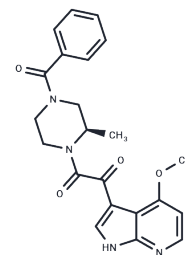


BMS-378806

Chemical Properties

CAS No. : 357263-13-9
 Formula: C₂₂H₂₂N₄O₄
 Molecular Weight: 406.43
 Storage: Powder: -20°C for 3 years | In solvent: -80°C for 1 year
 Actual storage temperature shall be subject to the COA.



Biological Description

Description	BMS-378806 (BMS-806) selectively inhibits the binding of HIV-1 gp120 to the CD4 receptor with EC ₅₀ of 0.85-26.5 nM in virus.
Targets(IC ₅₀)	HIV Protease, gp120/CD4
In vitro	BMS-806, a 7-azaindole derivative, binds gp120 and interferes with the interaction of HIV surface protein gp120 with the host cell receptor CD4. BMS-806 inhibits a panel of macrophage- and T cell-tropic HIV-1 strains, which are laboratory strains that use either CCR5 (M-tropic) or CXR4 (T-tropic) co-receptors to enter cells and are classified as B subtypes. The aqueous solubility from the crystalline form of BMS-806 (BMS 378806) is 170 µg/mL. The solubility of BMS-806 is 1.3 mg/mL at pH=2.1 and 3.3 mg/mL at pH=11, a solubility profile that reveals the amphoteric nature of BMS-806 and estimates the pK _a of the protonated form as 2.9 while that of the free base is approximately 9.6. BMS-806 competes with soluble CD4 binding to a monomeric form of gp120 in an ELISA assay with IC ₅₀ = ~ 100 nM. BMS-806 is specific towards HIV-1, with no significant inhibitory activity against HIV-2, SIV, MuLV, RSV, HCMV, BVDV, VSV, and influenza virus observed at concentrations ranging from 10 to 30 µM and no overt cytotoxicity toward host cells, CC ₅₀ values > 225 µM. [1] BMS-806 binds directly to gp120 at a stoichiometry of approximately 1:1, with a binding affinity similar to that of soluble CD4. The potential BMS-806 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. [2]
In vivo	When BMS-806 is administered dose-proportional increases in the AUC and C _{max} is observed. In rat, dog and monkey, plasma levels of drug exceeded the concentrations required to half-maximally inhibit virus replication in vitro. The volume of distribution of BMS-806 ranges from 0.4 to 0.6 L/kg, indicative of partitioning beyond plasma; however, examination of brain levels in the rat revealed minimal CNS penetration. [1] BMS-806 is stable in human, rat, dog and monkey blood at 37 °C during a 2-h incubation. The blood-to-plasma concentration ratios in humans, rats, dogs and monkeys are 1.1, 0.77, 1.2 and 0.92 (n=3), respectively, suggesting that BMS-806 is distributed to approximately the same extent between plasma and blood cells. The human clearance of BMS-806 predicted from microsomes is 9.2 ml/min/kg (46% of the hepatic blood flow). [3]

Kinase Assay	Drug susceptibility Assay: In general, host cells are infected with HIV-1 at a multiplicity of infection (MOI) of 0.005 50% tissue culture infective doses (TCID50)/cell followed by incubation in the presence of serially diluted inhibitors for 4 to 7 days. Virus yields are quantitated using an RT assay or a p24 enzyme-linked immunosorbent assay (ELISA) (NEN). The results from at least three experiments are used to calculate the 50% effective concentrations (EC50s). The EC50s of IDV, SQV, RTV, and NFV are compared to that of BMS-806 using Dunnett's test. These comparisons are made separately within each assay system. Dunnett's test is used to reduce the probability of false-positive results when a number of treatments are being compared to a control. Confidence bounds for the fold increases in EC50s observes when the same drug is tested in two different assay systems are computed using Fieller's theorem. The use of this theorem is necessary because ratios of parameters (in this case, EC50s) are known not to follow a standard probability distribution, such as the normal distribution. Numbers within the confidence interval are not significantly different from the observed fold increase at the
Cell Research	To determine cytotoxicity, MT-2 cells are incubated in the presence of serially diluted BMS-806 for 6 days and cell viability is quantitated using an XTT [2,3-bis(2-methoxy-4-nitro-5-sulfophenyl-2H-tetrazolium-5-carboxanilide)] assay to calculate the 50% cytotoxic concentrations (CC50s). (Only for Reference)

Solubility Information

Solubility	Ethanol: 3 mg/mL (7.38 mM),Sonication is recommended. H2O: < 1 mg/mL (insoluble or slightly soluble), DMSO: 81 mg/mL (199.3 mM),Sonication is recommended. (< 1 mg/ml refers to the product slightly soluble or insoluble)
In vivo Formulation	10% DMSO+40% PEG300+5% Tween 80+45% Saline: 3.3 mg/mL (8.12 mM),Sonication is recommended. <i>Please add the solvents sequentially, clarifying the solution as much as possible before adding the next one. Dissolve by heating and/or sonication if necessary. Working solution is recommended to be prepared and used immediately. The formulation provided above is for reference purposes only. In vivo formulations may vary and should be modified based on specific experimental conditions.</i>

Preparing Stock Solutions

	1mg	5mg	10mg
1 mM	2.4604 mL	12.3022 mL	24.6045 mL
5 mM	0.4921 mL	2.4604 mL	4.9209 mL
10 mM	0.246 mL	1.2302 mL	2.4604 mL
50 mM	0.0492 mL	0.246 mL	0.4921 mL

Please select the appropriate solvent to prepare the stock solution, according to the solubility of the product in different solvents. Please use it as soon as possible.

Note: The dilution table applies only to solid products. For liquid products, please calculate the stock solution based on the stated concentration and/or density.

Reference

- Wang T, et al, J Med Chem, 2003, 46(20), 4236-4239.
- Guo Q, et al, J Virol, 2003, 77(19), 10528-10536.
- Yang Z, et al, Biopharm Drug Dispos, 2005, 26(9)

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