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Synthesis and evaluation of pretomanid (PA-824) oxazolidinone hybrids

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ABSTRACT

Pretomanid (PA-824) is an important nitroimidazole antitubercular agent in late stage clinical trials. However, pretomanid is limited by poor solubility and high protein binding, which presents opportunities for improvement in its physiochemical properties. Conversely, the oxazolidinone linezolid has excellent physicochemical properties and has recently shown impressive activity for the treatment of drug resistant tuberculosis. In this study we explore if incorporation of the outer ring elements found in first and second generation oxazolidinones into the nitroimidazole core of pretomanid can be used to improve its physicochemical and antitubercular properties. The synthesis of pretomanid outer oxazolidinone ring hybrids was successfully performed producing hybrids that maintained antitubercular activity and had improved in vitro physicochemical properties. Three lead compounds were identified and evaluated in a chronic model of tuberculosis infection in mice. However, the compounds lacked efficacy suggesting that portions of PA-824 tail not found in the hybrid molecules are required for in vivo efficacy.

Mycobacterium tuberculosis is the causative agent of tuberculosis (TB) and is believed to have infected one third of the global population, resulting in nearly 2 million deaths every year.[1] The standard therapy requires 6–9 months of drug treatment, which contributes to patient noncompliance and the subsequent development of multidrug resistant tuberculosis (MDR-TB) and extensively drug resistant tuberculosis (XDR-TB).[2,3] After decades without the introduction of new antibiotics for treatment of TB, a few new drugs are emerging.

One promising class of candidates for the treatment of TB are the nitroimidazoles, including pretomanid (previously known as PA-824) and delamanid. Both compounds are currently in human clinical trials in US.[4] Pretomanid is a potent inhibitor of both actively replicating bacteria and hypoxic *M. tuberculosis*. Activity against this hypoxic nonreplicating population is particularly important for the development of new TB drugs. The presence of this drug tolerant subpopulation of granuloma-resident cells, contributes substantially to the need for lengthy treatment regimes. In *M. tuberculosis*, pretomanid is activated by the deazaflavin-dependant nitroreductase. Activation of pretomanid within the target bacteria results in production of nitric oxide and leads to nonspecific damage of intracellular macromolecules, including proteins and cell wall lipids.[5,6] Following the disclosure of pretomanid, several laboratories attempted to optimize its antitubercular properties and synthesized various analogs by modifying the nitroimidazole pyran A/B rings,[7] pyran B ring,[8] ether link[9] and hydrophobic side chain.[10] However, these studies tended to produce leads limited by poor solubility and high protein binding, which presents opportunities for improvement in its physiochemical properties.

Another promising class are the oxazoldinones, including linezolid and Sutezolid. Unlike pretomanid, they have excellent physiochemical properties. Linezolid has recently shown impressive activity for the treatment of drug resistant tuberculosis.[11] Linezolid has excellent penetration of lungs and infected tissues and is a drug of choice for the treatment acute MRSA pneumonia. In a previous study, we were able to improve the physiochemical properties of a series of antitubercular nitrofuran isoxazolidines by introducing and optimizing substituted C and D rings from the outer rings of first and second generation oxazolidinones.[12] In this study we employ a similar strategy, replacing pretomanid's (4-trifluoromethoxy)benzyl side chain with the C and D rings from our lead nitrofuran isoxazoline (compound **1**) to improve the pharmacokinetic profile of this promising scaffold as outlined in Figure 1.

Scheme 1 shows the general synthesis of the target compounds. The nitroimidazopyran nucleus **7** was synthesized as reported

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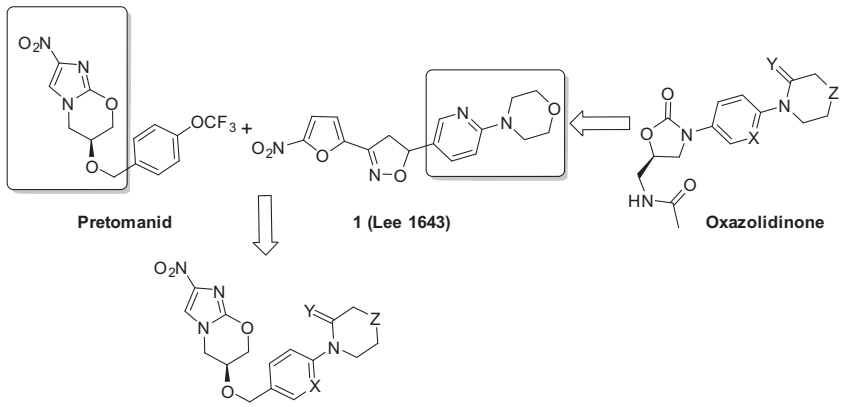
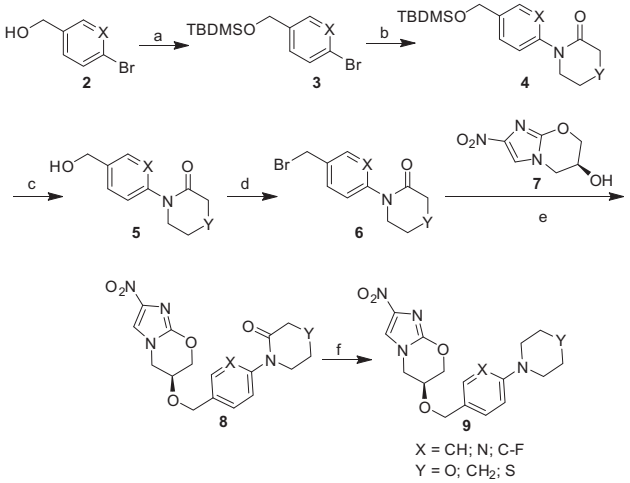


Figure 1. Nitroimidazole oxazolidinone hybrid series design.



Scheme 1. Synthesis of pretomanid analogues with modified side chains. Reagents and conditions: (a) TBDMSCl, imidazole, CH_2Cl_2, rt, 12 h; (b) *N*,*N*′-dimethyl ethylenediamine, K_2CO_3, CuI, toluene, reflux, 12 h; (c) TBAF, THF, rt, 12 h; (d) Ph_3P, CBr_4, CH_2Cl_2, rt, 2 h; (e) **7**, NaH, DMF, rt, 2 h; (f) $BH_3{\cdot}Me_2S$, THF, rt, 12 h.

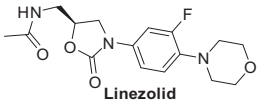
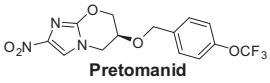
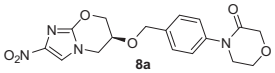
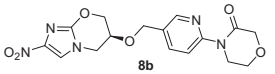
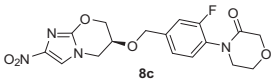
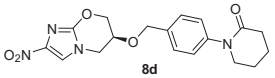
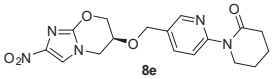
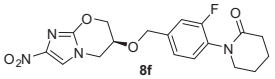
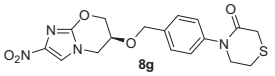
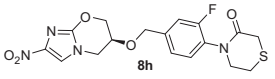
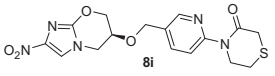
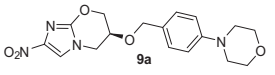
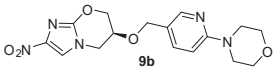
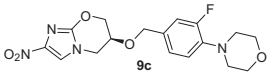
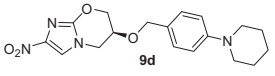
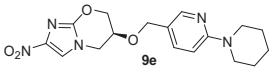
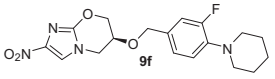
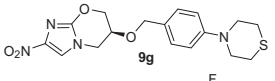
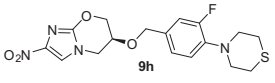
previously[13] while the outer side chain precursors were synthesized from appropriate bromo-substituted benzyl alcohols following a 4 step sequence. Alcohols **2** were protected as TBDMS ethers **3** using TBDMSCl and imidazole in dichloromethane in quantitative yields. The aryl bromide functionality of **3** was displaced with cyclic amides using *N*,*N*′-dimethyl ethylenediamine, K_2CO_3, CuI in toluene at reflux temperature in 55–70% yields.[14] The TBDMS group was then deprotected by using TBAF in THF at room temperature to afford alcohols **5**, which were then converted into bromides using triphenylphosphine and carbon tetrabromide in dichloromethane at room temperature. These bromides were used for alkylation of the nitroimidazopyran nucleus **7** to afford ethers **8**. The amide functionality of **8** was reduced where required to afford amines of general structure **9** using borane-dimethyl sulfide complex in THF at room temperature.

The series of pretomanid oxazolidinone hybrids were tested for sustained anti-tuberculosis activity using microbroth dilution (Table 1).[15] Incorporation of the C and D rings from the oxozolidone linezolid, which has a Minimum Inhibitory Concentration (MIC) of 0.3 μg/mL, yielded compound **9c** with an MIC of 0.8 μg/mL comparable to that of pretomanid and linezolid. Compounds **8a**, **8c**,[16] **9d**, and **9e**[17] also displayed comparable MIC activity to pretomanid (0.4–0.8 μg/mL) and linezolid. The potency of **9f**[18] was 0.02–0.05 μg/mL was markedly improved compared to other hybrid compounds in the series and about 10 fold more potent than pretomanid. Compounds were tested for in vitro cytotoxicity against mammalian cells. All hybrid compounds except **8i**, **9c**, **9d** and **9g** were less cytotoxic than the parent compound and the species selectivity index (calculated as the ratio of mammalian IC_{50} and *M. tuberculosis* MIC) was improved for compounds **8a**, **8c**, **9e**, and **9f**. The selectivity index for compound **9f** (>1000) was 10–25 times greater than that of pretomanid, a significant improvement. Like pretomanid, hybrid compounds maintained a narrow spectrum of antibacterial activity, lacking activity against a panel of common aerobic bacterial pathogens including *Bacillus anthracis*, *Bacillus subtilis*, *Enterococcus faecalis*, *Staphylococcus aureus*, *Streptococcus pyogenes*, *Streptococcus pneumoniae*, *Acinetobacter baumannii*, *Escherichia coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*.

Since several hybrid compounds maintained a similar antibacterial profile to pretomanid, the in vitro physicochemical properties of the series were evaluated. Incorporation of linezolid's outer phenyl and morpholine rings into pretomanid (compounds **8a** and **8c**) successfully increased solubility threefold in comparison to parent pretomanid. All compounds in the series except **9d**, **9f**, **9g** and **9h** had increased solubility. **8f** had the greatest solubility in the series (31 μg/mL), comparable to linezolid and threefold better than pretomanid, whose solubility was <10 μg/mL. Microsomal stability improved from a half-life of 8.1 h for pretomanid to >20 h for compounds **8e** and **9b**. Despite **9f**'s encouraging enhancement in potency against *M. tuberculosis*, the compound had a very short microsomal half-life of less than 30 min due to its high lipophilicity and metabolic susceptibility of the piperidine ring, precluding it from further development. Caco-2 permeability of hybrid compounds increased compared to pretomanid with comparable efflux ratios to pretomanid, these ratios remained below 2 for almost all compounds suggesting that hybrid compounds, like pretomanid and linezolid, are not subject to active cellular efflux. Pretomanid is also highly (93%) protein bound, leaving only 7% free, which may limit tissue distribution.[20] Binding to plasma proteins was greatly reduced for the pretomanid oxazolidinone hybrids. Average protein binding for the series was 60%, while compounds **8b** and **9b** were less than 30% bound, indicating increased free fraction of compounds available.

In vivo efficacy was tested for compounds **8a**, **8c**, and **9c**, which had the best solubility amongst compounds that maintained pretomanid's in vitro potency and exhibited equal or improved metabolic stability. Safety was first assessed in C57BL/6 mice in maximum tolerated dose studies. No toxicity was observed for daily oral administration of the 3 experimental compounds for 3 days even with the highest dose tested, 300 mg/kg. Although well-tolerated, daily oral administration of 100 mg/kg for 28 days

Table 1
Structures, inhibitory activity, and physicochemical properties[Δ]

Compound	MIC *M. tb* H37Rv[a] (μg/mL)	Cytotox Vero cell IC_{50}[b] (μg/mL)	Solubility (pH 7.4)[c] (μg/mL)	$t_{1/2}$ (mouse)[d] (h)	Caco-2[e]			Protein binding[f] (%)
					Papp A/B (nm/s)	Papp B/A (nm/s)	Efflux ratio (B2A/A2B)	
 Linezolid	0.3	—	34.6	>100	516.4	295.3	0.6	17.8
 Pretomanid	0.39	44.0	8.5	8.1	315.8	131.4	0.4	92.9
 8a	0.78	>100	28.4	18.3	400.8	305.6	0.7	50.4
 8b	3.13	>100	28.4	>4	434.1	238.2	0.5	27.9
 8c	0.78	>100	30.1	13.2	505.7	316.7	0.6	67.8
 8d	1.56	>100	28.7	6.7	472.5	342.0	0.7	66.4
 8e	3.13	>100	28.3	20.4	336.8	295.6	0.9	39.6
 8f	3.13	>100	30.5	3.5	462.6	304.5	0.7	74.8
 8g	25	>100	29.0	0.51	395.6	380.5	1.0	59.8
 8h	50	>100	28.0	0.60	333.9	370.5	1.1	77.6
 8i	50	15.3	27.6	0.63	400.0	314.4	0.8	32.1
 9a	3.13	42.3	22.2	8.3	414.9	322.5	0.8	39.4
 9b	3.13	>100	25.8	28.1	371.3	276.3	0.7	14.5
 9c	0.78	23.1	10.1	7.7	433.3	332.8	0.8	51.3
 9d	0.39	11.6	4.9	0.49	317.6	263.3	0.8	83.0
 9e	0.78	>100	22.7	1.3	376.4	290.4	0.8	76.7
 9f	<0.2	56.2	5.7	0.41	354.6	284.7	0.8	85.6
 9g	6.25	13.7	7.7	0.07	266.8	261.3	1.0	74.5
 9h	3.13	14.2	4.2	0.06	321.1	242.6	0.8	83.2

[Δ] Solubility, Caco-2 and protein binding were evaluated experimentally as previously described in Ref. 19.
[a] The lowest concentration of drug that prevented visible growth.
[b] Cytotoxicity against Vero epithelial cells using CellTiter Glo.
[c] Maximum solubility calculated by mSol Evolution Software.
[d] Metabolic stability performed with mouse liver microsomes.
[e] Caco-2 permeability.
[f] Plasma protein binding assays performed using human plasma.

Table 2
Intravenous pharmacokinetic profile in mice

Compound[+]	AUCinf (h μg/mL)	$t_{1/2}$ (h)	CL (mL/min/kg)	*Vss* (L/kg)
Pretomanid[*]	ND	1.6	12.1	1.6
8a	7.41	0.48	22.5	0.79
8c	5.18	0.28	32.3	0.63
9c	10.1	0.98	16.5	1.16

[+] All mice dosed at 10 mg/kg.
[*] Values obtained from Ref. 22.

did not yield significant reductions in bacterial loads for any of the compounds tested using a previously described model for chronic *M. tuberculosis* infection.[21] To explore if this was related unexpected in vivo metabolism a small pharmacokinetic study was performed with the results compared to prior published values of pretomanid (Table 2).[22] Results from this trial did indicate faster clearance and lower volume of distribution for compounds **8a**, **8c**, and **9c**. Based on this PK profile it is somewhat surprising that **9c,** with the linezolid outer ring elements, was not efficacious in the infection model. **9c**'s clearance (16.5 mL/min/kg) and volume of distribution (1.2 L/kg) are close to pretomanid (12.1 mL/min/kg and 1.6 L/kg, respectively) with similar MIC values (0.78 vs 0.39 μg/mL) and much improved serum protein binding properties (51% vs 93%).

It is notable that many of the tuberculosis specific drugs currently advancing clinically including: nitroimidazoles pretomanid and delamanid; and imidazopyridine amide Q203 all possess terminal trifluoromethoxy phenyl moiety, all also possessing physiochemical properties of very high serum binding that are not typically favored for antibacterial drug development. The pretomanid oxazolidinone hybrids explored in this study lack in vivo efficacy despite superior in vitro physiochemical properties normally associated with increased antibacterial activity. This suggests that the terminal trifluoromethoxy phenyl group may be required and afford privileged in vivo antitubercular efficacy in mouse infection models that do not contain caseous lesions. Important recent studies have shown that many highly bound, tubercular drugs do not penetrate well into caseous granulomas, limiting the sterilizing activity of these drugs in humans.[23] Thus we believe it may be worthwhile to further test compound **9c** in the new C3HeB/FeJ mouse model of tuberculosis, which better mimics the pathology of the human disease including caseous granuloma formation, because of its high free fraction, MIC activity and low clearance, especially if the dosing levels can be increased.[24]

Acknowledgments

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References and notes

1. World Health Organization global tuberculosis report, 2015 <http://www.who.int/tb/publications/global_report/en/>.
2. Yee, D.; Valiquette, C.; Pelletier, M.; Parisien, I.; Rocher, I.; Menzies, D. *Am. J. Respir. Crit. Care Med.* **2003**, *167*, 1472.
3. *Tuberculosis: Pathogenesis, Protection, and Control*; Bloom, B. R., Ed.; ASM Press: Washington, DC, 1994.
4. D'Ambrosio, L.; Centis, R.; Sotgiu, G.; Pontali, E.; Spanevello, A.; Migliori, G. B. *ERJ Open Res.* **2015**, *1*, 00010.
5. Stover, C. K.; Warrener, P.; VanDevanter, D. R.; Sherman, D. R.; Arain, T. M.; Langhorne, M. H.; Anderson, S. W.; Towell, J. A.; Yuan, Y.; McMurray, D. N.; Krelswirth, B. N.; Barry, C. E.; Baker, W. R. *Nature (London)* **2000**, *405*, 962.
6. Singh, R.; Manjunatha, U.; Boshoff, H. I. M.; Ha, Y. H.; Niyomrattanakit, P.; Ledwidge, R.; Dowd, C. S.; Lee, I. Y.; Kim, P.; Zhang, L.; Kang, S.; Keller, T. H.; Jiricek, J.; Barry, C. E., III *Science (Washington, DC, US)* **2008**, *322*, 1392.
7. Thompson, A. M.; Blaser, A.; Anderson, R. F.; Shinde, S. S.; Franzblau, S. G.; Ma, Z.; Denny, W. A.; Palmer, B. D. *J. Med. Chem.* **2009**, *52*, 637.
8. (a) Kim, P.; Kang, S.; Boshoff, H. I.; Jiricek, J.; Collins, M.; Singh, R.; Manjunatha, U. H.; Niyomrattanakit, P.; Zhang, L.; Goodwin, M.; Dick, T.; Keller, T. H.; Dowd, C. S.; Barry, C. E. *J. Med. Chem.* **2009**, *52*, 1329; (b) Li, X.; Manjunatha, U. H.; Goodwin, M. B.; Knox, J. E.; Lipinski, C. A.; Keller, T. H.; Barry, C. E., III; Dowd, C. S. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 2256.
9. (a) Blaser, A.; Palmer, B. D.; Sutherland, H. S.; Kmentova, I.; Franzblau, S. G.; Wan, B.; Wang, Y.; Ma, Z.; Thompson, A. M.; Denny, W. A. *J. Med. Chem.* **2012**, *55*, 312; (b) Cherian, J.; Choi, I.-H.; Nayyar, A.; Manjunatha, U. H.; Mukherjee, T.; Lee, Y.-S.; Boshoff, H. I.; Singh, R.; Ha, Y.-H.; Goodwin, M.; Lakshminarayana, S. B.; Niyomrattanakit, P.; Jiricek, J.; Ravindran, S.; Dick, T.; Keller, T. H.; Dartois, V., ; Barry, C. E., III *J. Med. Chem.* **2011**, *54*, 5639; (c) Thompson, A. M.; Sutherland, H. S.; Palmer, B. D.; Kmentova, I.; Blaser, A.; Franzblau, S. G.; Wan, B.-J.; Wang, Y.-H.; Ma, Z.-K.; Denny, W. A. *J. Med. Chem.* **2011**, *54*, 6563.
10. (a) Kmentova, I.; Sutherland, H. S.; Palmer, B. D.; Blaser, A.; Franzblau, S. G.; Wan, B.; Wang, Y.; Ma, Z.; Denny, W. A.; Thompson, A. M. *J. Med. Chem.* **2010**, *53*, 8421; (b) Palmer, B. D.; Thompson, A. M.; Sutherland, H. S.; Blaser, A.; Kmentova, I.; Franzblau, S. G.; Wan, B.; Wang, Y.; Ma, Z.; Denny, W. A. *J. Med. Chem.* **2010**, *53*, 282; (c) Sutherland, H. S.; Blaser, A.; Kmentova, I.; Franzblau, S. G.; Wan, B.; Wang, Y.; Ma, Z.; Palmer, B. D.; Denny, W. A.; Thompson, A. M. *J. Med. Chem.* **2010**, *53*, 855.
11. Lee, M.; Lee, J.; Carroll, M. W.; Choi, H.; Min, S.; Song, T.; Via, L. E.; Goldfeder, L. C.; Kang, E.; Jin, B.; Park, H.; Kwak, H.; Kim, H.; Jeon, H. S.; Jeong, I.; Joh, J. S.; Chen, R. Y.; Olivier, K. N.; Shaw, P. A.; Follmann, D.; Song, S. D.; Lee, J. K.; Lee, D.; Kim, C. T.; Dartois, V.; Park, S. K.; Cho, S. N.; Barry, C. E., 3rd. *N. Eng. J. Med.* **2012**, *367*, 1508.
12. Rakesh; Sun, D.; Lee, R. B.; Tangallapally, R. P.; Lee, R. E. *Eur. J. Med. Chem.* **2009**, *44*, 460.
13. Baker, W. R.; Cai, S.; Keeler, E. L. WO 9701562A1, 1997.
14. Iijima, T.; Yamamoto, Y.; Akatsuka, H.; Kawaguchi, T. WO 2,007,089,034, A1, 2007
15. Hurdle, J. G.; Lee, R. B.; Budha, N. R.; Carson, E. I.; Qi, J.; Scherman, M. S.; Cho, S. H.; McNeil, M. R.; Lenaerts, A. J.; Franzblau, S. G.; Meibohm, B.; Lee, R. E. *J. Antimicrob. Chemother.* **2008**, *62*, 1037.
16. *Representative analytical data of compound* **8c**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 (s, 1H)), 7.25–7.35 (m, 1H), 7.12–7.17 (m, 2H), 4.57–4.77 (m, 3H), 4.31–4.44 (m, 3H), 4.10–4.26 (m, 3H), 4.01–4.09 (m, 2H), 3.68–3.72 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 166.80, 159.02, 146.93, 138.71, 129.31, 128.44, 123.61, 115.94, 115.73, 114.95, 69.83, 68.50, 67.08, 66.65, 64.04, 49.70, 47.50; HRMS *m/z* $[M+H]^+$ calcd for $C_{17}H_{17}FN_4O_6$: 393.113. Found: 393.120.
17. *Representative analytical data of compound* **9e**: ^{1}H NMR (400 MHz, C. δ. d., J = 4.4 Hz, 1H), 7.39–7.43 (m, 1H), 7.37 (s, 1H), 6.64 (d, J = 8.8 Hz, 1H), 4.43–4.61 (m, 3H), 4.31 (dd, J = 12.0, 1.6 Hz, 1H), 4.01–4.18 (m, 3H), 3.54 (t, J = 4.9 Hz, 4H), 1.58–1.69 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 159.62, 147.97, 147.12, 143.55, 137.97, 119.52, 115.27, 107.00, 68.73, 67.54, 65.48, 47.57, 46.19, 25.47, 24.67; HRMS *m/z* $[M+H]^+$ calcd for $C_{17}H_{21}N_5O_4$: 360.159. Found: 360.171.
18. *Representative analytical data of compound* **9f**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.15 (s, 2H), 6.75–6.90 (m, 2H), 4.37–4.54 (m, 3H), 4.17–4.22 (m, 1H), 3.93–4.12 (m, 3H), 2.90 (t, 4H), 1.57–1.67 (m, 4H), 1.40–1.50 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 156.76, 154.30, 147.13, 143.50, 141.44, 130.15, 123.98, 119.17, 115.73, 115.46, 70.33, 67.54, 66.02, 51.95, 47.50, 29.70, 26.09, 24.17; HRMS *m/z* $[M+H]^+$ calcd for $C_{18}H_{21}FN_4O_4$: 377.154. Found: 377.165.
19. North, E. J.; Scherman, M. S.; Bruhn, D. F.; Scarborough, J. S.; Maddox, M. M.; Jones, V.; Grzegorzewicz, A.; Yang, L.; Hess, T.; Morisseau, C.; Jackson, M.; McNeil, M. R.; Lee, R. E. *Bioorg. Med. Chem.* **2013**, *21*, 2587.
20. Dartois, V.; Barry, C. E., 3rd *Bioorg. Med. Chem. Lett.* **2013**, *23*, 4741.
21. Lenaerts, A. J.; Gruppo, V.; Marietta, K. S.; Johnson, C. M.; Driscoll, D. K.; Tompkins, N. M.; Rose, J. D.; Reynolds, R. C.; Orme, I. M. *Antimicrob. Agents Chemother.* **2005**, *49*, 2294.
22. Lakshminarayana, S. B.; Boshoff, H. I.; Cherian, J.; Ravindran, S.; Goh, A.; Jiricek, J.; Nanjundappa, M.; Nayyar, A.; Gurumurthy, M.; Singh, R.; Dick, T.; Blasco, F.; Barry, C. E., 3rd; Ho, P. C.; Manjunatha, U. H. *PloS One* **2014**, *9*, e105222.
23. Prideaux, B.; Via, L. E.; Zimmerman, M. D.; Eum, S.; Sarathy, J.; O'Brien, P.; Chen, C.; Kaya, F.; Weiner, D. M.; Chen, P. Y.; Song, T.; Lee, M.; Shim, T. S.; Cho, J. S.; Kim, W.; Cho, S. N.; Olivier, K. N.; Barry, C. E., 3rd; Dartois, V. *Nat. Med.* **2014**, *20*, 152.
24. Irwin, S. M.; Gruppo, V.; Brooks, E.; Gilliland, J.; Scherman, M.; Reichlen, M. J.; Leistikow, R.; Kramnik, I.; Nuermberger, E. L.; Voskuil, M. I.; Lenaerts, A. J. *Antimicrob. Agents Chemother.* **2014**, *58*, 4026.