BMS-378806

Cat. No.: HY-14134

CAS No.: 357263-13-9

Molecular Formula: $C_{22}H_{22}N_4O_4$

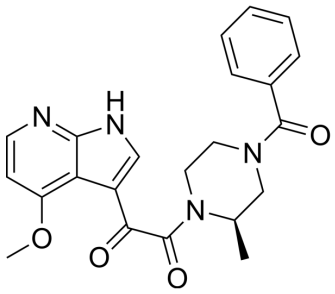
Molecular Weight: 406.43

Target: HIV

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 : 50 mg/mL (123.02 mM; Need ultrasonic)

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	2.4604 mL	12.3022 mL	24.6045 mL
5 mM	0.4921 mL	2.4604 mL	4.9209 mL
10 mM	0.2460 mL	1.2302 mL	2.4604 mL

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

In Vivo

1. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: ≥ 2.5 mg/mL (6.15 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.5 mg/mL (6.15 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 1.67 mg/mL (4.11 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

BMS-378806 is a potent HIV-1 attachment inhibitor that interferes with CD4-gp120 interactions. BMS-378806 selectively inhibits the binding of HIV-1 gp120 to the CD4 receptor with EC_{50} of 0.85-26.5 nM in virus.

IC_{50} & Target

HIV-1 | HIV-2

In Vitro

In a series of biochemical assays, BMS-378806 is not an effective inhibitor of HIV integrase, protease, or reverse transcriptase, but did compete with soluble CD4 binding to a monomeric form of gp120 in an ELISA assay with IC_{50}=100 nM.

	The specificity of BMS-378806 toward inhibition of HIV-1 is confirmed by evaluation against HIV-2, SIV, MuLV, RSV, HCMV, BVDV, VSV, and influenza virus, with no significant inhibitory activity observed at concentrations ranging from 10 to 30 μM and no overt cytotoxicity toward the host cells, CC_{50}>225 μM. BMS-378806 is not a potent inhibitor of any of the five major human CYP isoforms, evaluated as recombinant preparations, with IC_{50} values of >100 μM for CYP1A2 and CYP2C9, 23 μM for CYP2C19, 20 μM for CYP2D6, and 39 to 81 μM for CYP3A4. Moreover, since BMS-378806 is metabolized by CYP450 1A2, 2D6, and 3A4, it is unlikely to lead to severe drug−drug interactions in a clinical setting[1]. BMS-378806 inhibits viral replication by interfering with the binding interactions of gp120 with the cellular CD4 receptor. The IC_{50}s determined for the gp120s from HIV LAI, BAL, NA420LN40, SF162, NL4-3, NA420B33, YU2, AD8, JRCSF, and 92US15.6 are 0.1, 0.1, 0.3, 0.5, 0.6, 0.7, 0.9, 1.0, 1.1, and 1.6 μM, respectively. A similar observation is also made for BMS-378806 (IC_{50}s range from 0.2 to 9.6 μM)[2]. BMS-378806 binds directly to gp120 at a stoichiometry of approximately 1:1, with a binding affinity similar to that of soluble CD4. The potential BMS-378806 target site is localized to a specific region within the CD4 binding pocket of gp120 by using HIV-1 gp120 variants carrying either compound-selected resistant substitutions or gp120-CD4 contact site mutations[3]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	In toxicology studies, BMS-378806 is well tolerated in rats at doses of 100 mg/kg/day for 2 weeks and in dogs at doses of 90 mg/kg for 10 days. The dose-proportional increases in the AUC and C_{max} are observed between doses of 5 and 25 mpk, when BMS-378806 is administered either in the solution or suspension formulation. In all three species, plasma levels of drug exceeded the concentrations required to half-maximally inhibit virus replication in vitro. The volume of distribution of BMS-378806 ranges from 0.4 to 0.6 L/kg, indicative of partitioning beyond plasma; however, examination of brain levels in the rat reveals minimal CNS penetration[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Kinase Assay [3]	To measure gp120-CD4 binding, the wild-type or variant gp120 proteins are first captured onto a plate by D7324 antibody. CD4 binding is initiated by adding sCD4 to a gp120-coated plate. To determine the ability of BMS-378806 to compete with sCD4 for gp120 binding, the compound is added simultaneously with sCD4 and reactions are carried out in buffer C (50 mM Tris-HCl [pH 7.5], 100 mM NaCl, 1% bovine serum albumin) for 2 h at room temperature. After washing with buffer B (20 mM Tris-HCl, 500 mM NaCl, 0.05% Tween 20 [pH 7.5]), the bound CD4 is detected with OKT4 antibody (0.36 μg/mL) and goat anti-mouse peroxidase conjugate. Bound antibody is detected with 3,3′,5,5′-tetramethylbenzidine chromogenic substrate for peroxidase[3]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1]	Rats, Dogs and Monkeys[1] The pharmacokinetic properties of BMS-378806 in the rat, dog, and cynomolgus monkey are summarized. The oral bioavailability of BMS-378806 in rats, administered as a solution in PEG 400/EtOH (90:10 v/v), is 19% at a dose of 5 mg/kg while an aqueous crystalline suspension of free base in 0.75% (w/w) Methocel A4M Premium administered orally at the same dose afforded a relative bioavailability of 61%. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Sci Adv. 2024 Mar;10(9):eadn0042.
- Int J Antimicrob Agents. 2019 Dec;54(6):814-819.
- EMBO Rep. 2022 Apr 11;e53932.
- Patent. US20180263995A1.

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REFERENCES

[1]. Wang T, et al. Discovery of 4-benzoyl-1-[(4-methoxy-1H- pyrrolo[2,3-b]pyridin-3-yl)oxoacetyl]-2- (R)-methylpiperazine (BMS-378806): a novel HIV-1 attachment inhibitor that interferes with CD4-gp120 interactions. J Med Chem. 2003 Sep 25;46(20):4236-9.

[2]. Ho HT, et al. Envelope conformational changes induced by human immunodeficiency virus type 1 attachment inhibitors prevent CD4 binding and downstream entry events. J Virol. 2006 Apr;80(8):4017-25.

[3]. Guo Q, et al. Biochemical and genetic characterizations of a novel human immunodeficiency virus type 1 inhibitor that blocks gp120-CD4 interactions. J Virol. 2003 Oct;77(19):10528-36

Tel: 609-228-6898 Fax: 609-228-5909 E-mail: tech@MedChemExpress.com

Address: 1 Deer Park Dr, Suite Q, Monmouth Junction, NJ 08852, USA