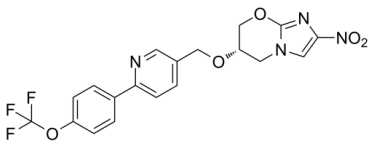
Data Sheet

Product Name:	TBA-354
Cat. No.:	CS-3576
CAS No.:	1257426-19-9
Molecular Formula:	C19H15F3N4O5
Molecular Weight:	436.34
Target:	Bacterial
Pathway:	Anti-infection
Solubility:	DMSO : ≥ 46 mg/mL (105.42 mM)



BIOLOGICAL ACTIVITY:

TBA-354 is a potent anti-tuberculosis compound; maintains activity against Mycobacterium tuberculosis H37Rv isogenic monoresistant strains and clinical drug-sensitive and drug-resistant isolates. IC50 value: Target: Anti-tuberculosis agent in vitro: TBA-354 is narrow spectrum and bactericidal in vitro against replicating and nonreplicating Mycobacterium tuberculosis, with potency similar to that of delamanid and greater than that of PA-824. TBA-354 maintains activity against Mycobacterium tuberculosis H37Rv isogenic monoresistant strains and clinical drug-sensitive and drug-resistant isolates [1]. TBA-354 is 5 to 10 times more potent than PA-824, but selected mutants are cross-resistant to PA-824 and delamanid. TBA-354 is 2 to 4 times more potent than PA-824 when combined with bedaquiline, and when administered at a dose equivalent to that of PA-824, TBA-354 demonstrated superior sterilizing efficacy [2]. in vivo: TBA-354 has high bioavailability and a long elimination half-life. In vitro studies suggest a low risk of drug-drug interactions. Low-dose aerosol infection models of acute and chronic murine tuberculosis reveal time- and dose-dependent in vivo bactericidal activity that is at least as potent as that of delamanid and more potent than that of PA-824.

PROTOCOL (Extracted from published papers and Only for reference)

Cell assay [1] The Caco-2 permeability assay was developed based on the method of Hidalgo et al. In brief, a 96-well multiscreen plate with Caco-2 cells was cultured for 21 to 25 days. TBA-354 at 1 and 10 μM was incubated at 37°C for 40 or 60 min with the Caco-2 cell monolayer in Hanks' balanced salt solution plus HEPES or morpholineethanesulfonic acid (MES) (containing a final concentration of 1% DMSO from a stock solution), in the absence and presence of ketoconazole (100 μM). The permeability through the cell barrier was measured in duplicate in both directions by taking aliquots from the apical (A) side and the basolateral (B) side. TBA-354 concentrations were analyzed by liquid chromatography-tandem mass spectroscopy (LC-MS/MS). Animal administration [1] Female ?20-g BALB/c mice were infected by aerosol with a low dose of M. tuberculosis Erdman. The protocol results in the deposition of approximately 50 to 100 bacilli into the lungs, and the course of infection was then followed by plating homogenates of the lungs on 7H11 agar and determining CFU. Controls consisted of mice treated with the vehicle only. The compounds were prepared weekly by suspension in 0.5% (wt/vol) carboxymethylcellulose (CMC) such that the target dosages were obtained by once-daily dosing by oral gavage of a 200-μl suspension. Groups of 6 or 7 mice were dosed for 5 consecutive days each week. The suspensions were stored at 4°C between daily doses. Mice were sacrificed 3 days after the final dose to minimize carryover from the lung homogenates to the plating medium. Both lungs were homogenized and diluted in Hanks' balanced salt solution (HBSS)-Tween, and aliquots were plated on Middlebrook 7H11 medium. CFU were determined after 3 weeks of incubation at 37°C. For statistical analysis of efficacy data, multiple comparisons among pairs were performed by the Bonferroni method.

References:

[1]. Upton AM, et al. In Vitro and In Vivo Activities of the Nitroimidazole TBA-354 against Mycobacterium tuberculosis. Antimicrob Agents Chemother. 2015 Jan;59(1):136-44.

[2]. Tasneen R, et al. Contribution of the Nitroimidazoles PA-824 and TBA-354 to the Activity of Novel Regimens in Murine Models of Tuberculosis. Antimicrob Agents Chemother. 2015 Jan;59(1):129-35.

CAIndexNames:

5H-Imidazo[2,1-b][1,3]oxazine, 6,7-dihydro-2-nitro-6-[[6-[4-(trifluoromethoxy)phenyl]-3-pyridinyl]methoxy]-, (6S)-

SMILES:

FC(F)(F)OC1=CC=C(C2=CC=C(CO[C@H]3CN4C(OC3)=NC([N+]([O-])=O)=C4)C=N2)C=C1

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