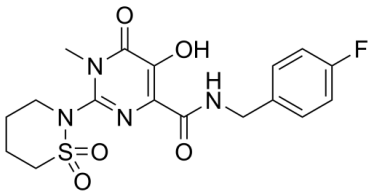
Data Sheet

Product Name: BMS-707035
Cat. No.: CS-0493
CAS No.: 729607-74-3
Molecular Formula: $C_{17}H_{19}FN_4O_5S$
Molecular Weight: 410.42
Target: HIV; HIV Integrase
Pathway: Anti-infection; Metabolic Enzyme/Protease
Solubility: DMSO : 50 mg/mL (121.83 mM; Need ultrasonic)



BIOLOGICAL ACTIVITY:

BMS-707035 is a potent orally active **HIV-1 integrase strand transfer** inhibitor (INSTI). BMS-707035 has enzyme inhibitory with an **IC_{50}** value of 3 nM. BMS-707035 also has weak CYP inhibiton and antiviral activity. BMS-707035 can be used for the research of human immunodeficiency virus-1 (HIV-1)[1]. ***In Vitro:*** BMS-707035 has antiviral activity with EC_{50} values of 2 nM and 17 nM in the presence of 10% FBS and 15 mg/mL human serum albumin, respectively[1].

BMS-707035 has high plasma protein binding and not overtly cytotoxicy to several cell lines, with CC_{50} value of ≥45 μM[1].

BMS-707035 has a relatively weak CYP inhibiton with IC_{50} value of ≥40 μM[1]. ***In Vivo:*** BMS-707035 has a low clearance effect in the rat, dog and monkey with moderate to long elimination half-lives in all species[1].

Pharmacokinetic Parameters of BMS-707035 in rat, dog and monkey (IV)[1].

	Rat	Monkey	Dog
IV dose (mg/kg)	0.87	1	1
CL (ml/min/kg)	9.7	6.8	2.0
$T_{1/2}$(h)	4.0	6.5	6.0
V_{ss}(L/kg)	0.86	0.87	0.45
PO dose (mg/kg)	4.4	5	5.2
C_{max}(μM)	4.51	6.12	72.8
t_{max}(h)	0.25	0.25	0.25
AUC (μM*h)	19.1	19.2	162
F (%)	86	56	129

PROTOCOL (Extracted from published papers and Only for reference)

Kinase assay [4] The in vitro activities of purified INs in combination with the various duplex LTRs are measured through a scintillation proximity assay (SPA). In a first step, the viral LTR duplexes are prepared by annealing individual oligonucleotides. The viral (donor) LTR DNA is then attached, via a 5'-biotin linker on the plus strand, to streptavidin-coated SPA PVT beads as follows. SPA PVT beads (10 mg) are suspended in 0.2 mL of PBS. The suspension is then centrifuged at <5000 × g for 15 min. The supernatant is removed, and the pellet is resuspended with 0.2 mL of PBS, 0.85 M NaCl, and 21 μL of 12 μM duplex HIV LTR DNA. The sequences of the duplexes are as follows, except for the variations in the underlined bases: plus strand, 5'-biotin-ACCCTTTTAGTCAGTGTGGAAAATCTCTAGCA; minus strand, 5'-ACTGCTAGAGATTTTCCACACTGACTAAAAG. The LTR DNA is allowed to bind for 60 min at room temperature with gentle rocking, after which time 0.8 mL of TE is added. The mixture is then centrifuged at <5000 × g and resuspended in 0.8 mL of TE, 50 mM NaCl. The beads are washed 4 additional times with TE, 50 mM NaCl, each time centrifuging to remove unbound viral LTR DNA. The final pellet is resuspended in 0.2 mL of PBS and stored at 4°C before use. Enzyme complexes for 80 strand transfer reactions are prepared as follows: 0.15 mL of bead-DNA complexes, 2.25 mL of SPA buffer (13.3 mM dithiothreitol, 32 mM MOPS, pH 7.0, 0.067% NP-40, 6.4% polyethylene glycol, 25.6 mM MgCl2, 12.8% (v/v) Me2SO, and 100 mM NaCl), and IN (37 μg of WT, 88 μg of N155H, and 36 μg of Q148R) are incubated at 37°C. After 1.5 hours, complexes are pelleted and resuspended with 2.4 mL of SPA buffer. The proper amount of each IN is determined through titration experiments and represented the minimal amount of enzyme required to produce the maximal amount of strand transfer products. The target DNA is prepared (5'-[33P]TGACCAAGGGCTAATTCACT-3' annealed to 5'-[33P]AGTGAATTAGCCCTTGGTCA-3') in a separate step by individually 5' end labeling each of the oligonucleotides with [γ-33P]ATP. The 33P-labeled oligonucleotides are then annealed to form the target duplex DNA. Strand transfer assays consists of combining 30 μL of IN complexes with 10 μL of 25% Me2SO/H2O) (v/v) in white microtiter plates. After 10 min of incubation at 37°C, 10 μL of 33P-labeled target DNA (1 × 106 cpm) is added (final concentration of target is 0.92 nM). Plates are returned to 37°C for 2 hours, after which time the strand transfer reactions are stopped by the addition of 200 μL of PBS, 50 mM EDTA. Plates are allowed to stand overnight before reading on a Topcount scintillation counter. HIV-1 IN complexes are evaluated for inhibitor sensitivity using the SPA assay, except that 10 μL of a 5-fold serial dilution of BMS-707035 in 25% (v/v) Me2SO/H2O is added in the place of 10 μL of 25% (v/v) Me2SO/H2O. Data are analyzed by fitting to a sigmoidal dose-response curve.

References:

[1]. B Narasimhulu Naidu, et al. The discovery and preclinical evaluation of BMS-707035, a potent HIV-1 integrase strand transfer inhibitor. Bioorg Med Chem Lett. 2018 Jul 1;28(12):2124-2130.

CAIndexNames:

4-Pyrimidinecarboxamide, N-[(4-fluorophenyl)methyl]-1,6-dihydro-5-hydroxy-1-methyl-6-oxo-2-(tetrahydro-1,1-dioxido-2H-1,2-thiazin-2-yl)-

SMILES:

FC1=CC=C(C=C1)CNC(C(N=C(N2C)N3S(CCCC3)(=O)=O)=C(C2=O)O)=O

Tel: 610-426-3128 Fax: 888-484-5008 E-mail: sales@ChemScene.com

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