ESI) calcd. for $C_{14}H_{14}NO_3$ $[M+H]^+$: 244.0941, found: 244.0946.

N-(3,5-Dihydroxyphenyl)benzamide (4)

Yield 52%, white solid, mp 212.5–214.3°C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.96 (s, 1H), 9.21 (s, 2H), 7.90 (d, *J* = 7.8 Hz, 2H), 7.59–7.55 (m, 1H), 7.51 (t, *J* = 7.1 Hz, 2H), 6.76 (s, 2H), 5.96 (s, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 165.90, 158.70, 141.00, 135.76, 131.83, 128.76, 128.11, 99.30, 98.84. HRMS (ESI) calcd. for $C_{13}H_{12}NO_3$ $[M+H]^+$: 230.0788, found: 230.0794.

4.1.3 | General procedure for the synthesis of 5a–h

To a solution of **4** (229 mg, 1 mmol) and potassium carbonate (276 mg, 2 mmol) in acetone (10 mL) was added iodoalkane (1.3 mmol) dropwise at room temperature. The mixture was refluxed and stirred for 6 h. After the solvent was removed in vacuum, the residue was purified by

TABLE 5 Antibacterial activities of selected compounds

	MIC_{90} (μg/mL)							
Bacteria	**12a**	**12j**	**12n**	**14c**	**14i**	**14j**	**Amoxicillin**	**Ofloxacin**
S. aureus	>50	>50	>50	>50	>50	>50	0.78	0.31
E. faecalis	>50	>50	>50	>50	>50	>50	6.25	1.25
E. coli	>50	>50	>50	>50	>50	>50	1.25	/

column chromatography on silica gel (petroleum ether/EtOAc = 2:1) to provide **5a–h**.

N-(3-Ethoxy-5-hydroxyphenyl)benzamide (5a)

Yield 35%, white solid, mp 140.5–142°C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.05 (s, 1H), 9.41 (s, 1H), 7.92 (d, *J* = 7.3 Hz, 2H), 7.58 (t, *J* = 7.3 Hz, 1H), 7.52 (t, *J* = 7.5 Hz, 2H), 6.97 (s, 1H), 6.88 (s, 1H), 6.08 (s, 1H), 3.95 (q, *J* = 6.9 Hz, 2H), 1.31 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 165.97, 159.99, 158.82, 141.14, 135.62, 131.93, 128.80, 128.09, 100.52, 98.12, 97.83, 63.25, 15.18. HRMS (ESI) calcd. for $C_{15}H_{16}NO_3$ $[M+H]^+$: 258.1125, found: 258.1131.

N-(3-Hydroxy-5-propoxyphenyl)benzamide (5b)

Yield 32%, white solid, mp 133.5–134.9°C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.04 (s, 1H), 9.41 (s, 1H), 7.91 (d, *J* = 6.1 Hz, 2H), 7.57 (d, *J* = 6.5 Hz, 1H), 7.53 (d, *J* = 6.3 Hz, 2H), 6.96 (s, 1H), 6.89 (s, 1H), 6.07 (s, 1H), 3.84 (s, 2H), 1.71 (d, *J* = 6.3 Hz, 2H), 0.97 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 165.95, 160.14, 158.81, 141.12, 135.58, 131.92, 128.79, 128.08, 100.48, 98.12, 97.85, 69.20, 22.52, 10.89. HRMS (ESI) calcd. for $C_{16}H_{18}NO_3$ $[M+H]^+$: 272.1281, found: 272.1274.

N-(3-Allyloxy-5-hydroxyphenyl)benzamide (5c)

Yield 37%, white solid, mp 135.6–137.2°C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.07 (s, 1H), 9.46 (s, 1H), 7.91 (d, *J* = 7.9 Hz, 2H), 7.58 (t, *J* = 7.0 Hz, 1H), 7.52 (t, *J* = 7.5 Hz, 2H), 6.98 (s, 1H), 6.91 (s, 1H), 6.11 (s, 1H), 6.04 (ddd, *J* = 16.0, 10.3, 5.1 Hz, 1H), 5.39 (d, *J* = 17.3 Hz, 1H), 5.26 (d, *J* = 10.5 Hz, 1H), 4.49 (d, *J* = 4.5 Hz, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 166.00, 159.68, 158.85, 141.16, 135.60, 134.25, 131.94, 128.80, 128.10, 117.72, 100.75, 98.42, 98.03, 68.50. HRMS (ESI) calcd. for $C_{16}H_{16}NO_3$ $[M+H]^+$: 270.1125, found: 270.1122.

N-(3-Butoxy-5-hydroxyphenyl)benzamide (5d)

Yield 31%, white solid, mp 132.0–133.5°C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.04 (s, 1H), 9.41 (s, 1H), 7.92 (d, *J* = 7.5 Hz, 2H), 7.58 (t, *J* = 7.2 Hz, 1H), 7.52 (t, *J* = 7.4 Hz, 2H), 6.97 (s, 1H), 6.89 (s, 1H), 6.08 (s, 1H), 3.96–3.79 (m, 2H), 1.78–1.58 (m, 2H), 1.50–1.35 (m, 2H), 0.94 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 165.95, 160.17, 158.82, 141.13, 135.60, 131.93, 128.80, 128.09, 100.51, 98.16, 97.88, 67.41, 31.23, 19.23, 14.18. HRMS (ESI) calcd. for $C_{17}H_{20}NO_3$ $[M+H]^+$: 286.1438, found: 286.1442.

TABLE 6 Cytotoxicities of selected compounds

	IC_{50} (μM)					
Cell line	**12a**	**12j**	**12n**	**14c**	**14i**	**14j**
Raw264.7	233	157	312	283	231	273
L-O_2	30	63	65	65	308	32

N-(3-Hydroxy-5-(pentyloxy)phenyl)benzamide (5e)

Yield 32%, white solid, mp 126.2–127.7°C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.05 (s, 1H), 9.42 (s, 1H), 7.92 (d, *J* = 7.3 Hz, 2H), 7.57 (t, *J* = 7.7 Hz, 1H), 7.52 (t, *J* = 7.0 Hz, 2H), 6.98 (s, 1H), 6.90 (s, 1H), 6.08 (s, 1H), 3.88 (s, 2H), 1.69 (d, *J* = 5.8 Hz, 2H), 1.35 (m, 4H), 0.91 (t, *J* = 6.1 Hz, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 165.95, 160.16, 158.82, 141.13, 135.59, 131.93, 128.80, 128.09, 100.49, 98.14, 97.84, 67.69, 28.86, 28.22, 22.39, 14.41. HRMS (ESI) calcd. for $C_{18}H_{22}NO_3$ $[M+H]^+$: 300.1594, found: 300.1589.

N-(3-(Hexyloxy)-5-hydroxyphenyl)benzamide (5f)

Yield 33%, white solid, mp 119.3–120.6°C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.05 (s, 1H), 9.41 (s, 1H), 7.92 (d, *J* = 7.1 Hz, 2H), 7.58 (d, *J* = 7.0 Hz, 1H), 7.52 (t, *J* = 7.2 Hz, 2H), 6.97 (s, 1H), 6.89 (s, 1H), 6.08 (s, 1H), 3.88 (s, 2H), 1.75–1.62 (m, 2H), 1.40 (s, 2H), 1.31 (d, *J* = 2.2 Hz, 4H), 0.88 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 165.93, 160.14, 158.80, 141.11, 135.57, 131.92, 128.79, 128.08, 100.47, 98.13, 97.83, 67.69, 31.48, 25.68, 22.57, 14.40. HRMS (ESI) calcd. for $C_{19}H_{24}NO_3$ $[M+H]^+$: 314.1751, found: 314.1747.

N-(3-(Cyclopentyloxy)-5-hydroxyphenyl)benzamide (5g)

Yield 28%, white solid, mp 154.5–156.3°C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.03 (s, 1H), 9.38 (s, 1H), 7.91 (dd, *J* = 5.2, 3.3 Hz, 2H), 7.62–7.54 (m, 1H), 7.56–7.48 (m, 2H), 6.95 (t, *J* = 1.9 Hz, 1H), 6.86 (t, *J* = 1.9 Hz, 1H), 6.05 (t, *J* = 2.2 Hz, 1H), 4.72–4.64 (m, 1H), 1.96–1.83 (m, 2H), 1.77–1.64 (m, 4H), 1.63–1.51 (m, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 165.96, 159.11, 158.77, 141.10, 135.64, 131.92, 128.80, 128.09, 100.33, 99.14, 98.79, 78.98, 32.84, 24.06. HRMS (ESI) calcd. for $C_{18}H_{20}NO_3$ $[M+H]^+$: 298.1438, found: 298.1432.

N-(3-(Benzyloxy)-5-hydroxyphenyl)benzamide (5h)

Yield 39%, white solid, mp 159.3–160.8°C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.08 (s, 1H), 9.47 (s, 1H), 7.92 (d, *J* = 7.5 Hz, 2H), 7.62–7.56 (m, 1H), 7.53 (t, *J* = 7.3 Hz, 2H), 7.45 (d, *J* = 7.4 Hz, 2H), 7.40 (t, *J* = 7.2 Hz, 2H), 7.34 (t, *J* = 6.9 Hz, 1H), 6.99 (s, 2H), 6.17 (s, 1H), 5.04 (s, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 166.01, 159.86, 158.87, 141.18, 137.67, 135.60, 131.92, 128.87, 128.79, 128.21, 128.09,

TABLE 7 Metabolic stability of compounds **14i** and **YZ-6** in mouse liver microsome

Compound	Solubility (μM) Tris/BSA (0.1%)	$T_{1/2}$ (min)	CL_{int} *in vitro* (mL/min/gprot)	CL_{int} *in vivo* Extpl (mL/min)	CL_{int} Hep *in vivo* Extpl (mL/min)	MF (%)
14i	10	5.43	387	26.1	2.69	10.3
YZ-6	50	6.60	318	21.5	2.63	12.3

128.00, 100.92, 98.68, 98.24, 69.55. HRMS (ESI) calcd. for $C_{20}H_{18}NO_3$ $[M+H]^+$: 320.1281, found: 320.1285.

4.1.4 | Synthesis of *N*-(3-hydroxy-5-phenoxyphenyl) benzamide (7)

To a suspension of *t*-BuOK (123.2 mg, 1.1 mmol) in THF (5 mL) was added compound **3** (243 mg, 1.0 mmol) at 0°C. The reaction mixture was stirred at 0°C for 15 min. After diphenyliodonium triflate (516 mg, 1.2 mmol) was added in one portion, the reaction mixture was stirred at room temperature until the complete consumption of **3** as indicated by TLC analysis. The reaction was quenched with water (10 mL) at 0°C. The organic phase was separated, and the aqueous phase was extracted with Et_2O (10 mL × 3). The combined organic phase was dried over anhydrous Na_2SO_4 and concentrated in vacuum. The residue was purified by flash chromatography to give compound **6** as a white solid (201 mg, 63% yield).

To a solution of compound **6** (160 mg, 0.5 mmol) in dichloromethane (5 mL) was added slowly a solution of BBr_3 in dichloromethane (1 mL, 1.0 M in CH_2Cl_2, 1 mmol) at −40°C. The resulting solution was warmed to 0°C and stirred for 12 h. Saturated aqueous sodium bicarbonate (5 mL) was added at 0°C. The solution was extracted with dichloromethane (5 mL × 3). The combined organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated in vacuum. The residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc = 2:1) to afford **7** as a white solid (104 mg, 68%). Mp 178.2–189.8°C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.16 (s, 1H), 9.66 (s, 1H), 7.92–7.88 (m, 2H), 7.58 (t, *J* = 7.3 Hz, 1H), 7.51 (t, *J* = 7.5 Hz, 2H), 7.41 (dd, *J* = 8.3, 7.6 Hz, 2H), 7.16 (dd, *J* = 9.0, 4.7 Hz, 2H), 7.05 (d, *J* = 7.7 Hz, 2H), 6.95 (t, *J* = 1.9 Hz, 1H), 6.14 (t, *J* = 2.1 Hz, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 166.10, 159.17, 158.35, 156.89, 141.62, 135.45, 131.99, 130.43, 128.78, 128.12, 123.99, 119.55, 102.94, 101.68, 101.58. HRMS (ESI) calcd. for $C_{19}H_{16}NO_3$
$[M+H]^+$: 306.1125, found: 306.1117.

4.1.5 | General procedure for the synthesis of 12a–o

A mixture of compound **8** (928 mg, 4 mmol), Cs_2CO_3 (1.95 g, 6 mmol), *rac*-BINAP (199 mg, 0.32 mmol), $Pd(OAc)_2$ (44 mg, 0.2 mmol), arylamine or thiophenol (4 mmol), and toluene (30 mL) was stirred at 120°C for 12 h. The reaction mixture was cooled to room temperature and filtered over a layer of Celite. The filter cake was washed with dichloromethane. After the solvent was evaporated in vacuum, the residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc = 5:1) to give compounds **9a–o**.

A solution of compounds **9a–o** (2 mmol) and 10% Pd/C (60 mg) in CH_3OH (10 mL) was purged with H_2 three times. The reaction mixture was stirred with a balloon of H_2 at room temperature for 4 h. The reaction mixture was filtered and the filtrate was concentrated in vacuum. The residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc = 3:1) to give compounds **10a–o**.

To a solution of compounds **10a–o** (1 mmol) and triethylamine (202 mg, 2 mmol) in THF (10 mL) was added slowly a solution of benzoyl chloride (154 mg, 1.1 mmol) in THF (10 mL) at 0°C. After the reaction mixture was stirred at room temperature for 3 h, the reaction was quenched with water (10 mL). The mixture was extracted with EtOAc (15 mL × 2). The combined organic layer was dried over

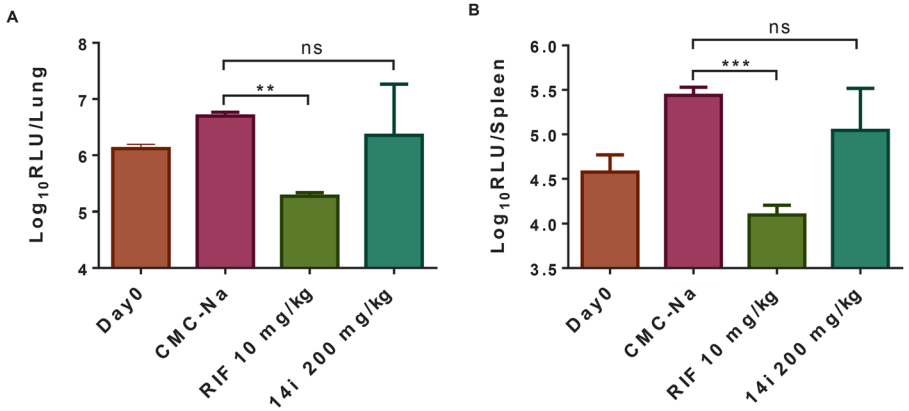


FIGURE 1 *In vivo* inhibitory activity of **14i** against *Mtb* H37Ra on a mouse infection model. Four mice per group were treated for 6 days. Data were presented as mean ± SD. ns: not significant. *: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$

anhydrous Na_2SO_4, filtered and concentrated in vacuum. Compounds **11a–o** were obtained and directly used in the next step without further purification.

To a solution of compounds **11a–o** (0.75 mmol) in dichloromethane (10 mL) was added slowly a solution of BBr_3 in dichloromethane (2 mL, 1.0 M in CH_2Cl_2, 2 mmol) at −40°C. The resulting solution was warmed to 0°C and stirred for 12 h. Saturated aqueous sodium bicarbonate (5 mL) was added at 0°C. The solution was extracted with dichloromethane (10 mL × 3). The combined organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated in vacuum. The residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc = 2:1) to give **12a–o**.

N-(3-Hydroxy-5-(phenylthio)phenyl)benzamide (12a)

Yield 78%, white solid, mp 157.8–158.9°C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.19 (s, 1H), 9.70 (s, 1H), 7.91 (d, *J* = 7.3 Hz, 2H), 7.59 (t, *J* = 7.3 Hz, 1H), 7.52 (t, *J* = 7.5 Hz, 2H), 7.43–7.36 (m, 4H), 7.35–7.31 (m, 2H), 7.28 (s, 1H), 6.42 (t, *J* = 1.7 Hz, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 166.12, 158.63, 141.47, 136.08, 135.33, 135.05, 132.07, 131.40, 130.01, 128.82, 128.15, 127.93, 113.36, 112.93, 106.91. HRMS (ESI) calcd. for $C_{19}H_{16}NO_2S$ $[M+H]^+$: 322.0896, found: 322.0889.

N-(3-Hydroxy-5-(phenylamino)phenyl)benzamide (12b)

Yield 72%, white solid, mp 192.2–193.5°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.01 (s, 1H), 9.24 (s, 1H), 8.07 (s, 1H), 7.97–7.87 (m, 2H), 7.61–7.54 (m, 1H), 7.51 (t, *J* = 7.3 Hz, 2H), 7.24 (t, *J* = 7.8 Hz, 2H), 7.16–7.05 (m, 3H), 6.85 (d, *J* = 5.9 Hz, 1H), 6.82 (t, *J* = 7.3 Hz, 1H), 6.27 (t, *J* = 1.8 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 165.89, 158.55, 144.89, 143.90, 141.05, 135.73, 131.82, 129.49, 128.74, 128.10, 120.01, 117.69, 100.34, 100.18, 99.98. HRMS (ESI) calcd. for $C_{19}H_{17}N_2O_2$ $[M+H]^+$: 305.1285, found: 305.1279.

N-(3-Hydroxy-5-(*o*-tolylamino)phenyl)benzamide (12c)

Yield 82%, white solid, mp 157.1–158.2°C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.94 (s, 1H), 9.13 (s, 1H), 7.89 (d, *J* = 7.6 Hz, 2H), 7.59–7.52 (m, 1H), 7.49 (t, *J* = 7.1 Hz, 2H), 7.31 (s, 1H), 7.19 (d, *J* = 7.6 Hz, 2H), 7.12 (t, *J* = 7.4 Hz, 1H), 6.91 (t, *J* = 7.2 Hz, 1H), 6.84 (s, 1H), 6.76 (s, 1H), 6.06 (s, 1H), 2.20 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 165.82, 158.48, 146.81, 141.75, 140.92, 135.76, 131.78, 131.23, 130.67, 128.72, 128.10, 126.84, 122.57, 121.64, 99.75, 99.34, 99.18, 18.51. HRMS (ESI) calcd. for $C_{20}H_{19}N_2O_2$ $[M+H]^+$: 319.1441, found: 319.1436.

N-(3-Hydroxy-5-(*p*-tolylamino)phenyl)benzamide (12d)

Yield 81%, white solid, mp 158.4–160.3°C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.98 (s, 1H), 9.20 (s, 1H), 8.04–7.85 (m, 3H), 7.57 (t, *J* = 7.1 Hz, 1H), 7.51 (t, *J* = 7.3 Hz, 2H), 7.05 (t, *J* = 7.5 Hz, 2H), 7.01 (t, *J* = 7.4 Hz, 3H), 6.80 (s, 1H), 6.20 (s, 1H), 2.24 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 165.84, 158.51, 145.58, 141.15, 141.01, 135.74, 131.80, 129.91, 129.09, 128.73, 128.10, 118.55, 99.60, 99.24, 20.77. HRMS (ESI) calcd. for $C_{20}H_{19}N_2O_2$ $[M+H]^+$: 319.1441, found: 319.1434.

N-(3-((2-Fluorophenyl)amino)-5-hydroxyphenyl)benzamide (12e)

Yield 85%, white solid, mp 180.1–181.4°C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.00 (s, 1H), 9.24 (s, 1H), 8.03 (s, 1H), 7.90 (d, *J* = 7.8 Hz, 2H), 7.57 (t, *J* = 7.2 Hz, 1H), 7.51 (t, *J* = 7.4 Hz, 2H), 7.09 (d, *J* = 6.8 Hz, 4H), 7.02 (s, 1H), 6.82 (s, 1H), 6.19 (s, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 165.87, 158.48, 154.33 (d, $^1J_{CF}$ = 242.0 Hz), 145.04, 140.92, 135.68, 131.83, 131.50 (d, $^2J_{CF}$ = 11.4 Hz), 128.74, 128.10, 125.03 (d, $^3J_{CF}$ = 3.2 Hz), 122.01 (d, $^3J_{CF}$ = 7.1 Hz), 121.19 (d, $^4J_{CF}$ = 2.2 Hz), 116.29 (d, $^2J_{CF}$ = 19.3 Hz), 100.34, 100.27, 100.14. HRMS (ESI) calcd. for $C_{19}H_{16}FN_2O_2$ $[M+H]^+$: 323.1190, found: 323.1182.

N-(3-((4-Fluorophenyl)amino)-5-hydroxyphenyl)benzamide (12f)

Yield 83%, white solid, mp 182.1–183.7°C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.02 (s, 1H), 9.26 (s, 1H), 7.91 (d, *J* = 7.5 Hz, 2H), 7.83 (s, 1H), 7.57 (t, *J* = 7.1 Hz, 1H), 7.51 (t, *J* = 7.3 Hz, 2H), 7.33 (t, *J* = 8.2 Hz, 1H), 7.25–7.17 (m, 1H), 7.10 (t, *J* = 7.6 Hz, 1H), 6.97 (d, *J* = 6.9 Hz, 1H), 6.97–6.90 (m, 1H), 6.88 (s, 1H), 6.19 (s, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 165.90, 158.62, 156.80 (d, $^1J_{CF}$ = 236.0 Hz), 145.41, 141.13, 140.22 (d, $^4J_{CF}$ = 1.7 Hz), 135.72, 131.84, 128.76, 128.11, 119.81 (d, $^3J_{CF}$ = 7.8 Hz), 116.01 (d, $^2J_{CF}$ = 22.7 Hz), 99.90, 99.62, 99.30. HRMS (ESI) calcd. for $C_{19}H_{16}FN_2O_2$ $[M+H]^+$: 323.1190, found: 323.1183.

N-(3-((2,4-Difluorophenyl)amino)-5-hydroxyphenyl)benzamide (12g)

Yield 88%, white solid, mp 184.5–186.3°C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.97 (s, 1H), 9.21 (s, 1H), 7.90 (d, *J* = 7.2 Hz, 2H), 7.73 (s, 1H), 7.60–7.54 (m, 1H), 7.50 (t, *J* = 7.1 Hz, 2H), 7.30 (m,2H), 7.02 (t, *J* = 7.1 Hz, 1H), 6.84 (d, *J* = 7.3 Hz, 2H), 6.07 (s, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 165.88, 158.55, 145.93, 141.01, 135.71, 131.83, 128.74, 128.10, 123.85, 111.83, 111.64, 105.19, 104.99, 104.78, 99.89, 99.33, 99.14. HRMS (ESI) calcd. for $C_{19}H_{15}F_2N_2O_2$ $[M+H]^+$: 341.1096, found: 341.1088.

N-(3-((4-(*tert*-Butyl)phenyl)amino)-5-hydroxyphenyl)benzamide (12h)

Yield 87%, white solid, mp 144.4–146.2°C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.99 (s, 1H), 9.19 (s, 1H), 7.97 (s, 1H), 7.91 (d, *J* = 7.0 Hz, 2H), 7.57 (d, *J* = 6.9 Hz, 1H), 7.52 (d, *J* = 7.2 Hz, 2H), 7.26 (d, *J* = 8.1 Hz, 2H), 7.05 (s, 3H), 6.82 (s, 1H), 6.22 (s, 1H), 1.27 (s, 9H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 165.87, 158.55, 145.44, 142.55, 141.11, 141.03, 135.75, 131.82, 128.74, 128.11, 126.10, 118.02, 99.65, 99.56, 99.34, 34.26, 31.82. HRMS (ESI) calcd. for $C_{23}H_{25}N_2O_2$ $[M+H]^+$: 361.1911, found: 361.1905.

N-(3-Hydroxy-5-((4-(trifluoromethyl)phenyl)amino)phenyl) benzamide (12i)

Yield 85%, white solid, mp 200.1–201.9°C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.08 (s, 1H), 9.42 (s, 1H), 8.63 (s, 1H), 7.92 (d, *J* = 7.4 Hz, 2H), 7.58 (t, *J* = 7.3 Hz, 1H), 7.52 (t, *J* = 7.6 Hz, 4H), 7.19 (d, *J* = 5.6 Hz, 2H), 7.17 (s, 1H), 6.99 (s, 1H), 6.33 (s, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 166.01, 158.69, 147.94, 142.97, 141.22, 135.63, 131.93, 128.79,

128.12, 126.89, 115.65, 102.11, 101.96, 101.75. HRMS (ESI) calcd. for $C_{20}H_{16}F_3N_2O_2$ $[M+H]^+$: 373.1158, found: 373.1153.

N-(3-Hydroxy-5-(methyl(phenyl)amino)phenyl)benzamide (12j)

Yield 57%, white solid, mp 171.6–173.5°C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.03 (s, 1H), 9.32 (s, 1H), 7.90 (d, *J* = 7.6 Hz, 2H), 7.56 (t, *J* = 7.2 Hz, 1H), 7.50 (t, *J* = 7.4 Hz, 2H), 7.29 (t, *J* = 7.5 Hz, 2H), 7.05 (d, *J* = 8.2 Hz, 3H), 6.96 (t, *J* = 7.2 Hz, 1H), 6.90 (s, 1H), 6.14 (s, 1H), 3.21 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 165.88, 158.54, 150.16, 149.11, 141.11, 135.60, 131.86, 129.62, 128.74, 128.08, 121.88, 121.44, 103.38, 102.89, 101.30, 40.56. HRMS (ESI) calcd. for $C_{20}H_{18}N_2O_2Na$ $[M+Na]^+$: 341.1260, found: 341.1251.

N-(3-(Ethyl(phenyl)amino)-5-hydroxyphenyl)benzamide (12k)

Yield 53%, white solid, mp 175.3–176.5°C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.01 (s, 1H), 9.27 (s, 1H), 7.90 (d, *J* = 7.6 Hz, 2H), 7.57 (t, *J* = 7.3 Hz, 1H), 7.50 (t, *J* = 7.4 Hz, 2H), 7.28 (t, *J* = 7.6 Hz, 2H), 7.02 (d, *J* = 6.5 Hz, 3H), 6.94 (t, *J* = 7.3 Hz, 1H), 6.88 (s, 1H), 6.09 (s, 1H), 3.70 (q, *J* = 6.9 Hz, 2H), 1.14 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 165.88, 158.58, 148.79, 147.66, 141.23, 135.63, 131.87, 129.72, 128.75, 128.09, 121.92, 121.76, 103.52, 103.14, 101.09, 46.39, 13.00. HRMS (ESI) calcd. for $C_{21}H_{21}N_2O_2$ $[M+H]^+$: 333.1598, found: 333.1589.

N-(3-(Diphenylamino)-5-hydroxyphenyl)benzamide (12l)

Yield 52%, white solid, mp 213.4–214.9°C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.07 (s, 1H), 9.40 (s, 1H), 7.88 (s, 2H), 7.55 (s, 1H), 7.49 (s, 2H), 7.30 (s, 4H), 7.17 (s, 1H), 7.03 (s, 6H), 6.96 (s, 1H), 6.14 (s, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 165.90, 158.63, 148.74, 147.75, 141.38, 135.44, 131.91, 129.88, 128.72, 128.10, 124.48, 123.28, 107.02, 106.67, 102.91. HRMS (ESI) calcd. for $C_{25}H_{21}N_2O_2$ $[M+H]^+$: 381.1598, found: 381.1590.

N-(3-Hydroxy-5-(methyl(pyridin-2-yl)amino)phenyl)benzamide (12m)

Yield 44%, white solid, mp 223.5–224.7°C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.14 (s, 1H), 9.59 (s, 1H), 8.16 (m, 1H), 7.95–7.88 (m, 1H), 7.58 (m, 1H), 7.51 (t, *J* = 7.3 Hz, 1H), 7.45 (t, *J* = 6.9 Hz, 1H), 7.26 (t, *J* = 1.9 Hz, 1H), 7.17 (s, 1H), 6.70–6.65 (m, 1H), 6.63 (d, *J* = 8.6 Hz, 1H), 6.41 (t, *J* = 2.0 Hz, 1H), 3.35 (s, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 166.02, 158.95, 158.62, 148.03, 147.80, 141.51, 137.31, 135.43, 132.03, 128.82, 128.12, 113.77, 109.70, 108.77, 108.46, 104.94, 38.41. HRMS (ESI) calcd. for $C_{19}H_{18}N_3O_2$ $[M+H]^+$: 320.1394, found: 320.1387.

N-(3-Hydroxy-5-(methyl(pyrimidin-2-yl)amino)phenyl) benzamide (12n)

Yield 51%, white solid, mp 220.2–221.5°C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.15 (s, 1H), 9.53 (d, *J* = 1.0 Hz, 1H), 8.37 (m 2H), 7.93 (d, *J* = 7.7 Hz, 2H), 7.58 (m, 1H), 7.52 (t, *J* = 7.0 Hz, 2H), 7.26 (d, *J* = 1.5 Hz, 1H), 7.19 (s, 1H), 6.78–6.67 (m, 1H), 6.47 (d, *J* = 1.7 Hz, 1H), 3.41 (d, *J* = 1.5 Hz, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 165.96, 161.92, 158.26, 158.19, 146.78, 140.83, 135.48, 131.98, 128.82, 128.10, 111.54, 109.89, 109.81, 105.35, 38.75. HRMS (ESI) calcd. for $C_{18}H_{17}N_4O_2$ $[M+H]^+$: 321.1364, found: 321.1358.

N-(3-Hydroxy-5-(methyl(pyrazin-2-yl)amino)phenyl)benzamide (12o)

Yield 47%, white solid, mp 193.1–194.4°C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.23 (s, 1H), 9.76 (s, 1H), 8.16 (s, 1H), 8.02 (s, 1H), 7.93 (d, *J* = 7.5 Hz, 2H), 7.87 (d, *J* = 2.0 Hz, 1H), 7.59 (t, *J* = 7.1 Hz, 1H), 7.53 (t, *J* = 7.4 Hz, 2H), 7.33 (s, 1H), 7.24 (s, 1H), 6.49 (s, 1H), 3.37 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 166.09, 159.24, 154.65, 146.24, 142.00, 141.73, 135.35, 133.17, 133.04, 132.08, 128.84, 128.13, 108.70, 108.46, 105.71, 38.22. HRMS (ESI) calcd. for $C_{18}H_{17}N_4O_2$ $[M+H]^+$: 321.1346, found: 321.1353.

4.1.6 | General procedure for the synthesis of 14a–k

To solution of compound **10k** (228 mg, 1 mmol) and triethylamine (202 mg, 2 mmol) in THF (10 mL) was added slowly a solution of acyl chloride (1.1 mmol) in THF (10 mL) at 0°C. After the reaction mixture was stirred for 3 h at room temperature, the reaction was quenched with water (10 mL). The mixture was extracted with EtOAc (15 mL × 2). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. Compounds **13a–k** was obtained and directly used in next step without further purification.

To a solution of compounds **13a–k** (0.75 mmol) in dichloromethane (10 mL) was added slowly a solution of BBr_3 (2 mL, 1.0 M in CH_2Cl_2, 2 mmol) at −40°C. The resulting solution was warmed to 0°C and stirred for 12 h. Saturated aqueous sodium bicarbonate (5 mL) was added at 0°C. The solution was extracted with dichloromethane (10 mL × 3). The combined organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated in vacuum. The residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc = 2:1) to give compounds **14a–k**.

N-(3-Hydroxy-5-(methyl(phenyl)amino)phenyl)furan-2-carboxamide (14a)

Yield 89%, white solid, mp 190.6–192.3°C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.92 (s, 1H), 9.31 (s, 1H), 7.90 (s, 1H), 7.30 (t, *J* = 7.4 Hz, 3H), 7.05 (d, *J* = 7.8 Hz, 2H), 7.01–6.92 (m, 2H), 6.84 (s, 1H), 6.67 (s, 1H), 6.11 (s, 1H), 3.21 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 158.53, 156.53, 150.17, 149.06, 148.05, 146.05, 140.45, 129.65, 122.04, 121.67, 114.92, 112.50, 103.14, 102.71, 101.16, 40.54. HRMS (ESI) calcd. for $C_{18}H_{17}N_2O_3$ $[M+H]^+$: 309.1234, found: 309.1228.

N-(3-Hydroxy-5-(methyl(phenyl)amino)phenyl)thiophene-2-carboxamide (14b)

Yield 87%, white solid, mp 156.6–158.2°C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.98 (s, 1H), 9.32 (s, 1H), 7.98 (s, 1H), 7.82 (d, *J* = 4.5 Hz, 1H), 7.30 (t, *J* = 7.5 Hz, 2H), 7.19 (s, 1H), 7.06 (d, *J* = 7.9 Hz, 2H), 7.01–6.93 (m, 2H), 6.83 (s, 1H), 6.13 (s, 1H), 3.22 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 160.18, 158.58, 150.21, 149.08, 140.78, 140.64, 132.20, 129.67, 129.41, 128.46, 122.06, 121.69, 103.09, 102.73, 101.14,

40.58. HRMS (ESI) calcd. for $C_{18}H_{17}N_2O_2S$ $[M+H]^+$: 325.1005, found: 325.1012.

2-Chloro-*N*-(3-hydroxy-5-(methyl(phenyl)amino)phenyl) nicotinamide (14c)

Yield 81%, white solid, mp 169.7–171.2°C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.36 (s, 1H), 9.32 (s, 1H), 8.50 (d, J = 2.9 Hz, 1H), 8.01 (d, J = 7.4 Hz, 1H), 7.56–7.48 (m, 1H), 7.30 (t, J = 7.3 Hz, 2H), 7.06 (d, J = 7.7 Hz, 2H), 6.99 (t, J = 7.1 Hz, 1H), 6.92 (s, 1H), 6.72 (s, 1H), 6.13 (s, 1H), 3.20 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 163.81, 158.73, 150.78, 150.44, 148.96, 146.87, 140.56, 138.55, 133.79, 129.68, 123.54, 122.39, 122.15, 102.57, 101.98, 100.21, 40.51. HRMS (ESI) calcd. for $C_{19}H_{17}ClN_3O_2$ $[M+H]^+$: 354.1044, found: 354.1036.

***N*-(3-Hydroxy-5-(methyl(phenyl)amino)phenyl)isobutyramide (14d)**

Yield 77%, white solid, mp 167.8–169.5°C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.55 (s, 1H), 9.19 (s, 1H), 7.28 (t, J = 7.5 Hz, 2H), 7.01 (d, J = 7.9 Hz, 2H), 6.95 (t, J = 7.2 Hz, 1H), 6.84 (s, 1H), 6.69 (s, 1H), 6.07 (s, 1H), 3.18 (s, 3H), 2.54 (m, 1H), 1.06 (d, J = 6.7 Hz, 6H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 175.47, 158.58, 150.24, 149.17, 141.36, 129.59, 121.81, 121.39, 102.32, 100.30, 40.36, 35.36, 19.97. HRMS (ESI) calcd. for $C_{17}H_{21}N_2O_2$ $[M+H]^+$: 285.1598, found: 285.1590.

***N*-(3-Hydroxy-5-(methyl(phenyl)amino)phenyl)pivalamide (14e)**

Yield 73%, white solid, mp 181.0–182.9°C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.21 (s, 1H), 8.97 (s, 1H), 7.27 (t, J = 7.4 Hz, 2H), 7.00 (d, J = 7.6 Hz, 2H), 6.97–6.90 (m, 2H), 6.79 (s, 1H), 6.09 (s, 1H), 3.19 (s, 3H), 1.19 (s, 9H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 176.69, 158.37, 149.99, 149.22, 141.41, 129.56, 121.47, 120.86, 103.65, 102.93, 101.47, 40.47, 27.66. HRMS (ESI) calcd. for $C_{18}H_{23}N_2O_2$ $[M+H]^+$: 299.1754, found: 299.1748.

***N*-(3-Hydroxy-5-(methyl(phenyl)amino)phenyl) cyclopropanecarboxamide (14f)**

Yield 78%, white solid, mp 160.9–162.4°C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.96 (s, 1H), 9.26 (s, 1H), 7.28 (d, J = 5.2 Hz, 2H), 7.03 (s, 2H), 6.96 (d, J = 5.1 Hz, 1H), 6.81 (s, 1H), 6.68 (s, 1H), 6.07 (s, 1H), 3.19 (s, 3H), 1.73 (d, J = 2.0 Hz, 1H), 0.75 (s, 4H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 171.85, 158.64, 150.26, 149.10, 141.24, 129.61, 121.94, 121.57, 102.06, 101.92, 99.99, 40.51, 14.99, 7.50. HRMS (ESI) calcd. for $C_{17}H_{19}N_2O_2$ $[M+H]^+$: 283.1441, found: 283.1437.

***N*-(3-Hydroxy-5-(methyl(phenyl)amino)phenyl) cyclobutanecarboxamide (14g)**

Yield 75%, white solid, mp 165.5–167.2°C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.48 (s, 1H), 9.24 (s, 1H), 7.28 (t, J = 7.6 Hz, 2H), 7.02 (d, J = 7.8 Hz, 2H), 6.96 (t, J = 7.2 Hz, 1H), 6.85 (s, 1H), 6.67 (s, 1H), 6.06 (s, 1H), 3.36 (s, 1H), 3.18 (s, 3H), 2.22–2.13 (m, 2H), 2.03 (m, 2H), 1.96–1.86 (m, 1H), 1.77 (d, J = 9.5 Hz, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 173.12, 158.59, 150.21, 149.12, 141.26, 129.60, 121.86, 121.46, 102.18, 100.16, 40.52, 40.09, 25.02, 18.16. HRMS (ESI) calcd. for $C_{18}H_{21}N_2O_2$ $[M+H]^+$: 297.1598, found: 297.1590.

***N*-(3-Hydroxy-5-(methyl(phenyl)amino)phenyl) cyclopentanecarboxamide (14h)**

Yield 75%, white solid, mp 187.2–189.1°C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.59 (s, 1H), 9.19 (s, 1H), 7.28 (t, J = 7.0 Hz, 2H), 7.01 (d, J = 7.4 Hz, 2H), 6.95 (t, J = 6.7 Hz, 1H), 6.83 (s, 1H), 6.69 (s, 1H), 6.06 (s, 1H), 3.18 (s, 3H), 2.70 (d, J = 6.8 Hz, 1H), 1.79 (s, 2H), 1.66 (s, 4H), 1.53 (s, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 158.59, 150.23, 149.17, 141.39, 129.58, 121.78, 121.34, 102.32, 102.30, 100.28, 45.77, 40.52, 30.53, 26.13. HRMS (ESI) calcd. for $C_{19}H_{23}N_2O_2$ $[M+H]^+$: 311.1754, found: 311.1748.

***N*-(3-Hydroxy-5-(methyl(phenyl)amino)phenyl) cyclohexanecarboxamide (14i)**

Yield 63%, white solid, mp 194.5–195.8°C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.54 (s, 1H), 9.19 (s, 1H), 7.32–7.23 (m, 2H), 7.03–6.98 (m, 2H), 6.95 (t, J = 7.3 Hz, 1H), 6.83 (d, J = 1.8 Hz, 1H), 6.69 (t, J = 1.8 Hz, 1H), 6.05 (t, J = 2.1 Hz, 1H), 3.18 (s, 3H), 2.30–2.20 (m, 1H), 1.74 (m, 4H), 1.64 (m,1H), 1.36 (m, 2H), 1.28–1.14 (m, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 174.60, 158.58, 150.22, 149.16, 141.43, 129.59, 121.80, 121.37, 102.24, 100.19, 45.36, 40.51, 29.60, 25.88, 25.72. HRMS (ESI) calcd. for $C_{20}H_{25}N_2O_2$ $[M+H]^+$: 325.1911, found: 325.1904.

***N*-(3-Hydroxy-5-(methyl(phenyl)amino)phenyl)tetrahydro-2*H*-pyran-4-carboxamide (14j)**

Yield 73%, white solid, mp 207.4–208.8°C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.65 (s, 1H), 9.25 (s, 1H), 7.29 (d, J = 4.8 Hz, 2H), 7.02 (s, 2H), 6.96 (s, 1H), 6.82 (s, 1H), 6.68 (s, 1H), 6.06 (s, 1H), 6.06 (s, 1H), 3.89 (d, J = 9.8 Hz, 2H), 3.31 (s, 2H), 3.18 (s, 3H), 1.63 (s, 4H), 1.24 (s, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 173.26, 158.58, 150.24, 141.23, 129.61, 121.93, 121.55, 102.19, 102.06, 100.08, 66.86, 42.24, 40.52, 29.31. HRMS (ESI) calcd. for $C_{19}H_{23}N_2O_3$ $[M+H]^+$: 327.1703, found: 327.1695.

4.2 | Biological assays

4.2.1 | Determination of MIC against *Mtb* H37Ra[13,14]

The assay was conducted over a range of fourfold increasing concentrations prepared in 1 mL of 7H9 broth containing 0.2 mL of a 1/100 dilution of autoluminescent *Mtb* H37Ra broth culture (OD_{600} = 0.8) grown in 7H9 broth. The tested compound was prepared as 10-point twofold serial dilutions in DMSO and diluted into 7H9 + Tween80 + OADC medium in 96-well plates with a final DMSO concentration of 2%. The highest concentration of compound was 100 μg/mL. To each well, 196 μL of a 1/100 dilution of autoluminescent *Mtb* H37Ra broth culture (OD_{600} = 0.8, grown in 7H9 broth) and 4 μL of the solution of the tested compound were added. For potent compounds, assays were repeated at a lower starting concentration.

Each plate included a control for zero growth (INH, 1 μg/mL), a maximum growth (DMSO only), as well as INH dose response curve. A total of 200 μL medium was added into each well on the inside edge of

the plate to prevent evaporation. RLU counts were determined daily in triplicate for 0–5 days. Growth was measured by fluorescence using the Glomax reader. For MIC, the 10-point dose response curve was plotted as percentage (%) of growth and fitted to the Gompertz model using GraphPad Prism 5. The MIC was defined as the minimum inhibitory concentration that can inhibit 90% growth compared with the drug-free control.

4.2.2 | Determination of MIC against *Mtb* H37Rv and MDR-TB[15]

MICs of the tested compounds were determined by a well-established microplate Alamar Blue assay (MABA) against H37Rv and clinically isolated MDR-TB strains (provided by Guangzhou Chest Hospital). *Mtb* H37Rv strain and MDR-TB strains in 7H9 + OADC were cultured in a 50 mL tube at 37°C with shaking. The strains were transferred into a 250 mL flask containing 50 mL 7H9 + Tween80 + OADC while OD_{600} reached 0.3–0.8. The tested compounds were prepared as *4.3.1*. Each well contained 196 µL broth culture of a 1/100 dilution of *Mtb* H37Rv or MDR-TB (OD_{600} = 0.8, grown in 7H9 broth) and 4 µL of the solution of tested compound. For potent compounds, assays were repeated at lower starting concentrations. INH and RIF were used as the positive controls. The plates were incubated at 37°C. On the seventh day, 12.5 µL of 20% Tween-80 and 20 µL of Alamar Blue were added to each well of the testing plate. A change in color from blue (oxidized state) to pink (reduced state) indicated the growth of bacteria after incubation at 37°C for 16–24 h. The MIC was defined as the lowest drug concentration that prevented this change in color.

4.2.3 | Determination of antibacterial activity

MIC was defined as the lowest concentration (the highest dilution) of each compound that 99% inhibited the growth of bacteria after incubation at 37°C for 18–24 h, by means of standard twofolds serial dilution method in 96-well microtest plates. Amoxicillin and ofloxacin were used as positive controls. The bacterial suspension was adjusted with sterile saline to a concentration of 1×10^5 CFU. Initially the tested compounds were dissolved in DMSO to prepare the stock solutions (10 mg/mL), and then the tested compounds and reference drugs were prepared in BHI broth to obtain the required concentrations 50–1.5125 µg/mL. These dilutions were inoculated and incubated at 37°C for 24 h.

4.2.4 | Determination of cytotoxicity

The cytotoxicities of compound **12j** and **14i** were assayed against RAW 264.7 and L-O_2 cell lines at concentrations from 100 to 6.25 µg/mL. The cells were seeded in the 96-well plate and then allowed to recover for 24 h. Different concentrations of the tested compound were added to the plate and each experiment was repeated three times. After being incubated for 72 h, cells were harvested and cell viability was assessed by MTT assay. The cytotoxicity was showed as IC_{50} values, which were calculated by GraphPad Prism software version 5.

4.2.5 | Evaluation of *in vivo* antitubercular activity[15]

Mtb H37Ra isolated on plates were homogenized with sterile glass beads in a 250 mL flask containing 50 mL 7H9 with Tween-80. When RLU reached 2 million/mL, the broth culture was used to infect 4- to 6-week-old male BALB/c mice by tail vein injection. The day after infection (day 0), RLU counts were determined. The mice were first anesthetized by isoflurane inhalation and the RLU count was determined by laying the breast of mouse on the detection hole of the luminometer and measuring light production twice for 3 s. Mice with similar RLU readings were randomly allocated to treatment groups (four mice/group) and individually marked. The treatment groups received: 0.5% CMC-Na alone as negative control; RIF (10 mg/kg) as positive control; **14i** (200 mg/kg). The treatment was administrated once daily by oral gavage for 6 days. On the final day of treatment, animals were sacrificed by cervical dislocation. The removed lungs and spleens were homogenized under sterile conditions in a 2 mL volume of PBS. Finally, RLU was detected for each homogenate.

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CONFLICT OF INTEREST

There are no conflicts of interest to declare.

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SUPPORTING INFORMATION

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