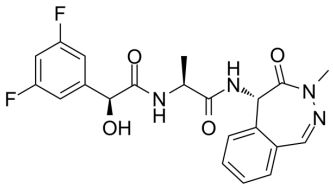
BMS 433796

Cat. No.:	HY-50884
CAS No.:	935525-13-6
Molecular Formula:	$C_{21}H_{20}F_2N_4O_4$
Molecular Weight:	430.4
Target:	γ-secretase
Pathway:	Neuronal Signaling; Stem Cell/Wnt
Storage:	Please store the product under the recommended conditions in the Certificate of Analysis.



BIOLOGICAL ACTIVITY

Description	BMS 433796 is a γ-secretase inhibitor with Aβ lowering activity in a transgenic mouse model of Alzheimer's disease.
IC_{50} & Target	γ-secretase[1]
In Vitro	BMS-433796 cause a concentration-dependent decrease in [^{3}H]IN973 binding, with IC_{50} value of 1.2 nM, very similar to the IC_{50} values for inhibition of Aβ40 in human embryonic kidney cells overexpressing the Swedish mutation of APP of 0.8 nM, respectively, and for inhibition of Aβ42 of 0.4 nM, respectively[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	BMS 433796 is characterized in pharmacokinetic studies in male Sprague-Dawley rats. Following a 10-min intravenous infusion at 2.3 μmol/kg in PEG-400, the total body clearance of 40 is 5.2±0.82 mL/min/kg (means±SEM; n=3), indicating low clearance. The apparent terminal elimination half-life is 4.6±0.48 h. Oral administration of a PEG-400 suspension at 35 μmol/kg shows an oral bioavailability of 31% with prolonged absorption. BMS 433796 has satisfactory metabolic stability in human liver microsomal preparations and is not an inhibitor of human CYPs (IC_{50}>100 μM)[1]. Brain Aβ40 is reduced as a result of administering BMS-433796 in a dose-dependent manner, with ED_{50} value of 2.4 mg/kg, respectively[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Kinase Assay [2]	The binding assay is performed in duplicate in an assay volume of 250 μl consisting of 25 μL of buffer (50 mM HEPES and 0.1% CHAPSO, pH 7.0) or 10 μM BMS-433796 to define nonspecific binding, 25 μL of buffer containing [^{3}H]IN973, and 200 μL of homogenate (200 μg of protein). Incubation is initiated by the addition of the membrane homogenates at 25°C for 1 h. Binding reactions are terminated by filtration through Whatman GF/B filters using a cell harvester. Unbound radioactivity is removed by rinsing the filters with ice-cold wash buffer (PBS; pH 7.0). Filters are counted using a 2500TR liquid scintillation counter. Saturation data are analyzed by the nonlinear regression analysis program LIGAND. Binding curves are best fit to a one-site model, yielding the equilibrium dissociation constant (K_d) and the maximal number of binding sites (B_{max})[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

REFERENCES

[1]. Prasad CV, et al. Discovery of (S)-2-((S)-2-(3,5-difluorophenyl)-2-hydroxyacetamido)-N-((S,Z)-3-methyl-4-oxo-4,5-dihydro-3H-benzo[d][1,2]diazepin-5-yl)propanamide (BMS-433796): a gamma-secretase inhibitor with Abeta lowering activity in a transgenic mouse model of Alzheimer's disease. Bioorg Med Chem Lett. 2007 Jul 15;17(14):4006-11.

[2]. Goldstein ME, et al. Ex vivo occupancy of gamma-secretase inhibitors correlates with brain beta-amyloid peptide reduction in Tg2576 mice. J Pharmacol Exp Ther. 2007 Oct;323(1):102-8.

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