Product Data Sheet

Product Name: BMS-378806 (BMS-806)
Cat. No.: GC10263

Chemical Properties

Cas. No.	357263-13-9		
Chemical Name	1-[(2R)-4-benzoyl-2-methylpiperazin-1-yl]-2-(4-methoxy-1H-pyrrolo[2,3-b]pyridin-3-yl)ethane-1,2-dione		
SMILES	CC1CN(CCN1C(=O)C(=O)C2=CNC3=NC=CC(=C23)OC)C(=O)C4=CC=CC=C4		
Formula	$C_{22}H_{22}N_4O_4$	M.Wt	406.43
Solubility	≥ 20.2mg/mL in DMSO	Storage	Store at -20°C
General tips	For obtaining a higher solubility , please warm the tube at 37 ℃ and shake it in the ultrasonic bath for a while.Stock solution can be stored below -20℃ 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	BMS-378806 (BMS-806)		

Protocol

Kinase experiment [1]:

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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 95% level.

Cell experiment:

Cell lines	MT-2 cells
Preparation method	The solubility of this compound in DMSO is >10 mM. General tips for obtaining a higher concentration: Please warm the tube at 37℃ for 10 minutes and/or shake it in the ultrasonic bath for a while. Stock solution can be stored below -20℃ for several months.

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Reacting condition	0-3 mM for 6 days; or 0.8, 1.6, and 3.2 μM
Applications	BMS-378806 showed HIV-1 inhibitory activity and cytotoxicity in MT-2 cells with EC50 value of 2.68 nM [1]. Moreover, BMS-378806 inhibited the interaction between viral gp120 and cellular CD4 receptors and showed direct binding affinity to gp120 [2].

Animal experiment:

Animal models	Rats, monkeys and dogs model.
Dosage form	i.v. 1 and 5 mg/kg and p.o. 5 and 25 mg/kg for 0.17, 0.5, 1, 1.5 and 2 h
Applications	BMS-378806 showed species-dependent oral bioavailability which was 19%–24% in rats and monkeys and 77% in dogs [3].
Other notes	Please test the solubility of all compounds indoor, and the actual solubility may slightly differ with the theoretical value. This is caused by an experimental system error and it is normal.

References:

1. Wang, T., Zhang, Z., Wallace, O. B., Deshpande, M., Fang, H., Yang, Z., Zadjura, L. M.,

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Tweedie, D. L., Huang, S., Zhao, F., Ranadive, S., Robinson, B. S., Gong, Y. F., Ricarrdi, K., Spicer, T. P., Deminie, C., Rose, R., Wang, H. G., Blair, W. S., Shi, P. Y., Lin, P. F., Colonno, R. J. and Meanwell, N. A. (2003) 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. 46, 4236-4239

2. Guo, Q., Ho, H. T., Dicker, I., Fan, L., Zhou, N., Friborg, J., Wang, T., McAuliffe, B. V., Wang, H. G., Rose, R. E., Fang, H., Scarnati, H. T., Langley, D. R., Meanwell, N. A., Abraham, R., Colonno, R. J. and Lin, P. F. (2003) Biochemical and genetic characterizations of a novel human immunodeficiency virus type 1 inhibitor that blocks gp120-CD4 interactions. J

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3. Yang, Z., Zadjura, L., D'Arienzo, C., Marino, A., Santone, K., Klunk, L., Greene, D., Lin, P. F., Colonno, R., Wang, T., Meanwell, N. and Hansel, S. (2005) Preclinical pharmacokinetics of a novel HIV-1 attachment inhibitor BMS-378806 and prediction of its human pharmacokinetics. Biopharm Drug Dispos. 26, 387-402

Background

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 EC50 of 0.85-26.5 nM in virus.

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 IC50=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, CC50>225 μM. BMS-378806 is not a potent inhibitor of any of the five major human CYP isoforms, evaluated as recombinant preparations, with IC50 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 IC50s 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 (IC50s 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].

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 Cmax 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].

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.