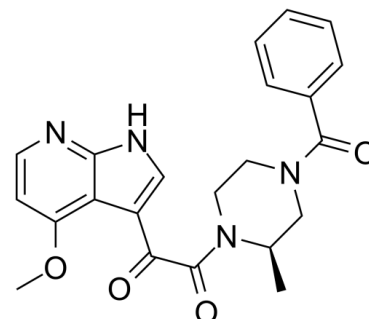


Data Sheet

Product Name:	BMS-378806
Cat. No.:	CS-0525
CAS No.:	357263-13-9
Molecular Formula:	C ₂₂ H ₂₂ N ₄ O ₄
Molecular Weight:	406.43
Target:	HIV
Pathway:	Anti-infection
Solubility:	DMSO : ≥ 50 mg/mL (123.02 mM)



BIOLOGICAL ACTIVITY:

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] **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 μ M and no overt cytotoxicity toward the host cells, CC_{50} >225 μ M. 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 μ M for CYP1A2 and CYP2C9, 23 μ M for CYP2C19, 20 μ M for CYP2D6, and 39 to 81 μ M 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 μ M, respectively. A similar observation is also made for BMS-378806 (IC_{50} s range from 0.2 to 9.6 μ M)^[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 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].

PROTOCOL (Extracted from published papers and Only for reference)

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 μ g/mL) and goat anti-mouse peroxidase conjugate. Bound antibody is detected with 3,3',5,5'-tetramethylbenzidine chromogenic substrate for peroxidase^[3]. **Animal Administration:** BMS-378806 is administered as a solution in PEG 400/EtOH (90:10 v/v)^{[1][1]} Rat, Dog and Monkey^[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%.

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

CAIndexNames:

1,2-Ethanedione, 1-[(2R)-4-benzoyl-2-methyl-1-piperazinyl]-2-(4-methoxy-1H-pyrrolo[2,3-b]pyridin-3-yl)-

SMILES:

COC1=C2C(NC=C2C(C(N3CCN(C[C@H]3C)C(C4=CC=CC=C4)=O)=O)=O)=NC=C1

Caution: Product has not been fully validated for medical applications. For research use only.

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