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Design, synthesis, and biological evaluation of *m*-amidophenol derivatives as a new class of antitubercular agents†

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A series of *m*-amidophenol derivatives (6a–6l, 7a–7q, 9a, 9b, 12a–12c, 14 and 15) were designed and synthesized. Their antitubercular activities were evaluated *in vitro* against *M. tuberculosis* strains H37Ra and H37Rv and clinically isolated multidrug-resistant *M. tuberculosis* strains. Ten compounds displayed minimal inhibitory concentrations (MICs) against *M. tuberculosis* H37Ra below 2.5 $\mu\text{g mL}^{-1}$ and **6g** was the most active compound (MIC = 0.625 $\mu\text{g mL}^{-1}$). Compounds **6g** and **7a** also showed potent inhibitory activity against *M. tuberculosis* H37Rv (MIC = 0.39 $\mu\text{g mL}^{-1}$) and several clinically isolated multidrug-resistant *M. tuberculosis* strains (MIC = 0.39–3.125 $\mu\text{g mL}^{-1}$). The compounds did not show inhibitory activity against normal Gram-positive and Gram-negative bacteria. They exhibited low cytotoxicity against HepG2 and RAW264.7 cell lines. The results demonstrated *m*-amidophenol as an attractive scaffold for the development of new antitubercular agents.

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Introduction

Tuberculosis (TB) is a highly infectious disease caused by *Mycobacterium tuberculosis* (Mtb). Today tuberculosis still remains one of the leading causes of human death in developing countries. According to a report of the World Health Organization (WHO), there were an estimated 10.4 million new TB cases worldwide and over 1.6 million people died from TB in 2016. Moreover, the resistance of Mtb to clinical antitubercular agents is a continuing threat. As reported, in 2016 there were 600 000 new cases with resistance to rifampicin, one of the most effective first-line drugs. Among these cases, 490 000 were multidrug-resistant TB (MDR-TB).¹ This situation brought a big challenge for clinical treatment. In the past four decades, only bedaquiline and delamanid had been approved by the Food and Drug Administration (FDA) of the United States and the European Medicines Agency (EMA) for the treatment of MDR-TB.^{2,3} Bedaquiline is an ATP

synthase inhibitor. Delamanid inhibits the mycolic acid synthesis of Mtb. The two drugs are still beset by side effects.^{4,5} Therefore, antitubercular agents with innovative action mechanisms and structural scaffolds are urgently desired.⁶

Mycobacterial enoyl-ACP reductase (InhA) is a validated drug target against Mtb.⁷ Isoniazid (INH), an inhibitor of InhA, is a powerful first-line antitubercular drug.^{8,9} INH is a prodrug that is activated by the catalase-peroxidase KatG to form an isonicotinoyl radical which reacts with NAD to produce an INH–NAD adduct. Unfortunately, the majority of INH-resistant *M. tuberculosis* clinical isolates have mutations in KatG.¹⁰ Thus, direct InhA inhibitors were developed to avoid resistance.^{11,12} In 2015, Manjunatha, Diagana and co-workers found a new class of direct InhA inhibitors, 4-hydroxy-2-pyridones, through unbiased phenotypic screening. Several compounds showed potent bactericidal activity against INH-resistant Mtb strains.¹³ The lead compound NITD-916 (Scheme 1) displayed good oral bioavailability and *in vivo* efficacy in mouse models of Mtb infection. Based on the co-crystal structure, key interactions of 4-hydroxy-2-pyridones with the InhA–NADH complex were identified as H-bonding, π -stacking and hydrophobic interactions. Inspired by the proposed interaction model of NITD-916, we designed and synthesized a class of *m*-amidophenol derivatives (Scheme 1). A number of compounds were found to exert potent inhibitory activity against Mtb H37Ra, Mtb H37Rv and clinically isolated MDR-Mtb strains. In addition, the compounds showed low cytotoxicity and did not inhibit normal Gram-positive and Gram-negative bacteria.

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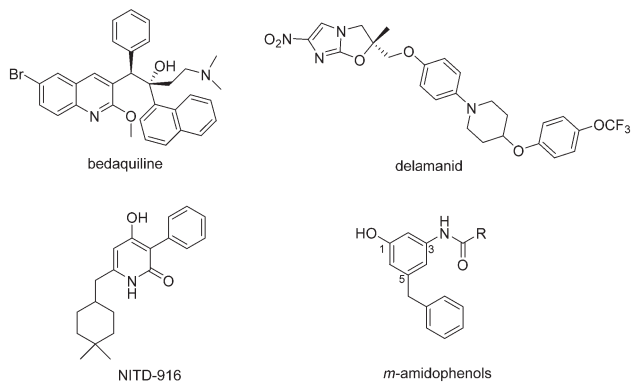
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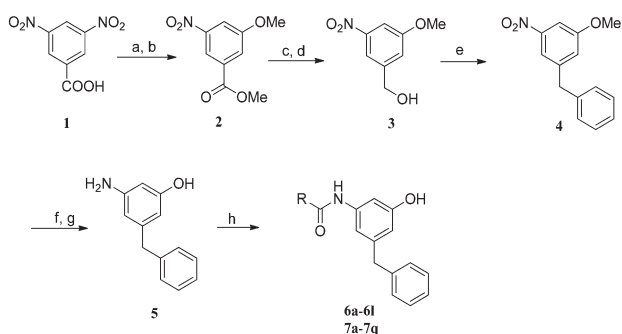
Scheme 1 Structures of antitubercular agents.

Results and discussion

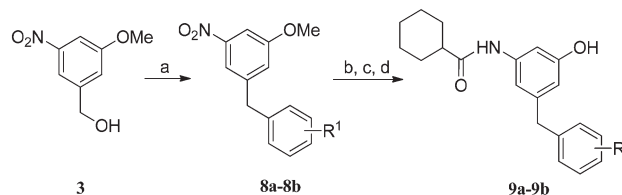
Chemistry

The synthetic pathways of *m*-amidophenol derivatives **6a–6l** and **7a–7q** are illustrated in Scheme 2. The synthesis started from 3,5-dinitrobenzoic acid **1**. Compound **1** was transformed into its methyl ester with thionylchloride in methanol. Then the nucleophilic substitution of the nitro group with lithium methoxide afforded methyl 3-methoxy-5-nitrobenzoate **2**. 3-Methoxy-5-nitrobenzoic acid was obtained by basic hydrolysis of **2**. The reduction of the acid with sodium borohydride yielded (3-methoxy-5-nitrophenyl)-methanol **3**. Friedel-Crafts alkylation of benzene with **3** gave 1-benzyl-3-methoxy-5-nitrobenzene **4**. Demethylation with boron tribromide provided 3-benzyl-5-nitrophenol, which was hydrogenated over Pd/C to provide 3-amino-5-benzylphenol **5**. The *m*-amidophenol derivatives **6a–6l** and **7a–7q** were obtained by the reaction of **5** with different acyl chlorides or by the coupling of **5** with the corresponding carboxylic acids.

The synthesis of compounds **9a–9b** is shown in Scheme 3. Friedel-Crafts reaction of *p*-xylene and mesitylene with compound **3** was achieved using hexafluoroisopropanol (HFIP) as



Scheme 2 Reagents and conditions: a) SOCl₂, CH₃OH, reflux, 4 h, 60%; b) lithium methoxide, anhydrous methanol, reflux, 12 h, 35%; c) NaOH, CH₂Cl₂, CH₃OH, rt, 3 h, 98%; d) NaBH₄, BF₃·OEt₂, THF, 0 °C–rt, 1 h, 99%; e) benzene, CH₂Cl₂, AlCl₃, reflux, 5 h, 52.6%; f) BBr₃, CH₂Cl₂, –40–0 °C, 12 h, 60%; g) H₂, 10% Pd/C, CH₂Cl₂/CH₃OH, 4 h, 99%; h) RCOCl, Et₃N, THF, 0 °C–rt, 50–80% or RCOOH, triphenyl phosphite, toluene. For the R group, see Table 1.



Scheme 3 Reagents and conditions: a) *p*-xylene or mesitylene, HFIP, TfOH, 100 °C, 24 h, 90–96%; b) BBr₃, CH₂Cl₂, –40–0 °C, 12 h, 40–50%; c) H₂, 10% Pd/C, CH₂Cl₂/CH₃OH, 4 h, 99%; d) cyclohexanecarbonyl chloride, Et₃N, THF, 0 °C–rt, 50–80%.

the solvent and trifluoromethanesulfonic acid (TfOH) as the catalyst.¹⁴ Compounds **8a–8b** were obtained in excellent yields. After demethylation, reduction of the nitro group and acylation with cyclohexanecarbonyl chloride, the products **9a–9b** were obtained.

Antitubercular activity against Mtb H37Ra

The antitubercular activities of the compounds were preliminarily screened and evaluated by using a cost-efficient *in vitro* assay against a selectable marker-free avirulent autoluminescent Mtb H37Ra strain.¹⁵ Bacteria growth was conveniently monitored by means of the bioluminescence intensity.

The effect of the 3-amido group

The antitubercular activities of compounds **6a–6l** and **7a–7q** were evaluated against Mtb H37Ra and the MIC values are summarized in Table 1. INH was used as the positive control and DMSO was used as the negative control.

The size and lipophilicity of the R group exert a strong effect on the antitubercular activity. The acetamide derivative **6a** and the trifluoroacetamide derivative **6b** did not show obvious activities. However, the increase in the lipophilicity of the amido group significantly improved the inhibitory activity. Compounds **6c** and **6d** (R = *i*-Pr and *c*-Pr, respectively) showed good inhibitory activity (MIC = 5 μg mL⁻¹). A further increase in antitubercular activity was achieved *via* the introduction of more lipophilic substituents such as *t*-Bu, cyclopentyl, and cyclohexyl. Compound **6g** with a cyclohexyl substituent showed the most potent activity (MIC = 0.625 μg mL⁻¹). The further increase in the lipophilicity and volume of the substituent led to the gradual loss of the inhibitory activity. Compound **6h** with a 4-ethyl-cyclohexyl substituent afforded a lower activity (MIC = 2.5 μg mL⁻¹). Compounds **6i** and **6j** with more bulky 4-*t*-butyl-cyclohexyl and adamantanyl almost lost their inhibitory activity completely. The incorporation of O (**6k**) and N (**6l**) into the cyclohexyl ring resulted in lower activities. These results indicated a hydrophobic pocket binding with the amido group. The size of the pocket can best accommodate a cyclohexyl group or similar groups.

We also found that the benzoamide derivative **7a** showed good inhibitory activity (MIC = 5 μg mL⁻¹). The 4-methyl substitution (**7b**) afforded a 4-fold increase in activity (MIC =

Table 1 *In vitro* antitubercular activity of compounds **6a–6l** and **7a–7q** against Mtb H37Ra

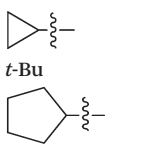
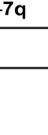
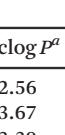
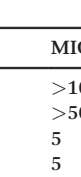
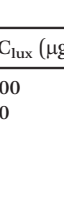
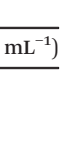
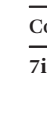

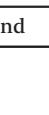

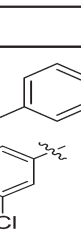
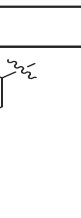


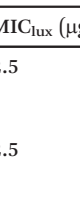

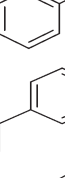
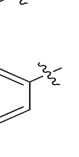
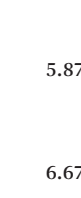




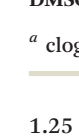
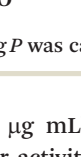
Compound	R	clog <i>P</i> ^a	MIC _{lux} (μg mL ⁻¹)
6a	Me	2.56	>100
6b	CF ₃	3.67	>50
6c	<i>i</i> -Pr	3.39	5
6d		3.14	5
6e	<i>t</i> -Bu	3.79	2.5
6f		4.03	2.5
6g		4.59	0.625
6h		5.64	2.5
6i		6.43	>50
6j		5.22	>50
6k		2.19	6.25
6l		2.20	12.5
7a		4.05	5
7b		4.54	1.25
7c		5.87	2.5
7d		6.67	>50
7e		5.28	5
7f		6.29	>25
7g		5.36	10
7h		4.13	2.5

Table 1 (continued)

Compound	R	clog <i>P</i> ^a	MIC _{lux} (μg mL ⁻¹)
7i		4.96	2.5
7j		4.96	2.5
7k		4.92	5
7l		5.17	5
7m		4.22	>50
7n		3.88	2.5
7o		3.22	10
7p		2.61	10
7q		3.26	5
INH			0.1
DMSO			—

^a clog *P* was calculated using ChemBioDraw Ultra 12.0.

1.25 μg mL⁻¹). 4-*t*-Butyl substitution (**7c**) showed a slightly lower activity (MIC = 2.5 μg mL⁻¹). The introduction of more bulk 4-cyclohexyl (**7d**) led to a loss of activity. The results are commendably consistent with the above observation. The substitution with CF₃ (**7e**, **7f**) and CF₃O (**7g**) exerted a detrimental effect on the activity. Chloro substitution at the 2-, or 3-, or 4-position of the phenyl ring (**7h**, **7i**, **7j**) exhibited a similar efficiency. A 2-fold increase in activity was achieved in comparison with **7a**. The introduction of more than one halogen atom at the phenyl ring (**7k**, **7l**) did not afford a beneficial result. The 4-nitro substitution (**7m**) resulted in a loss of inhibitory activity. The replacement of the benzene ring with heteroaryl rings is applicable. Thiophene-2-carboxamide **7n**, furan-2-carboxamide **7o**, 1,2,3-thiadiazole-5-carboxamide **7p** and 2-chloronicotinamide **7q** are all active against Mtb H37Ra. Among them, thiophene-2-carboxamide **7n** showed the best activity (MIC = 2.5 μg mL⁻¹).

The effect of the 5-substituent

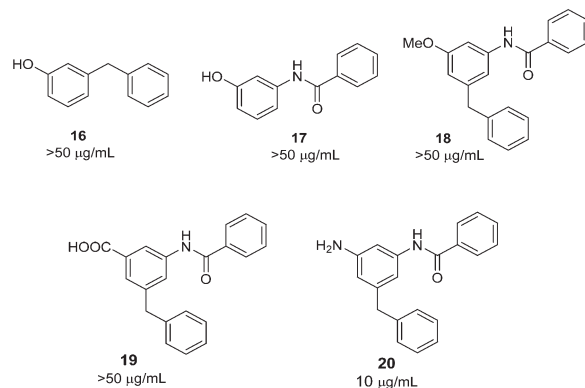
The effect of the 5-substituent was examined and the results are summarized in Table 2. The introduction of methyl substituents to the benzyl group (9a and 9b) resulted in a loss of activity. The replacement of 5-benzyl with methyl (12a), *n*-Pr (12b) and *i*-pr (12c) also led to a loss of antitubercular activity.¹⁶ The results implicated that the existence of the 5-benzyl group is important for antitubercular activity. A π - π interaction is possibly required. However, the binding pocket is relatively small. Even the methyl substitution also hampers the insertion of a benzyl group into the pocket. In addition, the benzyl oxidation product 14 showed a lower antitubercular activity compared to compound 7a. The reduction of 14 provided compound 15, which is completely inactive.¹⁷

The effect of other structural modifications

To verify the importance of 3-amido and 5-benzyl groups, we prepared compounds 16 and 17 (Scheme 4).^{18,19} As expected, both compounds did not show antitubercular activity. The 1-hydroxyl group is also imperative. The methylation of 1-hydroxy (18) led to a loss of activity. Similarly, the replacement of 1-hydroxyl with a carboxylic group (19) and an amino group (20) resulted in the complete loss of or decreased activities.

Structure–activity relationship (SAR) of *m*-amidophenol derivatives

The structure–activity relationship of *m*-amidophenol derivatives is summarized in Scheme 5. The crucial H-bonding interaction of the 1-hydroxyl group with the target is expected. The methylation or the replacement with a carbox-



Scheme 4 The effect of other structural modifications.

ylic group resulted in a loss of antitubercular activity. The 5-benzyl group is rather conservative. The replacement with an alkyl group or the introduction of substituents exerted a detrimental effect on the activity. A small binding pocket and an important π - π interaction are suggested. A 3-amido group is involved in a crucial hydrophobic interaction with the target. The size of the binding pocket is best suitable for a cyclohexyl group.

In vitro inhibitive activity against Mtb H37Rv and MDR-Mtb strains

Compounds 6g and 7a with potent inhibitory activities against H37Ra were selected for further evaluation against Mtb H37Rv and six clinically isolated MDR-Mtb strains. The results are summarized in Table 3. Compounds 6g and 7a showed similar activities against H37Rv and MDR-Mtb

Table 2 *In vitro* antitubercular activity of compounds 9a and 9b, 12a–12c, 14, and 15 against Mtb H37Ra

Compound	R ¹	clog <i>P</i> ^a	MIC _{lux} (µg mL ⁻¹)	Compound	R ²	clog <i>P</i> ^a	MIC _{lux} (µg mL ⁻¹)
9a–9b				12a–12c			
14	—	6.25	>50	12a	Me	4.08	>50
15	—	>50	>50	12b	<i>n</i> -Pr	5.14	>50
DMSO	—	—	—	12c	<i>i</i> -Pr	5.01	>50
				INH			0.1

^a clog *P* was calculated using ChemBioDraw Ultra 12.0.

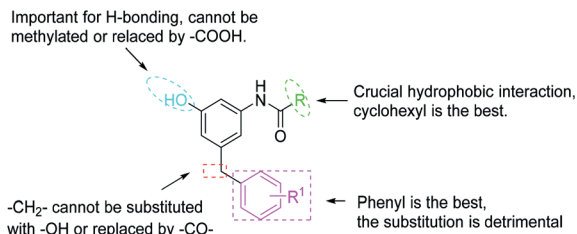
Scheme 5 SAR of *m*-amidophenol derivatives.

Table 3 Inhibitive activity against H37Rv and clinically isolated MDR-Mtb strains

Strains	MIC ($\mu\text{g mL}^{-1}$)		INH	RIF	DMSO
	6g	7a			
H37Rv	0.39	0.39	0.41	0.003	—
P103 ^a	0.39	0.39	—	—	—
P91 ^a	0.39	0.39	—	—	—
R7 ^a	3.125	0.78	—	—	—
P71 ^b	>100	>100	—	—	—
P90 ^a	>100	>100	—	—	—
P98 ^a	>100	>100	—	—	—

^a Resistant to rifampicin and INH. ^b Resistant to rifampicin, INH and pyrazinamide.

strains P103 and P91 ($0.39 \mu\text{g mL}^{-1}$). Compound 7a exhibited better inhibitory activity against MDR-Mtb strain R7 than 6g (MIC $0.78 \mu\text{g mL}^{-1}$ vs. $3.125 \mu\text{g mL}^{-1}$). However, both compounds 6g and 7a did not inhibit MDR-Mtb strains P71, P90 and P98. The reason for the selective inhibition against different MDR-Mtb strains is unclear at present.

Evaluation of antibacterial activity

The antibacterial activity of compounds 6g and 7a was examined against representative Gram-positive bacteria *Staphylococcus aureus* and *Enterococcus faecalis* and Gram-negative bacteria *Escherichia coli*. Amoxicillin and ofloxacin were used as the positive controls and DMSO was used as the negative control. The results are summarized in Table 4. Both 6g and 7a did not show antibacterial activity (MIC $> 50 \mu\text{g mL}^{-1}$) against the tested bacteria. This observation confirmed that the inhibitory activity of 6g and 7a against Mtb is highly ex-

Table 4 Evaluation of antibacterial activity of compounds 6g and 7a

	MIC ($\mu\text{g mL}^{-1}$)				
	6g	7a	Amoxicillin	Ofloxacin	DMSO
<i>Staphylococcus aureus</i>	>50	>50	0.78	0.31	—
<i>Escherichia coli</i>	>50	>50	6.25	1.25	—
<i>Enterococcus faecalis</i>	>50	>50	1.25	—	—

Table 5 Cytotoxicity of compounds 6g and 7a

Entry	IC ₅₀ (μM)	
	HepG2	RAW264.7
6g	>161 (SI > 80)	>323 (SI > 160)
7a	>330 (SI > 20)	>330 (SI > 20)

clusive. Such a property is favorable considering the long treatment course for tuberculosis (typically 12–24 months). The avoidance of inhibition against normal intestinal bacteria is advantageous for antitubercular agents.

Evaluation of cytotoxicity

The cytotoxicity of compounds 6g and 7a was evaluated against HepG2 and RAW264.7 cell lines. The IC₅₀ values are listed in Table 5. Compounds 6g and 7a are almost non-cytotoxic against the two cell lines. Both compounds have a selectivity index (SI = IC₅₀/MIC) of above 20.

3D-QSAR study

For further exploration of the structure–activity relationship, the CoMFA approach was employed on the test compounds to establish 3D-QSAR models. Their conformations were first generated by molecular mechanism-based structural optimization embedded in Tripos Sybyl X2.0 software. Compound 6g was selected as the template for alignment (Fig. 1).

Based on these conformations with the local minimum energies and partial charges assigned using the MMFF94 force field, the CoMFA model was performed with 33 molecules as the training set and 2 molecules as the test set. The best model (CoMFA) yielded a q^2 value of 0.616, an r^2 value of 0.950 and an F value of 102.537 with the optimum number of components (PC) being 5 (Table 6).

Fig. 2 shows a scatter plot of predicted pMIC versus experimental pMIC values of the training set and test set. A contour

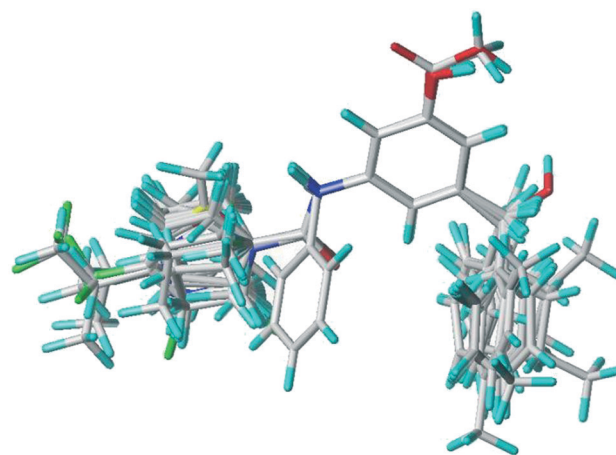
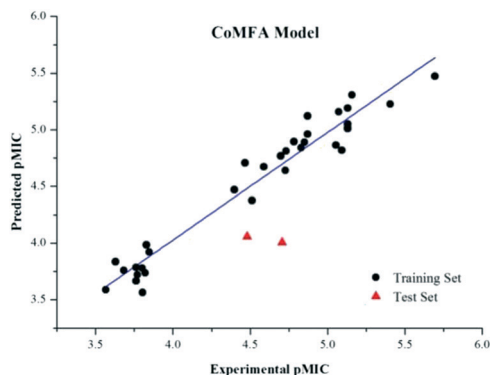


Fig. 1 3D-QSAR structure alignment using compound 6g as the template.

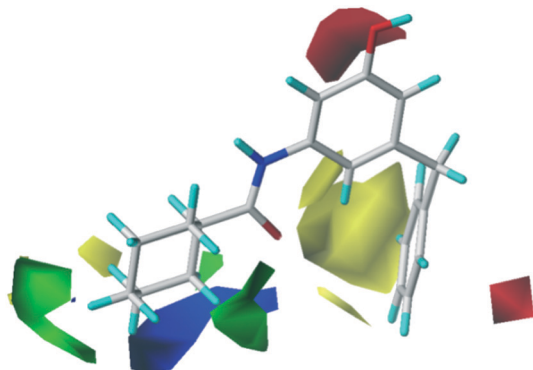
Table 6 The parameters derived from the CoMFA model

Parameters	CoMFA model
q^2	0.616
r^2	0.950
PC	5
F	102.537
Contributions (%)	
Steric	67.6
Electrostatics	32.4

**Fig. 2** A graph of predicted versus experimental pMIC values of the molecules.

map with $r_{\text{pred}}^2 = 0.6758$ provided visual and spatial information for future design and optimization of new compounds with enhanced activities.

The CoMFA contour map of the steric field and electrostatic field is shown in Fig. 3. The steric contour is shown in green (more bulk favored) and yellow (less bulk favored), suggesting that a sterically bulky group is disfavored at the 5-position of the phenyl. For example, compounds **9a** and **9b** containing methyl groups led to the complete loss of inhibitory activity. The green contour in the *o*-position of cyclohexyl indicates that this space is favorable for accommodating a sterically bulky group (for example, compound **7h** with 4-Cl substitution). The electrostatic contour was colored red and blue. The red contour near the 1-position of the phenyl ring

**Fig. 3** The steric and electrostatic field distribution around **6g**.

showed that the electron-withdrawing groups were favored at this position. Compound **7a** with 1-OH and compound **20** with 1-NH₂ exhibited good anti-TB activity. Compound **7b** with 4-CH₃ lies near the blue contour and exhibited good anti-TB activity, while compound **7m** with 4-NO₂ near the blue contour lost inhibitory activity.

Conclusion

We have discovered *m*-amidophenol derivatives as a new class of antitubercular agents. Several compounds showed potent inhibitory activities against Mtb H37Ra, Mtb H37Rv and clinically isolated MDR-Mtb strains. The compounds did not inhibit normal Gram-positive and Gram-negative bacteria. Their inhibition of Mtb is highly exclusive. The compounds showed low cytotoxicity and their selectivity indexes are acceptable. Further studies toward the elucidation of the inhibition mechanism and the development of more potent candidates are currently underway.²⁰

Experimental

Chemistry

¹H NMR and ¹³C NMR spectra were recorded on a Bruker AVANCE 400 or 500 spectrometer. Chemical shifts of protons are reported in parts per million downfield from tetramethylsilane. Peaks are labeled as single (s), broad singlet (br), doublet (d), triplet (t), double doublet (dd), doublet of triplets (dt), or multiplet (m). The high-resolution mass spectra were analyzed using a SHIMADZU LCMS-IT-TOF mass spectrometer. The purity of the synthesized compounds was determined by high-performance liquid chromatography (HPLC) using a TC-C18 column (250 mm × 4.6 mm, 5 μm) and a methanol/water mobile phase (0.50 mL min⁻¹). Melting points were determined in open capillary tubes on an MPA100 Optimelt automated melting point system. All chemicals were purchased from Sigma-Aldrich and Alfa Aesar chemical companies and were used without further purification.

Synthesis of *N*-(3-benzyl-5-hydroxyphenyl)acetamide (**6a**)

To a solution of 3-amino-5-benzylphenol **5** (99.5 mg, 0.5 mmol) and triethylamine (76.3 μL, 0.55 mmol) in THF (2 mL), a solution of acetyl chloride (40 μL, 0.55 mmol) in THF (1 mL) at 0 °C was added slowly. The reaction mixture was stirred for 3 h at room temperature. The reaction was quenched with water (10 mL) and the mixture was extracted with EtOAc (15 mL × 2). The combined organic layer was dried over anhydrous Na₂SO₄ and filtered. After the solvent was removed *in vacuo*, the crude product was purified by column chromatography (petroleum/EtOAc = 20:1–5:1) to afford **6a** as a colorless solid (72 mg, 60%). m.p. 158.5–160.2 °C; ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.72 (bs, 1H, NH), 9.26 (bs, 1H, OH), 7.28 (m, 2H, ArH), 7.19 (m, 3H, ArH), 7.06 (s, 1H, ArH), 6.76 (s, 1H, ArH), 6.29 (s, 1H, ArH), 3.78 (s, 2H, CH₂), 1.98 (s, 3H, CH₃); ¹³C NMR (101 MHz, DMSO-*d*₆) δ 168.59 (CONH), 158.01, 143.00, 141.58, 140.73, 129.20,

128.83, 126.41, 111.12, 110.65, 104.48, 41.75 (CH₂), 24.50 (CH₃); HRMS (ESI) calculated for C₁₅H₁₆NO₂ [M + H]⁺: 242.1176, found: 242.1173. Purity: 98.1% (by HPLC).

Synthesis of *N*-(3-benzyl-5-hydroxyphenyl)-2,2,2-trifluoroacetamide (**6b**)

To a solution of **5** (160 mg, 0.8 mmol) and trifluoroacetic acid (137 mg, 1.2 mmol) in 4 mL toluene, P(OPh)₃ (314 μL, 1.2 mmol) was added. The reaction mixture was stirred at 110 °C for 12 h. After being cooled to room temperature, water (20 mL) was added. The reaction mixture was extracted with ethyl acetate (20 mL × 2). The combined organic layer was dried over anhydrous Na₂SO₄, filtered and evaporated under reduced pressure. The residue was purified by column chromatography over silica gel (petroleum/EtOAc = 4:1) to yield **6b** as a red solid (94 mg, 40%). m.p. 95.8–98.7 °C; ¹H NMR (400 MHz, CD₃OD) δ 7.25 (m, 2H, ArH), 7.16 (m, 3H, ArH), 7.10 (m, 1H, ArH), 6.91 (m, 1H, ArH), 6.50 (m, 1H, ArH), 3.87 (s, 2H, CH₂); ¹³C NMR (101 MHz, CD₃OD) δ 157.68, 155.26 (q, ²J = 37.2 Hz, CONH), 143.63, 140.71, 137.19, 128.58, 128.08, 116.04 (q, ¹J = 286 Hz), 125.78, 113.11, 112.44, 105.77, 41.33 (CH₂); HRMS (ESI) calculated for C₁₅H₁₂NO₂F₃ [M - H]⁻: 294.0747, found: 294.0746. Purity: 98.9% (by HPLC).

N-(3-Benzyl-5-hydroxyphenyl)-isobutyramide (**6c**)

The compound was synthesized *via* a procedure similar to that of **6a**. Orange solid, yield 86%, m.p. 169.8–171.6 °C; ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.59 (bs, 1H, NH), 9.23 (bs, 1H, OH), 7.31–7.24 (m, 2H), 7.22–7.12 (m, 3H), 7.04 (m, 1H), 6.84 (m, 1H), 6.29 (m, 1H), 3.78 (m, 2H, CH₂), 2.54 (m, 1H, CH), 1.06 (s, 3H, CH₃), 1.05 (s, 3H, CH₃); ¹³C NMR (101 MHz, DMSO-*d*₆) δ: 175.50 (CONH), 157.98, 142.93, 141.60, 140.85, 129.18, 128.82, 126.40, 111.10, 110.92, 104.69, 41.81 (CH₂), 35.33 (CH), 19.97 (CH₃); HRMS (ESI) calculated for C₁₇H₁₉NO₂ [M + H]⁺: 270.1489, found: 270.1491. Purity: 96.2% (by HPLC).

N-(3-Benzyl-5-hydroxyphenyl)cyclopropanecarboxamide (**6d**)

The compound was synthesized *via* a procedure similar to that of **6a**. Orange solid, yield 63%, m.p. 163.8–165.3 °C; ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.95 (bs, 1H, NH), 9.24 (bs, 1H, OH), 7.28 (m, 2H), 7.23–7.14 (m, 3H), 7.01 (m, 1H), 6.82 (m, 1H), 6.29 (m, 1H), 3.78 (s, 2H, CH₂), 1.73 (dq, *J* = 7.6, 5.0 Hz, 1H, CH), 0.82–0.64 (m, 4H); ¹³C NMR (101 MHz, DMSO-*d*₆) δ 171.86 (CONH), 158.02, 143.01, 141.58, 140.76, 129.19, 128.82, 126.40, 111.09, 110.74, 104.55, 41.79 (ArCH₂Ar), 14.94 (cyclopropanyl-CH), 7.47 (2CH₂); HRMS (ESI) calculated for C₁₇H₁₇NO₂ [M + H]⁺: 268.1332, found: 268.1332. Purity: 98.456% (by HPLC).

N-(3-Benzyl-5-hydroxyphenyl)pivalamide (**6e**)

The compound was synthesized *via* a procedure similar to that of **6b**. Yellow solid, yield 52%, m.p. 142.6–144.3 °C; ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.20 (bs, 1H, NH), 8.98 (bs,

1H, OH), 7.35–7.25 (m, 2H), 7.21 (d, *J* = 5.1 Hz, 3H), 7.09 (m, 1H), 6.93 (m, 1H), 6.32 (m, 1H), 3.80 (s, 2H, CH₂), 1.19 (s, 9H, CH₃); ¹³C NMR (101 MHz, CD₃OD) δ 178.41 (CONH), 157.33, 142.91, 141.06, 139.34, 128.55, 128.00, 125.65, 113.01, 111.68, 106.23, 41.47 (CH₂), 39.11 (CMe₃), 26.39 (CH₃); HRMS (ESI) calculated for C₁₈H₂₁NO₂ [M + H]⁺: 284.1645, found: 284.1649. Purity: 98.8% (by HPLC).

N-(3-Benzyl-5-hydroxyphenyl)cyclopentanecarboxamide (**6f**)

The compound was synthesized *via* a procedure similar to that of **6a**. Orange solid, yield 70%, m.p. 182.4–184.3 °C; ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.62 (bs, 1H, NH), 9.22 (bs, 1H, OH), 7.34–7.24 (m, 2H), 7.18 (m, 3H), 7.04 (s, 1H), 6.84 (m, 1H), 6.28 (m, 1H), 3.78 (s, 2H, ArCH₂Ar), 2.78–2.65 (m, 1H, cyclopentyl-CH), 1.86–1.71 (m, 2H), 1.73–1.58 (m, 4H), 1.52 (m, 2H); ¹³C NMR (101 MHz, DMSO-*d*₆) δ 174.67 (CONH), 157.98, 142.93, 141.61, 140.88, 129.18, 128.82, 126.39, 111.07, 110.88, 104.65, 45.72 (cyclopentyl-CH), 41.81 (ArCH₂Ar), 30.54 (cyclopentyl-CH₂), 26.14 (cyclopentyl-CH₂); HRMS (ESI) calculated for C₁₉H₂₁NO₂ [M + H]⁺: 296.1645, found: 296.1648. Purity: 97.9% (by HPLC).

N-(3-Benzyl-5-hydroxyphenyl)cyclohexanecarboxamide (**6g**)

The compound was synthesized *via* a procedure similar to that of **6a**. White solid, yield 49%, m.p. 200.9–202.8 °C; ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.59 (bs, 1H, NH), 9.24 (bs, 1H, OH), 7.28 (m, 2H), 7.19 (m, 3H), 7.04 (m, 1H), 6.84 (m, 1H), 6.28 (m, 1H), 3.77 (s, 2H, ArCH₂Ar), 2.27 (t, *J* = 11.4 Hz, 1H), 1.73 (d, *J* = 9.2 Hz, 4H), 1.63 (d, *J* = 9.6 Hz, 1H), 1.37 (m, 2H), 1.30–1.14 (m, 3H); ¹³C NMR (101 MHz, DMSO-*d*₆) δ 174.62 (CONH), 157.96, 142.93, 141.62, 140.91, 129.18, 128.82, 126.39, 111.02, 110.82, 104.55, 45.31 (cyclohexyl-CH), 41.80 (ArCH₂Ar), 29.61 (cyclohexyl-CH₂), 25.88 (cyclohexyl-CH₂), 25.71 (cyclohexyl-CH₂); HRMS (ESI) calculated for C₂₀H₂₄NO₂ [M + H]⁺: 310.1802, found: 310.1800. Purity: 97.1% (by HPLC).

N-(3-Benzyl-5-hydroxyphenyl)-4-ethylcyclohexanecarboxamide (**6h**)

The compound was prepared *via* a procedure similar to that of **6b**. White solid, yield 69%, m.p. 201.4–203.3 °C; ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.57 (bs, 1H, NH), 9.21 (bs, 1H, OH), 7.28 (m, 2H), 7.17 (m, 3H), 7.03 (m, 1H), 6.84 (m, 1H), 6.28 (m, 1H), 3.77 (s, 2H, ArCH₂Ar), 2.21 (dd, *J* = 16.5, 7.7 Hz, 1H), 1.78 (d, *J* = 11.2 Hz, 4H), 1.45–1.31 (m, 2H), 1.20 (dt, *J* = 14.2, 7.3 Hz, 2H), 1.11 (m, 1H), 0.86 (m, 5H); ¹³C NMR (101 MHz, DMSO-*d*₆) δ 174.64 (CONH), 157.96, 142.91, 141.61, 140.90, 129.18, 128.81, 126.39, 111.04, 110.86, 104.61, 45.51 (cyclohexyl-CH), 41.81 (ArCH₂Ar), 38.72 (–CH₂CH₃), 32.09 (cyclohexyl-CH₂), 29.91 (cyclohexyl-CH₂), 29.55 (cyclohexyl-CH₂), 11.74 (CH₃); HRMS (ESI) calculated for C₂₂H₂₇NO₂ [M + H]⁺: 338.2115, found: 338.2117. Purity: 98.8% (by HPLC).

N-(3-Benzyl-5-hydroxyphenyl)-4-(*tert*-butyl)-cyclohexanecarboxamide (6i)

This compound was prepared *via* a procedure similar to that of **6b**. White solid, yield 76%, m.p. 227.2–229.0 °C; ^1H NMR (400 MHz, DMSO- d_6) δ 9.56 (bs, 1H, NH), 9.21 (bs, 1H, OH), 7.32–7.23 (m, 2H), 7.17 (m, 3H), 7.02 (m, 1H), 6.84 (m, 1H), 6.27 (m, 1H), 3.77 (s, 2H, ArCH₂Ar), 2.29–2.11 (m, 1H), 1.80 (m, 4H), 1.37 (m, 2H), 1.05–0.91 (m, 3H), 0.84 (s, 9H, *t*-Bu); ^{13}C NMR (101 MHz, DMSO- d_6) δ 174.67 (CONH), 157.96, 142.91, 141.61, 140.88, 129.17, 128.81, 126.38, 111.05, 110.87, 104.61, 47.30, 45.47, 41.82 (ArCH₂Ar), 32.62, 30.00, 27.80, 26.66; HRMS (ESI) calculated for C₂₄H₃₁NO₂ [M + H]⁺: 366.2428, found: 366.2445. Purity: 98.6% (by HPLC).

N-(3-Benzyl-5-hydroxyphenyl)adamantane-1-carboxamide (6j)

The compound was prepared *via* a procedure similar to that of **6a**. White solid, yield 31%, m.p. 183.5–185.4 °C; ^1H NMR (400 MHz, CD₃OD) δ 7.23 (m, 2H), 7.15 (m, 3H), 7.00 (m, 1H), 6.83 (m, 1H), 6.37 (m, 1H), 3.79 (m, 2H, ArCH₂Ar), 2.01 (s, 3H), 1.94 (m, 6H), 1.75 (s, 6H); ^{13}C NMR (101 MHz, CD₃-OD) δ 177.88 (CONH), 157.31, 142.89, 141.07, 139.28, 128.55, 128.01, 125.65, 112.99, 111.64, 106.18, 41.48 (ArCH₂Ar), 41.26, 38.56, 36.13, 28.31; HRMS (ESI) calculated for C₂₄H₂₇NO₂ [M + H]⁺: 362.2115, found: 362.2118. Purity: 96.6% (by HPLC).

N-(3-Benzyl-5-hydroxyphenyl)tetrahydro-2H-pyran-4-carboxamide (6k)

The compound was synthesized *via* a procedure similar to that of **6a**. White solid, yield 63%, m.p. 151.2–152.6 °C; ^1H NMR (400 MHz, CD₃OD) δ 7.30–7.21 (m, 1H), 7.16 (m, 1H), 7.02 (m, 1H), 6.79 (m, 1H), 6.38 (m, 1H), 3.98 (dd, J = 11.4, 2.6 Hz, 2H), 3.84 (s, 2H, ArCH₂Ar), 3.45 (td, J = 11.7, 2.1 Hz, 2H), 2.57 (tt, J = 11.4, 4.0 Hz, 1H), 1.89–1.67 (m, 4H); ^{13}C NMR (101 MHz, DMSO- d_6) δ 173.29 (CONH), 157.98, 142.99, 141.58, 140.73, 129.19, 128.83, 126.40, 111.20, 110.91, 104.66, 66.87 (CH₂O⁻), 42.19, 41.79, 29.33 (CHCO); HRMS (ESI) calculated for C₁₉H₂₁NO₃ [M + H]⁺: 312.1594, found: 312.1602. Purity: 97.3% (by HPLC).

N-(3-Benzyl-5-hydroxyphenyl)morpholine-4-carboxamide (6l)

The compound was synthesized *via* a procedure similar to that of **6a**. White solid, yield 39%, m.p. 155.6–157.0 °C; ^1H NMR (400 MHz, DMSO- d_6) δ 9.11 (bs, 1H, NH), 8.32 (bs, 1H, OH), 7.28 (m, 2H), 7.22–7.15 (m, 3H), 6.87 (m, 1H), 6.72 (m, 1H), 6.21 (m, 1H), 3.76 (s, 2H, ArCH₂Ar), 3.59–3.55 (t, J = 4 Hz, 4H, CH₂), 3.40–3.35 (t, J = 1 Hz, 4H, CH₂); ^{13}C NMR (101 MHz, DMSO- d_6) δ 157.82, 155.56, 142.49, 141.80, 141.74, 129.16, 128.79, 126.35, 111.40, 110.08, 105.09, 66.48 (CH₂O), 44.68 (CH₂N), 41.89 (ArCH₂Ar); HRMS (ESI) calculated for C₁₈H₂₀N₂O₃ [M + H]⁺: 313.1547, found: 313.1549. Purity: 97.1% (by HPLC).

N-(3-Benzyl-5-hydroxyphenyl)benzamide (7a)

The compound was synthesized *via* a procedure similar to that of **6a**. White solid, yield 52%, m.p. 215.8–217.6 °C; ^1H NMR (400 MHz, DMSO- d_6) δ 10.02 (bs, 1H, NH), 9.29 (bs, 1H, OH), 7.94–7.88 (m, 1H), 7.59–7.53 (m, 1H), 7.50 (m, 1H), 7.29 (m, 1H), 7.20 (m, 2H), 7.06 (m, 1H), 6.37 (m, 1H), 3.83 (s, 2H, ArCH₂Ar); ^{13}C NMR (101 MHz, DMSO- d_6) 165.90 (CONH), 157.97, 142.91, 141.60, 140.59, 135.60, 131.86, 129.20, 128.84, 128.75, 128.09, 126.42, 112.18, 111.85, 105.90, 41.86 (ArCH₂Ar); HRMS (ESI) calculated for C₂₀H₁₇NO₂ [M + H]⁺: 304.1332, found: 304.1332. Purity: 98.7% (by HPLC).

N-(3-Benzyl-5-hydroxyphenyl)-4-methylbenzamide (7b)

The compound was synthesized *via* a procedure similar to that of **6a**. Light red solid, yield 64%, m.p. 184.5–186.7 °C; ^1H NMR (400 MHz, DMSO- d_6) δ 9.96 (bs, 1H, NH), 9.32 (bs, 1H, OH), 7.83 (d, J = 8.1 Hz, 2H), 7.30 (t, J = 7.7 Hz, 4H), 7.20 (m, 4H), 7.05 (s, 1H), 6.36 (s, 1H), 3.82 (s, 2H, ArCH₂Ar), 2.37 (s, 3H, CH₃); ^{13}C NMR (101 MHz, DMSO- d_6) δ 165.69 (CONH), 157.93, 142.89, 141.89, 141.63, 140.66, 132.66, 129.29, 129.20, 128.85, 128.14, 126.42, 112.10, 111.70, 105.80, 41.85 (ArCH₂-Ar), 21.46 (CH₃); HRMS (ESI) calculated for C₂₁H₁₉NO₂ [M + H]⁺: 318.1489, found: 318.1488. Purity: 99.2% (by HPLC).

N-(3-Benzyl-5-hydroxyphenyl)-4-(*tert*-butyl)benzamide (7c)

The compound was synthesized *via* a procedure similar to that of **6a**. White solid, yield 81%, m.p. 178.3–179.3 °C; ^1H NMR (400 MHz, DMSO- d_6) δ : 9.99 (bs, 1H, NH), 9.33 (bs, 1H, OH), 7.85 (d, J = 7.9 Hz, 2H), 7.51 (d, J = 8.1 Hz, 2H), 7.51 (d, J = 8.1 Hz, 2H), 7.30 (m, 2H), 7.20 (m, 4H), 7.07 (m, 1H), 6.36 (m, 1H), 3.83 (s, 2H, ArCH₂Ar), 1.31 (s, 9H, *t*-Bu); ^{13}C NMR (101 MHz, DMSO- d_6) δ 165.83 (CONH), 157.93, 154.72, 142.90, 141.63, 140.68, 132.87, 129.20, 128.85, 127.97, 126.42, 125.54, 112.03, 111.69, 105.72, 41.84 (ArCH₂Ar), 35.12, 31.41 (CH₃); HRMS (ESI) calculated for C₂₄H₂₅NO₂ [M + H]⁺: 360.1958, found: 360.1954. Purity: 99.5% (by HPLC).

N-(3-Benzyl-5-hydroxyphenyl)-4-cyclohexylbenzamide (7d)

The compound was synthesized *via* a procedure similar to that of **6b**. Yellow solid, yield 49%, m.p. 243.8–245.6 °C; ^1H NMR (400 MHz, DMSO- d_6) δ : 9.97 (bs, 1H, NH), 9.31 (bs, 1H, OH), 7.83 (d, J = 8.3 Hz, 2H), 7.34 (d, J = 8.3 Hz, 2H), 7.29 (m, 2H), 7.24–7.16 (m, 4H), 7.05 (s, 1H), 6.35 (s, 1H), 3.82 (s, 2H, ArCH₂Ar), 2.58 (m, 1H, cyclohexyl-CH), 1.80 (m, 4H), 1.71 (m, 1H), 1.42 (m, 4H), 1.25 (m, 1H); ^{13}C NMR (101 MHz, DMSO- d_6) δ 165.83 (CONH), 157.93, 151.67, 142.88, 141.62, 140.70, 133.23, 129.20, 128.84, 128.21, 127.05, 126.42, 112.01, 111.67, 105.71, 44.16, 41.84 (ArCH₂Ar), 34.18, 26.73, 26.00; HRMS (ESI) calculated for C₂₆H₂₇NO₂ [M + H]⁺: 386.2115, found: 386.2120. Purity: 99.8% (by HPLC).

N-(3-Benzyl-5-hydroxyphenyl)-4-(trifluoromethyl)benzamide (7e)

The compound was synthesized *via* a procedure similar to that of **6a**. White solid, yield 86%, m.p. 177.6–178.5 °C; ^1H

NMR (400 MHz, DMSO- d_6) δ 10.26 (bs, 1H, NH), 9.36 (bs, 1H, OH), 8.10 (d, J = 8.1 Hz, 2H), 7.88 (d, J = 8.3 Hz, 2H), 7.30 (m, 2H), 7.20 (m, 4H), 7.05 (m, 1H), 6.40 (m, 1H), 3.84 (s, 2H, ArCH₂Ar); ¹³C NMR (101 MHz, DMSO- d_6) δ 164.73, 158.00, 143.08, 141.55, 140.24, 139.37, 131.71 (q, ² J = 31.8 Hz), 129.21, 129.04, 128.86, 126.44, 125.76 (q, ³ J = 3.4 Hz), 124.40 (q, ¹ J = 270 Hz), 112.16, 112.11, 105.84, 41.79 (ArCH₂Ar); HRMS (ESI) calculated for C₂₁H₁₆NO₂F₃ [M + H]⁺: 372.1206, found: 372.1208. Purity: 98.5% (by HPLC).

N-(3-Benzyl-5-hydroxyphenyl)-3,5-bis(trifluoromethyl)-benzamide (7f)

The compound was synthesized *via* a procedure similar to that of 6a. White solid, yield 48%, m.p. 167.9–169.8 °C; ¹H NMR (400 MHz, DMSO- d_6) δ 10.48 (bs, 1H, NH), 9.46 (bs, 1H, OH), 8.58 (s, 1H), 8.34 (s, 1H), 7.30 (m, 1H), 7.21 (m, 4H), 7.02 (s, 1H), 6.45 (s, 1H), 3.86 (s, 1H, ArCH₂Ar); ¹³C NMR (101 MHz, DMSO- d_6) δ 162.82 (CONH), 158.05, 143.16, 141.51, 139.89, 137.69, 130.86 (q, ² J = 33.4 Hz), 129.21, 129.01 (q, ⁴ J = 1 Hz), 128.88, 126.47, 125.44 (q, ³ J = 3 Hz), 123.60 (q, ¹ J = 272 Hz), 112.50, 112.26, 106.08, 41.76 (ArCH₂Ar); HRMS (ESI) calculated for C₂₂H₁₆NO₂F₆ [M + H]⁺: 440.1080, found: 440.1092. Purity: 96.6% (by HPLC).

N-(3-Benzyl-5-hydroxyphenyl)-4-(trifluoromethoxy)benzamide (7g)

The compound was synthesized *via* a procedure similar to that of 6a. White solid, yield 80%, m.p. 129.3–131.3 °C; ¹H NMR (400 MHz, DMSO- d_6) δ 10.15 (bs, 1H, NH), 9.34 (bs, 1H, OH), 8.08–7.96 (m, 2H), 7.50 (d, J = 8.1 Hz, 2H), 7.30 (t, J = 7.4 Hz, 2H), 7.25–7.15 (m, 4H), 7.04 (s, 1H), 6.39 (s, 1H), 3.84 (s, 2H, ArCH₂Ar); ¹³C NMR (101 MHz, DMSO- d_6) δ 164.82 (CONH), 157.91, 150.84, 143.11, 141.53, 140.28, 134.61, 130.46, 129.17, 128.87, 126.46, 121.09, 120.43 (q, ¹ J = 256 Hz), 112.14, 112.03, 105.83, 41.77 (ArCH₂Ar); HRMS (ESI) calculated for C₂₁H₁₆NO₃F₃ [M + H]⁺: 386.1010, found: 386.1015. Purity: 99.6% (by HPLC).

N-(3-Benzyl-5-hydroxyphenyl)-2-chlorobenzamide (7h)

The compound was synthesized *via* a procedure similar to that of 6a. White solid, yield 52%, m.p. 159.2–161.3 °C; ¹H NMR (400 MHz, DMSO- d_6) δ 10.29 (bs, 1H, NH), 9.34 (bs, 1H, OH), 7.57–7.45 (m, 3H), 7.42 (m, 1H), 7.29 (m, 2H), 7.19 (m, 3H), 7.15 (m, 1H), 6.98 (m, 1H), 6.98 (m, 1H), 6.37 (m, 1H), 3.82 (s, 1H, ArCH₂Ar); ¹³C NMR (101 MHz, DMSO- d_6) δ 163.87 (CONH), 158.12, 150.82, 146.89, 143.35, 141.46, 140.08, 138.59, 133.79, 129.23, 128.87, 126.46, 123.57, 112.20, 111.27, 105.05, 41.72 (ArCH₂Ar); HRMS (ESI) calculated for C₂₀H₁₇NO₂Cl [M + H]⁺: 338.0942, found: 338.0942. Purity: 99.9% (by HPLC).

N-(3-Benzyl-5-hydroxyphenyl)-4-chlorobenzamide (7i)

The compound was synthesized *via* a procedure similar to that of 6a. Red solid, yield 62%, m.p. 191.6–192.8 °C; ¹H

NMR (500 MHz, DMSO- d_6) δ 10.12 (bs, 1H, NH), 9.36 (bs, 1H, OH), 7.94 (d, J = 8.3 Hz, 2H), 7.58 (d, J = 8.3 Hz, 2H), 7.30 (m, 2H), 7.25–7.16 (m, 4H), 7.04 (s, 1H), 6.38 (s, 1H), 3.83 (s, 2H, ArCH₂Ar); ¹³C NMR (101 MHz, DMSO- d_6) δ 164.77 (CONH), 157.97, 142.98, 141.56, 140.38, 136.74, 134.25, 130.06, 129.20, 128.85, 128.83, 126.43, 112.17, 112.00, 105.91, 41.83 (ArCH₂Ar); HRMS (ESI) calculated for C₂₀H₁₆NO₂Cl [M + H]⁺: 338.0942, found: 338.0940. Purity: 99.3% (by HPLC).

N-(3-Benzyl-5-hydroxyphenyl)-3-chlorobenzamide (7j)

The compound was synthesized *via* a procedure similar to that of 6a. Red solid, yield 74%, m.p. 167.2–169.1 °C; ¹H NMR (500 MHz, DMSO- d_6) δ 10.16 (bs, 1H, NH), 9.37 (bs, 1H, OH), 7.96 (s, 1H), 7.87 (d, J = 7.7 Hz, 1H), 7.64 (d, J = 8.0 Hz, 1H), 7.54 (m, 1H), 7.33–7.25 (m, 2H), 7.20 (m, 4H), 7.04 (s, 1H), 6.39 (s, 1H), 3.83 (s, 2H, ArCH₂Ar); ¹³C NMR (101 MHz, DMSO- d_6) δ 164.38 (CONH), 157.98, 143.00, 141.56, 140.29, 137.51, 133.62, 131.71, 130.77, 129.20, 128.85, 127.86, 126.92, 126.44, 112.18, 112.10, 105.92, 41.82 (ArCH₂Ar); HRMS (ESI) calculated for C₂₀H₁₆NO₂Cl [M + H]⁺: 336.0797, found: 336.0797. Purity: 98.7% (by HPLC).

N-(3-Benzyl-5-hydroxyphenyl)-2,4-dichlorobenzamide (7k)

The compound was synthesized *via* a procedure similar to that of 6a. White solid, yield 55%, m.p. 130.2–132.0 °C; ¹H NMR (400 MHz, CD₃OD) δ 7.55 (d, J = 1.9 Hz, 1H), 7.49 (d, J = 8.2 Hz, 1H), 7.41 (dd, J = 8.2, 1.9 Hz, 1H), 7.29–7.22 (m, 2H), 7.22–7.12 (m, 5H), 6.92 (s, 1H), 3.87 (s, 2H, ArCH₂Ar); ¹³C NMR (101 MHz, CD₃OD) δ 165.70 (CONH), 157.48, 143.41, 140.91, 139.02, 135.95, 135.26, 131.76, 129.69, 129.37, 128.57, 128.08, 127.14, 125.75, 112.12, 111.96, 105.11, 41.43 (ArCH₂Ar); HRMS (ESI) calculated for C₂₀H₁₅NO₂Cl₂ [M + H]⁺: 372.0553, found: 372.0561. Purity: 99.1% (by HPLC).

N-(3-Benzyl-5-hydroxyphenyl)-3-chloro-4-fluorobenzamide (7l)

The compound was synthesized *via* a procedure similar to that of 6a. White solid, yield 43%, m.p. 159.3–160.9 °C; ¹H NMR (400 MHz, CD₃OD) δ 8.02 (d, J = 7.0 Hz, 1H), 7.92–7.80 (m, 1H), 7.33 (t, J = 8.8 Hz, 1H), 7.25 (m, 2H), 7.21–7.10 (m, 4H), 6.95 (s, 1H), 6.44 (s, 1H), 3.86 (s, 2H, ArCH₂Ar); ¹³C NMR (101 MHz, CD₃OD) δ 164.79 (CONH), 159.93 (d, ¹ J = 253.0 Hz), 157.51, 143.22, 140.96, 139.17, 132.49 (d, ⁴ J = 3.7 Hz), 130.10, 128.58, 128.11, 128.03, 125.69, 120.73 (d, ² J = 18.2 Hz), 116.35 (d, ² J = 21.9 Hz), 112.65, 112.06, 105.86, 41.45 (ArCH₂Ar); HRMS (ESI) calculated for C₂₀H₁₅NO₂FCl [M + H]⁺: 356.0848, found: 356.0845. Purity: 99.3% (by HPLC).

N-(3-Benzyl-5-hydroxyphenyl)-4-nitrobenzamide (7m)

The compound was synthesized *via* a procedure similar to that of 6a. Yellow solid, yield 82%, m.p. 205.9–207.6 °C; ¹H NMR (400 MHz, DMSO- d_6) δ 10.38 (bs, 1H, NH), 9.42 (bs, 1H, OH), 8.34 (d, J = 8.8 Hz, 2H), 8.14 (d, J = 8.8 Hz, 2H), 7.30 (m, 2H), 7.21 (m, 4H), 7.05 (s, 1H), 6.41 (s, 1H), 3.84 (s, 2H, ArCH₂Ar); ¹³C NMR (101 MHz, DMSO- d_6) δ 164.24 (CONH),

158.01, 149.52, 143.13, 141.52, 141.22, 140.12, 129.66, 129.21, 128.87, 126.46, 123.93, 112.31, 112.12, 105.86, 41.78 (ArCH₂-Ar); HRMS (ESI) calculated for C₂₀H₁₆N₂O₄ [M + H]⁺: 349.1183, found: 349.1190. Purity: 98.3% (by HPLC).

N-(3-Benzyl-5-hydroxyphenyl)thiophene-2-carboxamide (7n)

The compound was synthesized *via* a procedure similar to that of 6a. White solid, yield 61%, m.p. 180.6–182.3 °C; ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.01 (bs, 1H, NH), 9.34 (bs, 1H, OH), 7.99 (d, *J* = 3.3 Hz, 1H), 7.82 (d, *J* = 4.8 Hz, 1H), 7.36–7.25 (m, 2H), 7.20 (m, 4H), 7.16 (s, 1H), 6.99 (s, 1H), 6.38 (s, 1H), 3.83 (s, 2H, ArCH₂Ar); ¹³C NMR (101 MHz, DMSO-*d*₆) δ 160.21 (CONH), 157.99, 143.02, 141.56, 140.74, 140.12, 132.15, 129.42, 129.20, 128.86, 128.45, 126.44, 112.10, 111.93, 105.87, 41.81 (ArCH₂Ar); HRMS (ESI) calculated for C₁₈H₁₅NO₂S [M + H]⁺: 310.0896, found: 310.0892. Purity: 97.2% (by HPLC).

N-(3-Benzyl-5-hydroxyphenyl)furan-2-carboxamide (7o)

The compound was synthesized *via* a procedure similar to that of 6a. White solid, yield 46%, m.p. 193.9–195.5 °C; ¹H NMR (400 MHz, CD₃OD) δ 7.70 (s, 1H), 7.30–7.23 (m, 2H), 7.21 (m, 3H), 7.19–7.12 (m, 2H), 6.95 (s, 1H), 6.61 (m, 1H), 6.43 (s, 1H), 3.88 (s, 2H, ArCH₂Ar); ¹³C NMR (126 MHz, DMSO-*d*₆) δ 157.95 (CONH), 156.55, 148.03, 146.08, 142.99, 141.55, 139.92, 129.21, 128.85, 126.43, 114.93, 112.49, 112.07, 111.87, 105.80, 41.80 (ArCH₂Ar); HRMS (ESI) calculated for C₁₈H₁₅NO₃ [M + H]⁺: 294.1125, found: 294.1118. Purity: 97.8% (by HPLC).

N-(3-Benzyl-5-hydroxyphenyl)-4-methyl-1,2,3-thiadiazole-5-carboxamide (7p)

The compound was synthesized *via* a procedure similar to that of 6b. Yellow solid, yield 44%, m.p. 134.1–135.9 °C; ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.52 (bs, 1H, NH), 9.43 (bs, 1H, OH), 7.29 (m, 2H), 7.22 (m, 3H), 7.11 (s, 1H), 6.93 (s, 1H), 6.43 (s, 1H), 3.84 (s, 2H, ArCH₂Ar), 2.78 (s, 3H, CH₃); ¹³C NMR (101 MHz, CD₃OD) δ 159.28 (CONH), 158.18, 157.64, 144.18, 143.49, 140.84, 138.69, 128.58, 128.07, 125.75, 112.49, 112.09, 105.40, 41.40 (ArCH₂Ar), 12.01 (CH₃); HRMS (ESI) calculated for C₁₇H₁₅N₃O₂S [M + H]⁺: 326.0958, found: 326.0956. Purity: 98.5% (by HPLC).

N-(3-Benzyl-5-hydroxyphenyl)-2-chloronicotinamide (7q)

The compound was synthesized *via* a procedure similar to that of 6a. White solid, yield 48%, m.p. 157.6–159.3 °C; ¹H NMR (400 MHz, DMSO-*d*₆) δ: 10.42 (bs, 1H, NH), 9.39 (bs, 1H, OH), 8.51 (d, *J* = 4.7 Hz, 1H), 8.02 (d, *J* = 7.4 Hz, 1H), 7.54 (dd, *J* = 7.3, 4.9 Hz, 1H), 7.30 (m, 1H), 7.21 (m, 1H), 7.14 (s, 1H), 6.94 (s, 1H), 6.40 (s, 1H), 3.84 (s, 1H, ArCH₂Ar); ¹³C NMR (101 MHz, DMSO-*d*₆) δ 163.87 (CONH), 158.12, 150.82, 146.89, 143.35, 141.46, 140.08, 138.59, 133.79, 129.23, 128.87, 126.46, 123.57, 112.20, 111.27, 105.05, 41.72 (ArCH₂Ar);

HRMS (ESI) calculated for C₁₉H₁₆N₂O₂Cl [M + H]⁺: 339.0895, found: 339.0896. Purity: 98.9% (by HPLC).

Synthesis of *N*-(3-(2,5-dimethylbenzyl)-5-hydroxyphenyl)-cyclohexanecarboxamide (9a)

A solution of (3-methoxy-5-nitrophenyl) methanol 3 (460 mg, 2.5 mmol), *p*-xylene (1.5 mL, 12.5 mmol), TfOH (38 mg, 0.25 mmol) and hexafluoroisopropanol (5 mL) in a 10 mL glass pressure tube was stirred at 100 °C for 24 h. After being cooled to room temperature, water (50 mL) was added. The reaction mixture was extracted with EtOAc (50 mL × 2). The combined organic layer was dried over anhydrous Na₂SO₄, filtered and evaporated under reduced pressure. The residue was purified by flash column chromatography over silica (petroleum ether/EtOAc = 50:1) to give 2-(3-methoxy-5-nitrobenzyl)-1,4-dimethylbenzene 8a. ¹H NMR (400 MHz, CDCl₃) δ 7.60 (s, 1H), 7.54 (s, 1H), 7.04 (m, 1H), 6.98 (m, 2H), 6.91 (s, 1H), 3.97 (s, 2H, ArCH₂Ar), 3.82 (s, 3H, CH₃O), 2.29 (s, 3H), 2.17 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 160.13, 149.34, 143.76, 136.89, 135.81, 133.30, 130.76, 130.56, 127.84, 121.80, 116.19, 105.52, 55.79 (CH₃O), 39.21 (ArCH₂Ar), 20.99, 19.21.

To a solution of compound 8a (271 mg, 1 mmol) in methylene chloride (2 mL), a solution of BBr₃ in dichloromethane (1.0 M, 5 mL, 5 mmol) was added slowly at –80 °C. The resulting red 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 vacuo*. The residue was purified by flash chromatography over silica gel (petroleum/EtOAc = 20:1 ~ 5:1) to give 3-(2,5-dimethylbenzyl)-5-nitrophenol (141 mg, 55%). ¹H NMR (400 MHz, CD₃OD) δ 7.40 (m, 2H), 7.02 (m, 1H), 6.95 (m, 2H), 6.88–6.84 (m, 1H), 3.93 (s, 2H, ArCH₂Ar), 2.26 (s, 3H), 2.12 (s, 3H).

A solution of 3-(2,5-dimethylbenzyl)-5-nitrophenol (141 mg, 0.55 mmol) and 10% Pd/C (28 mg) in a mixed solvent (CH₃OH/CH₂Cl₂ = 1:1 (V/V), 5 mL) was purged with H₂ three times. The reaction mixture was stirred with a balloon of H₂ at room temperature for 4 h. The reaction mixture was filtered and concentrated *in vacuo*. 3-Amino-5-(2,5-dimethylbenzyl)phenol was obtained and directly used in the next step without further purification. ¹H NMR (400 MHz, CDCl₃) δ 7.04 (m, 1H), 7.00–6.91 (m, 2H), 6.04 (m, 1H), 6.01 (t, *J* = 2.1 Hz, 1H), 5.98 (m, 1H), 3.79 (s, 2H, ArCH₂Ar), 2.29 (s, 3H, CH₃), 2.19 (s, 3H, CH₃).

A solution of cyclohexanecarbonyl chloride (73.3 μL, 0.55 mmol) in THF (1 mL) was slowly added at 0 °C to a solution of 3-amino-5-(2,5-dimethylbenzyl)phenol (113.5 mg, 0.5 mmol) and triethylamine (76.3 μL, 0.55 mmol) in THF (2 mL). After the reaction mixture was stirred for 3 h at room temperature, the reaction was quenched with water (10 mL) and the mixture was extracted with EtOAc (15 mL × 2). The combined organic phase was dried over anhydrous Na₂SO₄ and filtered. After the solvent was removed under reduced pressure, the

crude product was purified by column chromatography (petroleum/EtOAc = 20:1–2:1) to afford **9a** as a white solid. m.p. 179.5–181.7 °C; ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.56 (bs, 1H, NH), 9.19 (bs, 1H, OH), 7.09–7.00 (m, 2H), 6.93 (m, 2H), 6.72 (s, 1H), 6.18 (s, 1H), 3.75 (s, 2H, ArCH₂Ar), 2.25 (m, 4H), 2.14 (s, 3H), 1.73 (m, 4H), 1.63 (m, 1H), 1.36 (m, 2H), 1.26–1.12 (m, 3H); ¹³C NMR (101 MHz, CD₃OD) δ 176.27 (CONH), 157.34, 142.53, 139.56, 138.33, 134.94, 133.17, 130.51, 129.78, 126.70, 111.38, 110.97, 104.75, 45.78 (cyclohexyl-CH), 38.99 (ArCH₂Ar), 29.27, 25.49, 25.38, 19.65, 17.91; HRMS (ESI) calculated for C₂₂H₂₇NO₂ [M – H][–]: 336.1969, found: 336.1955. Purity: 99.4% (by HPLC).

N-(3-Hydroxy-5-(2,4,6-trimethylbenzyl)phenyl)-cyclohexanecarboxamide (**9b**)

This compound was synthesized *via* a procedure similar to that of **9a**. Yellow solid, yield 44%, m.p. 248.5–249.7 °C; ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.49 (bs, 1H, NH), 6.96 (bs, 1H, OH), 6.84 (s, 2H), 6.60 (s, 1H), 6.06 (s, 1H), 3.80 (s, 2H, ArCH₂Ar), 2.32–2.19 (m, 4H), 2.15 (s, 6H), 1.72 (m, 3H), 1.63 (m, 1H), 1.36 (m, 2H), 1.28–1.10 (m, 3H); ¹³C NMR (101 MHz, DMSO-*d*₆) δ 174.56 (CONH), 158.28, 141.65, 140.83, 136.84, 135.17, 134.24, 129.09, 110.13, 109.61, 104.58, 45.28 (cyclohexyl-CH), 34.74 (ArCH₂Ar), 29.61, 25.88, 25.72, 20.99, 20.25; HRMS (EI) calculated for C₂₃H₂₉NO₂ [M + H]⁺: 352.2271, found: 352.2261. Purity: 96.4% (by HPLC).

Biological assays

Determination of minimum inhibitory concentration (MIC) against Mtb H37Ra²¹. The assay was conducted over a range of 4-fold increasing concentrations prepared in 1 mL of 7H9 broth containing 0.2 mL of a 1/100 dilution of an autoluminescent Mtb H37Ra broth culture (OD₆₀₀, 0.8) grown in 7H9 broth. The test compound was prepared as 10-point two-fold serial dilutions in DMSO and diluted in 7H9-Tw-OADC medium in 96-well plates with a final DMSO concentration of 2%. The highest concentration of the compound was 100 μg mL^{–1}. To each well, 196 μL of a 1/100 dilution of an autoluminescent Mtb H37Ra broth culture (OD₆₀₀ = 0.8, grown in 7H9 broth) and 4 μL of the solution of the test 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^{–1}) and maximum growth (DMSO only), for generating the INH dose–response curve. 200 μL medium was added into holes 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 a GloMax reader. For MIC, the 10-point dose response curve was plotted as the percentage (%) of growth and fitted to the Gompertz model using GraphPad Prism 5. The MIC was defined as the minimum concentration at which growth was completely inhibited and was calculated from the inflection point of the fitted curve to the lower asymptote (zero growth).

Determination of minimum inhibitory concentration (MIC) against Mtb H37Rv and MDR-Mtb. The MICs of the test compounds were determined by the well-established microplate alamar blue assay (MABA) against H37Rv and clinically isolated MDR-Mtb strains (provided by the Guangzhou Chest Hospital).²² Mtb H37Rv and MDR-Mtb strains in 7H9-Tw-OADC were cultivated in a 50 mL tube containing glass beads at 37 °C. The strains were transferred into a 250 mL flask containing 50 mL 7H9-Tw-OADC while the OD₆₀₀ value reached 0.3–0.8. The test compounds were prepared as in 4.2.1. Each well contained 196 μL broth culture of a 1/100 dilution of Mtb H37Rv or MDR-Mtb (OD₆₀₀ = 0.8, grown in 7H9 broth) and 4 μL of the solution of the test 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 7th day, 12.5 μL of 20% Tween 80 and 20 μL of alamarBlue (Bio-Rad) were added to the test plate. A change in color from blue (oxidized state) to pink (reduced) indicated the growth of bacteria after incubation at 37 °C for 16–24 h. The MIC was defined as the lowest concentration of drug that prevented this change in color.

Determination of the antibacterial activity. The minimum inhibitory concentration (MIC) of compounds **6g** and **7a** was defined as the lowest concentration (the highest dilution) of each compound that completely inhibited the growth of bacteria after incubation at 37 °C for 18–24 h, by means of the standard twofold serial dilution method in 96-well microtest plates. Amoxicillin and ofloxacin were used as the positive controls. The bacterial suspension was adjusted with sterile saline to a concentration of 1 × 10⁵ CFU. Initially the compounds were dissolved in DMSO to prepare the stock solutions (10 mg mL^{–1}), and then the test compounds and reference drugs were prepared in BHI broth to obtain the required concentrations 50–1.5125 μg mL^{–1}. These dilutions were inoculated and incubated at 37 °C for 24 h.

Cytotoxicity studies. The cytotoxicities of compounds **6g** and **7a** were assayed against RAW 264.7 and HepG2 cell lines at concentrations from 100 to 6.25 μg mL^{–1}. The cells were seeded in 96-well plates and then allowed to recover for 24 h. Different concentrations of the test 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 cytotoxicities were reported as IC₅₀ values, which were calculated by GraphPad Prism Software version 5.²³

Conflicts of interest

There are no conflicts to declare.

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