AMG-8718

Cat. No.: HY-12938

CAS No.: 1215868-94-2

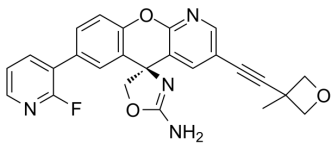
Molecular Formula: $C_{25}H_{19}FN_4O_3$

Molecular Weight: 442.44

Target: Beta-secretase

Pathway: Neuronal Signaling

Storage: Please store the product under the recommended conditions in the Certificate of Analysis.



BIOLOGICAL ACTIVITY

Description

AMG-8718 is a potent, selective and orally active BACE1 inhibitor with IC_{50} values of 0.0007, 0.005 μM for BACE1 and BACE2, respectively. AMG-8718 significantly decreases $Aβ_{40}$ levels in the CSF and brain[1].

IC_{50} & Target

BACE1	BACE2
0.0007 μM (IC_{50})	0.005 μM (IC_{50})

In Vitro

AMG-8718 (compound 42) shows good stability in human and rat liver microsomes, hERG binding activity with an K_i value of >10 μM[1].

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

In Vivo

AMG-8718 (compound 42) (10 mg/kg; p.o.)shows significantly decreases $Aβ_{40}$ levels in the CSF and brain[1].

AMG-8718 (i.v. for 2 mg/kg or p.o. for 5 mg/kg) shows good bioavailability of 70%, 96%,101% for rats, beagle dog, monkey, respectively[1].

AMG-8718 (30 mg/kg for; p.o.) dose-dependent decreases in both CSF and brain Aβ levels at 4 h time points with 50% Aβ reduction (EC_{50}) values of 18 and 67 nM for CSF and brain respectively in rats[1].

AMG-8718 (2.5, 8, 16 mg/kg; i.v.; a series of three 30 min infusions) shows high unbound plasma concentrations with 0.298, 1.70, 3.62 μM at the end of each infusion in chloralose-anesthetized dogs[1].

Pharmacokinetic Parameters ofAMG-8718 in rats, beagle dog, cynomolgus monkey[1].

species	Cl (L/h/kg)	V_{dss}(L/kg)	$t_{1/2}$(h)	C_{max} (μM)	t_{max}(h)	% F	plasma protein binding (F_u)
	i.v.			p.o.			
rat	0.33	1.1	4.8	3.8	1.7	70	0.013
beagle dog	0.26	1.6	5.2	8.1	1.0	96	0.038
monkey	0.61	2.2	7.7	6.1	1.7	101	0.054

2 mg/kg i.v.; rats (DMSO), dog (1% Tween80/2% HMPC/97% water at pH = 4), cynomolgus monkey (25% HBC/75% water at pH = 4); 5 mg/kg p.o. (1% Tween80/2% HMPC/97% water at pH = 2)[1].

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

Animal Model:	Male Sprague-Dawley rats[1]
Dosage:	10 mg/kg
Administration:	Oral gavage
Result:	Significantly decreased $A\beta_{40}$ levels in the CSF at the 4 h time point at 69%, produced a robust response in the brain with 48% reduction of Aβ40 levels.

Animal Model:	Rats, beagle dog, monkey[1]
Dosage:	2, 5 mg/kg
Administration:	I.v. for 2 mg/kg or p.o. for 5 mg/kg
Result:	Showed moderate total clearance, moderate Vdss, and half-lives of ca. 5-8 h across all three species, and bioavailability was high (70–101%).

Animal Model:	Rats[1]
Dosage:	30 mg/kg
Administration:	P.o.
Result:	Demonstrated dose-dependent decreases in both CSF and brain Aβ levels at 4 h and 8 h time points.

REFERENCES

[1]. Dineen TA,et al. Inhibitors of β-site amyloid precursor protein cleaving enzyme (BACE1): identification of (S)-7-(2-fluoropyridin-3-yl)-3-((3-methyloxetan-3-yl)ethynyl)-5'H-spiro[chromeno[2,3-b]pyridine-5,4'-oxazol]-2'-amine (AMG-8718). J Med Chem. 2014 Dec 11;57(23):9811-31.

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