Identification of *N*-Benzyl 3,5-Dinitrobenzamides Derived from PBTZ169 as Antitubercular AgentsLinhu Li,^{†,§,‡} Kai Lv,^{†,‡} Yupeng Yang,[¶] Jingquan Sun,[§] Zeyu Tao,[†] Apeng Wang,[†] Bin Wang,[‡] Hongjian Wang,[†] Yunhe Geng,[†] Mingliang Liu,^{*,†,¶} Huiyuan Guo,[†] and Yu Lu^{*,‡,⊥}[†]Institute of Medicinal Biotechnology, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100050, China[§]Limin Chemical Co., Ltd., Xinyi 221422, China[¶]Department of Stomatology, Hebei General Hospital, Shijiazhuang 050051, China[⊥]Beijing Key Laboratory of Drug Resistance Tuberculosis Research, Department of Pharmacology, Beijing Tuberculosis and Thoracic Tumor Research Institute, Beijing Chest Hospital, Capital Medical University, Beijing 101149, China

S Supporting Information

ABSTRACT: A series of benzamide scaffolds were designed and synthesized by the thiazinone ring opening of PBTZ169, and *N*-benzyl 3,5-dinitrobenzamides were finally identified as anti-TB agents in this work. 3,5-Dinitrobenzamides **D5**, **6**, **7**, and **12** exhibit excellent *in vitro* activity against the drug susceptible *Mycobacterium tuberculosis* H37Rv strain (MIC: 0.0625 µg/mL) and two clinically isolated multidrug-resistant strains (MIC < 0.016–0.125 µg/mL). Compound **D6** displays acceptable safety and better pharmacokinetic profiles than PBTZ169, suggesting its promising potential to be a lead compound for future antitubercular drug discovery.

KEYWORDS: Antitubercular agents, *N*-benzyl 3,5-dinitrobenzamides, structure–activity relationships, pharmacokinetics

Tuberculosis (TB) is an airborne infectious disease mainly caused by *Mycobacterium tuberculosis* (MTB).¹ The World Health Organization (WHO) reported that MTB still caused an estimated approximately 10.4 million infections and 1.3 million deaths in 2016.² Recently, the increase of multidrug-resistant (MDR) TB and even the emergence of extensively drug-resistant (XDR) TB, together with coinfection with Human Immunodeficiency Virus (HIV), have challenged us seriously.^{3–5} Two drugs with new mechanisms of action, Bedaquiline⁶ and Delamanid (Figure 1),⁷ were approved (in 2012 and 2014, respectively) for the treatment of MDR-TB, but some adverse events have been noted.³ Therefore, it is urgently needed to develop novel anti-TB agents active against MDR- and XDR-TB.⁸

Recently, 8-nitro-6-(trifluoromethyl)-1,3-benzothiazin-4-ones (BTZs), a novel class of TB agents targeting DprE1,^{9–11} have been extensively studied, and candidate PBTZ169 (Figure 2) is in Phase II clinical trials at present.² Meanwhile, some nitroaromatic compounds that contain an electron-withdrawing substituent (NO₂, CF₃) in the position *meta* to the nitro group were also identified as DprE1 inhibitors, such as dinitrobenzamide DNB1¹² and its analogue

Figure 1. Structures of selected dinitrobenzene derivatives, Q203, and Delamanid.

CT319,¹³ dinitrobenzene derivatives (here abbreviated as DNDs),¹⁴ and xanthone derivative 1-methyl-2,4,7-trinitroxanthone (MTX) (Figure 1).^{13,15} Moreover, 3,5-dinitrophenylme-

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Figure 2. Design of the new molecules.

thanethiol derivatives DNPT1–4 (Figure 1)^{16–18} targeting the synthesis of mycobacterial nucleic acids were found to have considerable antimycobacterial activity.

In our previous studies, many BTZs containing various cyclic ketoxime, spiro-heterocycle, and piperidine moieties were identified as potential antitubercular agents.^{19–21} Moreover, replacement of the *N*-benzyl group on the amide linker of Q203 (Figure 1) with a *N*-(2-phenylamino)ethyl or *N*-(2-phenoxy)ethyl moiety maintains potent activity.^{22,23} Given that above compounds belong to aromatic carboxamides, we intended to simplify the structure of PBTZ169 to benzamide scaffolds by the thiazinone ring opening in this work. Thus, a series of 3-nitro-5-(trifluoromethyl)benzamides bearing *N*-oxyethyl (A1–7), *N*-aminoethyl (B1–4), and *N*-benzyl (C1), as well as *N*-benzyl-3,5-dinitro-benzamide (D1), were first designed to identify the optimal benzamide cores (Figure 2), and then the effect of substituents on the amide linker was further investigated. Our primary objective was to find optimized benzamides with potent antimycobacterial activity. A preliminary structure–activity relationship (SAR) study was also explored.

Detailed synthetic pathways to side chains 3, 5, and 12 and target compounds A–D are outlined in Schemes 1 and 2,

Scheme 1. Synthesis of Side Chain Compounds 3, 5, and 12^a

^aReagents and conditions: (i) DEAD, PPh₃, THF, 0–5 °C; (ii) hydrazine hydrate, EtOH, 50 °C; (iii) toluene, reflux, then NaOH, rt. (iv) K₂CO₃, MeCN, reflux; (v) K₂CO₃, DMSO; (vi) LiAlH₄, THF.

respectively. Coupling of different phenols (RH) with *N*-(2-hydroxyethyl)phthalimide 1 in the presence of diethyl azodicarboxylate (DEAD) and PPh₃ (2a–g) followed by treatment with hydrazine hydrate in ethanol at 50 °C yielded desired amines 3a–g. Treatment of anilines (R₁H) with 2-bromoethanamine hydrobromide 4 in toluene under reflux condition gave the corresponding 1,2-diamines 5a,b. Nucleophilic substitution of 1-(cyclohexylmethyl)piperazine 6 and 1-phenylpiperazine 7 with 2-(2-bromoethyl)isoindoline-1,3-

Scheme 2. Synthesis of Target Compounds A–D (See Tables 1 and 2)^a

^aReagents and conditions: (i) BOP-Cl, TEA, CH₂Cl₂

dione in acetonitrile in the presence of potassium carbonate gave intermediate compounds 8 and 9, which were treated with hydrazine hydrate in ethanol yielded side chains 5c and 5d, respectively. 4-Fluorobenzonitrile 10 was treated with various nitrogen heterocyclic amines (YH) in DMSO in the presence of K₂CO₃, and the resulting intermediates 11a–l were subsequently reduced with LiAlH₄ in THF to produce the desired benzylamines 12a–l (Scheme 1).

Target compounds A–D were easily obtained by amidation of acids 13a,b with the above side chain compounds 3a–g, 5a–d, and 12a–l in the presence of triethylamine (TEA) and condensation agent bis(2-oxo-3-oxazolidinyl)phosphonic chloride (BOP-Cl) (Scheme 2).

The target compounds A1–7, B1–4, and C1 bearing different kinds of substituents on the amide linker to ensure side chain flexibility and structure diversity and *N*-benzyl 3,5-dinitro-benzamide (D1) were first synthesized. They were preliminarily examined for *in vitro* activity against drug sensitive MTB strain (H37Rv ATCC27294), using the Microplate Alamar Blue Assay (MABA).²⁴ The minimum inhibitory concentration (MIC) is defined as the lowest concentration effecting a reduction in fluorescence of >90% relative to the mean of replicate bacterium-only controls. The MIC values of the compounds along with PBTZ169, isoniazid (INH), and rifampicin (RFP) as references were obtained in Table 1.

Synthesized compound A1 exhibits a MIC value of 1 μg/mL against the H37Rv strain of MTB, much less than that (75 ng/mL)¹² of DNB1 (a bioisostere of A1), which reveals that replacement of the nitro group of DNB1 with trifluoromethyl is detrimental. Except for *N*-(2-pyridin-4-yloxy)ethyl compound A7 (MIC: 8 μg/mL), activity of the other *N*-phenoxyethyl analogues (A2–6) is, as expected, comparable to A1. However, compound B1, wherein a 4-(cyclohexylmethyl)piperazine ring (the same side chain of PBTZ169) is directly attached to the amide through an ethylene, displays obviously decreased activity (MIC: 4 μg/mL) compared to PBTZ169 (MIC: 0.0625 μg/mL), but introduction of a benzene ring on the piperazine instead of the alkyl group is beneficial to the activity (B1 vs B2). Furthermore, *N*-phenoxyethyl group is preferred over *N*-phenylaminoethyl (A3 vs B3).

Table 1. Structures and Activity of Compounds A–D against MTB H37Rv

A1–7			B1–4			C1, D1		
Cpds.	R or NHR ₁	MIC ^a	Cpds.	NHR ₁ or X	MIC ^a	Cpds.	NHR ₁ or X	MIC ^a
A1		1	B2		1	C1		0.5
A2		1	B3		8	D1		0.0625
A3		1	B4		> 8	PBTZ 169	/	0.0625
A4		1				INH	/	0.0781
A5		1				RFP	/	0.0781
A6		2						
A7		8						
B1		4						

^aMIC determined in $\mu\text{g/mL}$; Cpds., compounds; INH, isoniazid; RFP, rifampicin.

Interestingly enough, compound **C1**, having the same side chain as Q203, shows better activity (MIC: 0.5 $\mu\text{g/mL}$) than **A1–7** and **B1–4**. Replacement of the trifluoromethyl group of **C1** with another electron-withdrawing one (NO_2) in compound **D1** leads to a MIC of 0.0625 $\mu\text{g/mL}$ (Table 1). These results indicate that the 3,5-dinitrobenzamide core and *N*-benzyl group are preferred over the corresponding 3-nitro-5-(trifluoromethyl)benzamide and *N*-phenoxyethyl or *N*-aminoethyl, respectively.

Encouraged by the above SAR, *N*-benzyl 3-nitro-5-(trifluoromethyl)/3,5-dinitro benzamides with various groups at the para-position of the benzene ring were further designed and synthesized. As shown in Table 2, 12 compounds show considerable activity against MTB H37Rv strain (MIC: < 1 $\mu\text{g/mL}$). Among them, six compounds **C6** and **D1**, **5–7**, and **12** (MIC: 0.0625 $\mu\text{g/mL}$) are more active than INH/RFP (MIC: 0.0781 $\mu\text{g/mL}$) and comparable to PBTZ169. Overall, the data reveal that with a few exceptions (**C3**, **C4**, **C6**, and **C11**), 3-nitro-5-(trifluoromethyl) benzamides are less active than the corresponding 3,5-dinitrobenzamides. Based on this, we here only discuss the effect of the substituent (*Y*) on the benzene ring of 3,5-dinitrobenzamide series. The nature of the substituents greatly influences activity. Compound **D2** having the same side chain as Delamanid, namely, insertion of an oxygen atom between the piperidine and 4-trifluoromethoxybenzene rings of **D1**, displays less activity (MIC: 0.5 $\mu\text{g/mL}$) than **D1**. Removal of 4-trifluoromethoxybenzene ring of **D1** was found to be detrimental (**D1** vs **D3**). Replacement of the piperidine ring of **D3** (MIC: 2 $\mu\text{g/mL}$) with morpholine in compound **D4** leads to a complete loss of activity, but thiomorpholine in **D5** or introduction of an electron-withdrawing group (CF_3) in **D6** leads to obviously increased activity (MIC: 0.0625 $\mu\text{g/mL}$). Interestingly, octahydro-1*H*-isindole analogue **D7** also demonstrates the most potent MIC value of 0.0625 $\mu\text{g/mL}$. However, among the different para-groups on the piperazine ring, compounds with alkyl groups, **D8** (methyl) and **D9** (isopropyl), or heteroaromatic groups,

Table 2. Structures and Activity of *N*-Benzylated Analogues C1–12 and D1–12^a

		MIC ($\mu\text{g/mL}$)		
Cpds.	Y	H37Rv	MDR-MTB1	MDR-MTB2
C1		0.5	/	/
D1		0.0625	0.210	0.474
C2		2	/	/
D2		0.5	/	/
C3		0.25	/	/
D3		2	/	/
C4		>8	/	/
D4		>8	/	/
C5		0.125	/	/
D5		0.0625	0.017	0.085
C6		0.0625	0.138	>40
D6		0.0625	<0.016	0.075
C7		0.5	/	/
D7		0.0625	0.031	0.125
C8		>8	/	/
D8		4	/	/
C9		8	/	/
D9		4	/	/
C10		8	/	/
D10		2	/	/
C11		1	/	/
D11		1	/	/
C12		0.5	/	/
D12		0.0625	0.047	0.077
PBTZ		0.0625	0.116	0.232
169				
INH		0.0781	>40	>40
RFP		0.0781	>40	>40

^aCpds., compounds; INH, isoniazid; RFP, rifampicin; MDR-MTB1, MDR-MTB12525; MDR-MTB2, MDR-MTB14231.

D10 (4-pyridyl) and **D11** (2-pyridyl), display comparatively less activity (MIC: 1–4 $\mu\text{g/mL}$), and the only exception is compound **D12** with an aromatic group (4-fluorophenyl) (MIC: 0.0625 $\mu\text{g/mL}$).

Considering their strong potency against the drug sensitive MTB H37Rv strain (MIC: 0.0625 $\mu\text{g/mL}$), compounds **C6** and **D1**, **5–7**, and **12** were further evaluated against two clinical isolated MTB-MDR (12525 and 14231) strains resistant to both INH and RFP. Except for **C6** and **D1**, the other four compounds exhibit better activity (MIC < 0.016–0.125 $\mu\text{g/mL}$) than PBTZ169 (Table 2), suggesting their promising potential for both drug-sensitive and resistant MTB strains (Tables 1, 2).

Based on the measured activity levels against all of the tested strains, compounds **D1**, **5–7**, and **12** were tested for in vivo tolerability by recording the number of survivors after a single oral dose in mice of 500 mg/kg, followed by a 7-day

observation. All of them display the low oral acute lethal toxicity (Table 3). The *in vivo* PK profiles of these compounds

Table 3. Acute Toxicity and PK Profiles of Selected Compounds

Cpds.	acute toxicity ^a	PK ^b			
		<i>T</i> _{1/2} (h)	<i>T</i> _{max} (h)	<i>C</i> _{max} (ng/mL)	AUC _{0-∞} (h·ng/mL)
D1	5/5	5.52	0.83	366	3262
D5	5/5	3.30	2.75	19.0	41.1
D6	5/5	3.63	0.92	1719	5605
D7	5/5	NA	NA	NA	NA
D12	5/5	13.6	1.08	15.0	219
PBTZ169	NT	2.87	0.83	1300	5478

^aNumber of animals that survived/total. ^bDosed orally in mice at 50 mg/kg (*n* = 3); NT, not tested; NA, unavailable; Cpds., compounds.

were further evaluated in mice after a single oral administration of 50 mg/kg. As shown in Table 3, compared to PBTZ169, compound D1 has a relatively longer *T*_{1/2} of 5.52 h, but less *T*_{max}, *C*_{max}, and AUC_{0-∞}. Absorption of compounds D5, 7, and 12 in plasma is very poor, or not detectable. Compound D6, with a 4-trifluoro-methylpiperidine moiety, displays better PK properties, with *T*_{1/2} of 3.63 h, *T*_{max} of 0.92 h, *C*_{max} of 1719 ng/mL, and AUC_{0-∞} of 5605 h·ng/mL.

In conclusion, a series of various benzamide scaffolds were designed and synthesized by the thiazinone ring opening of PBTZ169, and *N*-benzyl 3,5-dinitrobenzamides were finally identified as anti-TB agents in this work. Four *N*-benzyl 3,5-dinitrobenzamides D5, 6, 7, and 12 exhibit excellent *in vitro* inhibitory activity against both drug-sensitive MTB strain H37Rv (MIC: 0.0625 μg/mL) and drug-resistant clinical isolates (MIC < 0.016–0.125 μg/mL). Moreover, compound D6 displays acceptable safety and better PK properties than PBTZ169, and it may serve as a promising lead compound for further antitubercular drug discovery. Studies to determine the *in vivo* efficacy of D6 are currently underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsmedchemlett.8b00177.

Experimental procedures and analytical data of the synthesized compounds (PDF)

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†These authors contributed equally. M.L.L. and Y.L. conceived and designed the project. L.H., K.L., Z.T., A.W., H.W., and Y.G. synthesized the compounds. Y.Y. and J.S. analyzed checked the data. B.W. and Y.L. evaluated the antimycobacterial activity. The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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Notes

The authors declare no competing financial interest.

■ ABBREVIATIONS

MTB, *Mycobacterium tuberculosis*; MDR-TB, multidrug-resistant tuberculosis; XDR-TB, extensively drug-resistant tuberculosis; WHO, World Health Organization; HIV, human immunodeficiency virus; BTZs, 8-nitro-6-(trifluoromethyl)-1,3-benzothiazin-4-ones; DprE1, decaprenyl phosphoryl-β-D-ribose 2-epimerase; DEAD, diethyl azodicarboxylate; DMSO, dimethyl sulfoxide; MIC, minimum inhibitory concentration; MABA, Microplate Alamar Blue Assay; *C*_{max}, maximum concentration; *T*_{max}, time to maximum concentration; AUC_{0-∞}, area under curve from time zero to infinity; *t*_{1/2}, plasma elimination half-life

■ REFERENCES

- (1) Borsari, C.; Ferrari, S.; Venturelli, A.; Costi, M. P. Target-based approaches for the discovery of new antimycobacterial drugs. *Drug Discovery Today* **2017**, 22 (3), 576–584.
- (2) World Health Organization. Global Tuberculosis Report 2017. <http://www.who.int/tb/publications/lpa-mdr-diagnostics/en/>.
- (3) Hoagland, D. T.; Liu, J.; Lee, R. B.; Lee, R. E. New agents for the treatment of drug-resistant *Mycobacterium tuberculosis*. *Adv. Drug Delivery Rev.* **2016**, 102, 55–72.
- (4) Wallis, R. S.; Maeurer, M.; Mwaba, P.; Chakaya, J.; Rustomjee, R.; Migliori, G. B.; Marais, B.; Schito, M.; Churchyard, G.; Swaminathan, S.; Hoelscher, M.; Zumla, A. Tuberculosis—advances in development of new drugs, treatment regimens, host-directed therapies, and biomarkers. *Lancet Infect. Dis.* **2016**, 16 (4), e34–46.
- (5) Nusrath Unissa, A.; Hanna, L. E.; Swaminathan, S. A Note on Derivatives of Isoniazid, Rifampicin, and Pyrazinamide Showing Activity Against Resistant *Mycobacterium tuberculosis*. *Chem. Biol. Drug Des.* **2016**, 87 (4), 537–50.
- (6) Kakkar, A. K.; Dahiya, N. Bedaquiline for the treatment of resistant tuberculosis: promises and pitfalls. *Tuberculosis (Oxford, U. K.)* **2014**, 94 (4), 357–62.
- (7) Gler, M. T.; Skripconoka, V.; Sanchez-Garavito, E.; Xiao, H.; Cabrera-Rivero, J. L.; Vargas-Vasquez, D. E.; Gao, M.; Awad, M.; Park, S. K.; Shim, T. S.; Suh, G. Y.; Danilovits, M.; Ogata, H.; Kurve, A.; Chang, J.; Suzuki, K.; Tupasi, T.; Koh, W. J.; Seaworth, B.; Geiter, L. J.; Wells, C. D. Delamanid for multidrug-resistant pulmonary tuberculosis. *N. Engl. J. Med.* **2012**, 366 (23), 2151–60.
- (8) Beena; Rawat, D. S. Antituberculosis drug research: a critical overview. *Med. Res. Rev.* **2013**, 33 (4), 693–764.
- (9) Trefzer, C.; Rengifo-Gonzalez, M.; Hinner, M. J.; Schneider, P.; Makarov, V.; Cole, S. T.; Johnsson, K. Benzothiazinones: Prodrugs That Covalently Modify the Decaprenylphosphoryl-beta-D-ribose 2'-epimerase DprE1 of *Mycobacterium tuberculosis*. *J. Am. Chem. Soc.* **2010**, 132 (39), 13663–13665.
- (10) Makarov, V.; Manina, G.; Mikusova, K.; Mollmann, U.; Ryabova, O.; Saint-Joanis, B.; Dhar, N.; Pasca, M. R.; Buroni, S.; Lucarelli, A. P.; Milano, A.; De Rossi, E.; Belanova, M.; Bobovska, A.; Dianiskova, P.; Kordulakova, J.; Sala, C.; Fullam, E.; Schneider, P.; McKinney, J. D.; Brodin, P.; Christophe, T.; Waddell, S.; Butcher, P.; Albrethsen, J.; Rosenkrands, I.; Brosch, R.; Nandi, V.; Bharath, S.; Gaonkar, S.; Shandil, R. K.; Balasubramanian, V.; Balganes, T.; Tyagi, S.; Grosset, J.; Riccardi, G.; Cole, S. T. Benzothiazinones Kill

Mycobacterium tuberculosis by Blocking Arabinan Synthesis. *Science* **2009**, 324 (5928), 801–804.

(11) Trefzer, C.; Skovierova, H.; Buroni, S.; Bobovska, A.; Nenci, S.; Molteni, E.; Pojer, F.; Pasca, M. R.; Makarov, V.; Cole, S. T.; Riccardi, G.; Mikusova, K.; Johnsson, K. Benzothiazinones are suicide inhibitors of mycobacterial decaprenylphosphoryl-beta-D-ribofuranose 2'-oxidase DprE1. *J. Am. Chem. Soc.* **2012**, 134 (2), 912–5.

(12) Christophe, T.; Jackson, M.; Jeon, H. K.; Fenistein, D.; Contreras-Dominguez, M.; Kim, J.; Genovesio, A.; Carralot, J. P.; Ewann, F.; Kim, E. H.; Lee, S. Y.; Kang, S.; Seo, M. J.; Park, E. J.; Skovierova, H.; Pham, H.; Riccardi, G.; Nam, J. Y.; Marsollier, L.; Kempf, M.; Joly-Guillou, M. L.; Oh, T.; Shin, W. K.; No, Z.; Nehrbass, U.; Brosch, R.; Cole, S. T.; Brodin, P. High Content Screening Identifies Decaprenyl-Phosphoribose 2'Epimerase as a Target for Intracellular Antimycobacterial Inhibitors. *PLoS Pathog.* **2009**, 5, e1000645.

(13) Trefzer, C.; Rengifo-Gonzalez, M.; Hinner, M. J.; Schneider, P.; Makarov, V.; Cole, S. T.; Johnsson, K. Benzothiazinones: prodrugs that covalently modify the decaprenylphosphoryl-beta-D-ribose 2'-epimerase DprE1 of Mycobacterium tuberculosis. *J. Am. Chem. Soc.* **2010**, 132 (39), 13663–5.

(14) Kappes, B.; Neumann, T.; Unger, E.; Dahse, H.-M.; Mollmann, U.; Schlegel, B. Use of 3,5-dinitrobenzoate ester, 3,5-dinitrobenzamide or 3,5-dinitrophenyl ketone derivatives for therapy and/or diagnosis of microbial infections, especially tuberculosis or malaria. Patent DE10158057, 2003.

(15) Schaper, K. J.; Pickert, M.; Frahm, A. W. Substituted xanthenes as antimycobacterial agents Part 3: QSAR investigations. *Arch. Pharm.* **1999**, 332 (3), 91–102.

(16) Karabanovich, G.; Roh, J.; Smutny, T.; Nemecek, J.; Vicherek, P.; Stolarikova, J.; Vejsova, M.; Dufkova, I.; Vavrova, K.; Pavek, P.; Klimesova, V.; Hrabalek, A. 1-Substituted-5-[(3,5-dinitrobenzyl)sulfanyl]-1H-tetrazoles and their isosteric analogs: A new class of selective antitubercular agents active against drug-susceptible and multidrug-resistant mycobacteria. *Eur. J. Med. Chem.* **2014**, 82, 324–40.

(17) Karabanovich, G.; Roh, J.; Soukup, O.; Pavkova, I.; Pasdiorova, M.; Tambor, V.; Stolarikova, J.; Vejsova, M.; Vavrova, K.; Klimesova, V.; Hrabalek, A. Tetrazole regioisomers in the development of nitro group-containing antitubercular agents. *MedChemComm* **2015**, 6 (1), 174–181.

(18) Karabanovich, G.; Zemanová, J.; Smutný, T.; Székely, R.; Šarkan, M.; Centárová, I.; Vocat, A.; Pávková, I.; Conka, P.; Němeček, J.; Stolaříková, J.; Vejsová, M.; Vávrová, K.; Klimešová, V.; Hrabálek, A.; Pávek, P.; Cole, S. T.; Mikušová, K.; Roh, J. Development of 3,5-Dinitrobenzylsulfanyl-1,3,4-oxadiazoles and Thiadiazoles as Selective Antitubercular Agents Active Against Replicating and Nonreplicating Mycobacterium tuberculosis. *J. Med. Chem.* **2016**, 59 (6), 2362–2380.

(19) Zhang, R.; Lv, K.; Wang, B.; Li, L.; Wang, B.; Liu, M.; Guo, H.; Wang, A.; Lu, Y. Design, synthesis and antitubercular evaluation of benzothiazinones containing an oximido or amino nitrogen heterocycle moiety. *RSC Adv.* **2017**, 7 (3), 1480–1483.

(20) Lv, K.; You, X.; Wang, B.; Wei, Z.; Chai, Y.; Wang, B.; Wang, A.; Huang, G.; Liu, M.; Lu, Y. Identification of Better Pharmacokinetic Benzothiazinone Derivatives as New Antitubercular Agents. *ACS Med. Chem. Lett.* **2017**, 8 (6), 636–641.

(21) Lv, K.; Tao, Z.; Liu, Q.; Yang, L.; Wang, B.; Wu, S.; Wang, A.; Huang, M.; Liu, M.; Lu, Y. Design, synthesis and antitubercular evaluation of benzothiazinones containing a piperidine moiety. *Eur. J. Med. Chem.* **2018**, 151, 1–8.

(22) Lv, K.; Li, L.; Wang, B.; Liu, M.; Wang, B.; Shen, W.; Guo, H.; Lu, Y. Design, synthesis and antimycobacterial activity of novel imidazo[1,2-a]pyridine-3-carboxamide derivatives. *Eur. J. Med. Chem.* **2017**, 137, 117–125.

(23) Wu, Z.; Lu, Y.; Li, L.; Zhao, R.; Wang, B.; Lv, K.; Liu, M.; You, X. Identification of N-(2-Phenoxyethyl)imidazo[1,2-a]pyridine-3-carboxamides as New Antituberculosis Agents. *ACS Med. Chem. Lett.* **2016**, 7 (12), 1130–1133.

(24) Lu, Y.; Zheng, M.; Wang, B.; Fu, L.; Zhao, W.; Li, P.; Xu, J.; Zhu, H.; Jin, H.; Yin, D.; Huang, H.; Upton, A. M.; Ma, Z. Clofazimine analogs with efficacy against experimental tuberculosis and reduced potential for accumulation. *Antimicrob. Agents Chemother.* **2011**, 55 (11), 5185–93.