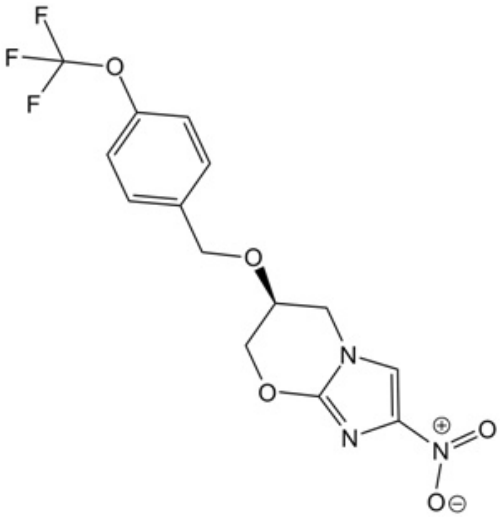
Product Data Sheet

Product Name: PA-824
Cat. No.: GC13561

Chemical Properties

Cas. No.	187235-37-6		
Chemical Name	(6S)-2-nitro-6-[[4-(trifluoromethoxy)phenyl]methoxy]-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine		
SMILES	C1C(COC2=NC(=CN21)[N+](=O)[O-])OCC3=CC=C(C=C3)OC(F)(F)F		
Formula	$C_{14}H_{12}F_3N_3O_5$	M.Wt	359.26
Solubility	≥ 17.85mg/mL in DMSO	Storage	Store at -20°C
General tips	For obtaining a higher solubility , please warm the tube at 37 °C and shake it in the ultrasonic bath for a while.Stock solution can be stored below -20°C for several months.		
Shipping Condition	Evaluation sample solution : ship with blue ice All other available size: ship with RT , or blue ice upon request.		

Structure



Protocol

Cell experiment [1]:

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Cell lines	*Mycobacterium tuberculosis*, *Mycobacterium leprae*
Preparation Method	Resident peritoneal macrophages from Swiss mice were harvested and adhered. For M. leprae, macrophages were infected overnight with fresh, mouse-derived *M. leprae* at a multiplicity of infection (MOI) of 20:1 at 33°C. For *M. tuberculosis*, macrophages were infected with *M. tuberculosis* at an MOI of 2:1 for 30 min at 37°C. Infected macrophages were incubated with PA-824 (2.5-10μg/ml) in culture medium for 7 days. PA-824 was also tested in axenic BACTEC 7H12B medium with *M. leprae*.
Reaction Conditions	2.5-10μg/ml; 7 day.
Applications	PA-824 had no effect on the metabolic activity of *M. leprae* in either axenic culture or within infected macrophages. In contrast, in *M. tuberculosis*-infected macrophages, PA-824 treatment resulted in at least a 2-log (100-fold) reduction in colony-forming units.

Animal experiment [2]:

Animal models	BALB/c mice
Preparation Method	Mice were inoculated intravenously in the tail vein with *M. avium*, *M. abscessus*, *M. chelonae,* or *M. fortuitum*. Dexamethasone (5mg/kg; daily) was administered 1 week prior to infection and stopped 6 days after infection. Mice were treated with drugs for 28 days starting 7 days after infection. PA-824 (200mg/kg/day) was administered by gavage.

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Dosage form	200mg/kg/day; Oral gavage; 28 days.
Applications	In *M. abscessus*-infected mice, PA-824 treatment significantly reduced the bacterial load in the lungs and spleen compared to the untreated control. In *M. fortuitum*-infected mice, PA-824 showed only weak activity in the kidneys. PA-824 showed no significant inhibitory effect against *M. avium* and had little activity against *M. chelonae* in mice.

References:
[1] Manjunatha UH, Lahiri R, Randhawa B, et al. Mycobacterium leprae is naturally resistant to PA-824. Antimicrob Agents Chemother. 2006 Oct;50(10):3350-4.
[2] Zheng L, Qi X, Zhang W, et al. Efficacy of PBTZ169 and pretomanid against Mycobacterium avium, Mycobacterium abscessus, Mycobacterium chelonae, and Mycobacterium fortuitum in BALB/c mice models. Front Cell Infect Microbiol. 2023 Mar 22;13:1115530.

Background

PA-824 is a nitroimidazole anti-tuberculosis drug. PA-824 kills bacteria by inhibiting Mycobacterium tuberculosis cell wall synthesis and interfering with energy metabolism[1-2]. PA-824 can be used in research related to multidrug-resistant tuberculosis and extensively drug-resistant tuberculosis[3-4].

In vitro, PA-824 (2.5-10μg/ml) was used to treat *M. leprae* and *M. tuberculosis* for 7 days. PA-824 had no effect on the viability of *M. leprae*, PA-824 significantly reduced the proliferation of *M. tuberculosis*[5]. PA-824 (0.015-16μg/ml) was used to treat *M. avium*, *M. intracellulare*, *M. abscessus*, and *M. massiliense* for 3-14 days. The inhibitory effect of PA-824 on these five mycobacterial species was generally weak, with minimum inhibitory concentration (MIC) values all greater than 16μg/ml[6].

In vivo, PA-824 (200mg/kg/day) was administered by oral gavage to BALB/c mice infected with *M. avium*, *M. abscessus*, *M. chelonae*, or *M. fortuitum* (once daily, starting 7 days after infection, for 28 days). PA-824 demonstrated strong antibacterial activity in the lungs and spleens of mice infected with *M. abscessus*, and weak activity in the kidneys of mice infected with *M. fortuitum*. PA-824

showed no significant antibacterial effect in the mouse models infected with *M. avium* or *M. chelonae*[7]. PA-824 (40-80mg/kg/day) was administered by oral gavage to Tg.rasH2 mice (once daily for 26 weeks). The mice, exposed to PA-824 at levels exceeding the clinical human exposure dose, did not exhibit drug-related early death, tumors, or non-tumorigenic microscopic pathological changes[8].

References:

[1] Keam SJ. Pretomanid: First Approval. Drugs. 2019 Nov;79(16):1797-1803. doi: 10.1007/s40265-019-01207-9.
[2] Gils T, Lynen L, de Jong BC, et al. Pretomanid for tuberculosis: a systematic review. Clin Microbiol Infect. 2022 Jan;28(1):31-42.
[3] Deb U, Biswas S. Pretomanid: The latest USFDA-approved anti-tuberculosis drug. Indian J Tuberc. 2021 Apr;68(2):287-291.
[4] Koehler N, Andres S, Merker M, et al. Pretomanid-resistant tuberculosis. J Infect. 2023 May;86(5):520-524.
[5] Manjunatha UH, Lahiri R, Randhawa B, et al. Mycobacterium leprae is naturally resistant to PA-824. Antimicrob Agents Chemother. 2006 Oct;50(10):3350-4.
[6] Zheng H, Wang Y, He W, et al. In Vitro Activity of Pretomanid against Nontuberculous Mycobacteria. Antimicrob Agents Chemother. 2022 Jan 18;66(1):e0181021.
[7] Zheng L, Qi X, Zhang W, et al. Efficacy of PBTZ169 and pretomanid against Mycobacterium avium, Mycobacterium abscessus, Mycobacterium chelonae, and Mycobacterium fortuitum in BALB/c mice models. Front Cell Infect Microbiol. 2023 Mar 22;13:1115530.
[8] Ambroso JL, Dillberger J, Bruning-Barry R, et al. Assessment of the Carcinogenic Potential of Pretomanid in Transgenic Tg.rasH2 Mice. Int J Toxicol. 2022 Sep-Oct;41(5):367-379.