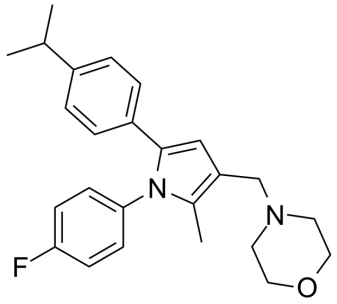
BM635

Cat. No.:	HY-109587
CAS No.:	1493762-74-5
Molecular Formula:	$C_{25}H_{29}FN_2O$
Molecular Weight:	392.51
Target:	Bacterial
Pathway:	Anti-infection
Storage:	Powder -20°C 3 years 4°C 2 years In solvent -80°C 2 years -20°C 1 year



SOLVENT & SOLUBILITY

In Vitro

DMSO : 31 mg/mL (78.98 mM; Need ultrasonic and warming)

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	2.5477 mL	12.7385 mL	25.4771 mL
5 mM	0.5095 mL	2.5477 mL	5.0954 mL
10 mM	0.2548 mL	1.2739 mL	2.5477 mL

Please refer to the solubility information to select the appropriate solvent.

BIOLOGICAL ACTIVITY

Description

BM635 is a MmpL3 inhibitor with outstanding anti-mycobacterial activity. BM635 has an MIC_{50} of 0.12 μM against M. tuberculosis H37Rv.

IC_{50} & Target

MIC50: 0.12 μM (M. tuberculosis H37Rv)[1]

In Vivo

BM635 has potent MIC (0.12 μM), Tox_{50}:MIC ratio of >100, and good microsomal stability in mice (1.4 mL/min/g). When tested in an acute murine infection model at multiple doses, BM635 exhibits potent anti-tubercular activity, with an ED_{99} of 49 mg/Kg ($IC_{95\%}$: 43–54 mg/Kg)[1]. The half-life in vivo of BM635 is 1h, allowing a reasonable maximum concentration (C_{max} =1.62 μM) and a moderate bioavailability (46%). Its poor aqueous solubility together with its high lipophilicity leads to low exposure in vivo[2].

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Cell Assay	The measurement of the minimum inhibitory concentration (MIC) for each tested compounds (including BM635) are performed in 96 wells flat-bottom, polystyrene microtiter plates. Ten two-fold drug dilutions in neat DMSO starting at 200 µM are performed. Five µL of these drug solutions are added to 95 µL of Middlebrook 7H9 medium. Isoniazid is used as a positive control, 8 two-fold dilutions of Isoniazid starting at 160 µg/mL are prepared and 5 µL of this control curve is added to 95 µL of Middlebrook 7H9 medium. Five µL of neat DMSO are added 95 µL of Middlebrook 7H9 medium in row 12 (growth and Blank controls). The inoculum is standardized to approximately 1×10^7 cfu/mL and diluted 1 in 100 in Middlebrook 7H9 broth to produce the final inoculum of H37Rv strain. One hundred µL of this inoculum is added to the entire plate but G-12 and H-12 wells (Blank controls). All plates are placed in a sealed box to prevent drying out of the peripheral wells and they are incubated at 37°C without shaking for six days. A resazurin solution is prepared by dissolving one tablet of resazurin in 30 mL sterile PBS (phosphate buffered saline). Of this solution, 25 µL are added to each well. Fluorescence is measured after 48 hours to determine the MIC value[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration	Mouse: Nine (one per dose) 8-10 week old B6 female mice are infected by intratracheal route with 10^5CFU H37Rv per mouse suspended in 50 µL phosphate buffer saline. BM635 is administered once a day at nine doses ranging from 40 to 300 mg/kg from day 1 to day 8 after infection, and 24 hours after the last dose the mice are sacrificed. To measure the infection burden in lungs, all lobes are aseptically removed and homogenized. The homogenates are supplemented with 5% glycerol and stored frozen (−80°C) until plating. Plates (10%OADC-7H11 medium) are incubated for 14 days at 37°C[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

REFERENCES

[1]. Poce G, et al. Improved BM212 MmpL3 inhibitor analogue shows efficacy in acute murine model of tuberculosis infection. PLoS One. 2013;8(2):e56980.

[2]. Poce G, et al. Pharmaceutical salt of BM635 with improved bioavailability. Eur J Pharm Sci. 2017 Mar 1;99:17-23.

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