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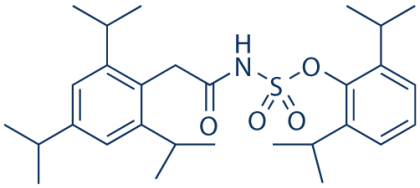
Avasimibe (P450 Inhibitor)

Cat. No.	Product Name	Pack Size
SD7212-10mM	Avasimibe (P450 Inhibitor)	10mM×0.2ml
SD7212-5mg	Avasimibe (P450 Inhibitor)	5mg
SD7212-25mg	Avasimibe (P450 Inhibitor)	25mg

Description:

➢ Chemical information:

Chemical Name	[2,6-di(propan-2-yl)phenyl] N-[2-[2,4,6-tri(propan-2yl)phenyl]acetyl]sulfamate
Abbreviations	Avasimibe
Alias	Avasimibe sodium, CI 1011, CI-1011, CI1011
Chemical Formula	$C_{29}H_{43}NO_4S$
Molecular Weight	501.72
CAS No.	166518-60-1
Purity	98%
Solvent/Solubility	Water <1mg/ml; DMSO 100mg/ml; Ethanol 8mg/ml
Solution Preparation	Add 1.00ml of DMSO for 5mg, or 1ml of DMSO for every 5.02mg to prepare a 10 mM solution. SD7212-10mM is formulated with DMSO.



➢ Biological information:

Description	Avasimibe inhibits ACAT with an IC50 of 3.3μM and also inhibits the human P450 isozymes CYP2C9, CYP1A2, and CYP2C19 with IC50s of 2.9μM, 13.9μM, and 26.5μM, respectively.				
Signaling Pathways	Metabolism				
Targets	CYP2C9	ACAT	CYP1A2	CYP2C19	—
IC50	2.9μM	3.3μM	13.9μM	26.5μM	—
In vitro Studies	Avasimibe acting on human monocyte-derived macrophages (HMMs) at a concentration of 1μg/ml reduced total cholesterol (TC) and esterified cholesterol (EC) by inhibiting LDL binding and reducing scavenger receptor number during the foam cell formation phase. Avasimibe at a concentration of 2μg/ml, prewarmed with 10μg/ml LDL, enhanced cholesterol efflux from HMM foam cells. Avasimibe inhibited lipoprotein(a) accumulation in primary monkey liver cell cultures by 11.9%-31.3%, and this effect was dose-dependent, an alteration associated with a decrease in ApoA. Avasimibe at concentrations of 10nM, 1μM and 10μM, incubated in HepG2 cells for 24h, reduced ApoB secretion into the medium by 25%, 27% and 43%, respectively. Avasimibe reduces ApoB secretion by enhancing intracellular degradation of ApoB rather than reducing ApoB synthesis. Avasimibe acting on IC-21 macrophages inhibited ACTC with an IC50 of 3.3μM. Avasimibe inhibited human P450 isoenzymes CYP2C9, CYP1A2 and CYP2C19 with IC50s of 2.9μM, 13.9μM and 26.5μM, respectively. Avasimibe acting on glioma cells inhibited ACAT-1 expression and cholesteryl ester synthesis. Avasimibe inhibited glioma cell growth by inducing apoptosis caused by cell cycle arrest and caspase-8 and caspase-3 activation.				
In vivo Studies	Avasimibe acted on 9 healthy male monkeys and significantly reduced lipoprotein(a) and total cholesterol levels. Avasimibe was fed orally at a dose of 30mg/kg daily for 3 weeks and reduced lipoprotein(a) and total cholesterol levels to 68 and 73% of control levels, respectively. Avasimibe				

	lowered total cholesterol mainly because of the reduction of low-density lipoprotein (LDL).
Clinical Trials	N/A
Characterization	N/A

- Relevant experimental data (this data is from published literature and Beyotime does not guarantee its validity):

Enzyme Activity Assay Experiment	
Method	Human liver microsomes (HLM) from at least 15 donors were used for all inhibition experiments. To determine the IC50, appropriate substrate probes were used according to in vitro Km values. Warming was performed using 100mM potassium phosphate buffer (pH 7.4) and 1mM NADPH. For CYP1A2 inhibition studies, the reactions were repeated in a total volume of 0.5ml using 0.1mg/ml HLM, 30μM phenacetin, 1mM NADPH in Avasimibe (0, 0.3, 0.75, 1.5, 3, 7.5, 15, 30, and 40μM) in potassium phosphate buffer pH 7.4. After incubation at 37ºC for 7 min, the enzyme reaction was started by adding NADPH. 25 min later, the reaction mixture was burst using 500μl of chilled 100ng/ml paracetamol-D4/CH3CN. Standards (4-acetaminophen) and mass controls (in triplicate in low, medium and high) were prepared at room temperature. After mixing, 0.2ml of the sample was transferred to another experimental plate and centrifuged at 3000rpm for 10 min before LC/MS/MS analysis.

Cell Experiment	
Cell Line	Primary human monocyte-derived macrophages
Concentration	1μg/ml or 2μg/ml
Treatment Time	48h
Method	Growth medium (RPMI medium containing 10% human serum) was aspirated and BMMs were rinsed 4 times using RPMI medium and then treated with RPMI medium containing bovine serum protein (BSA, 0.2%) and DMSO (0.2%) (blank medium) in the presence or absence of agacLDL (100μg/ml) and Avasimibe (1μg/ml). For cholesterol efflux experiments, HMMs were pre-incubated with agacLDL (100μg/ml) for 14h and then treated with control RPMI medium for 24-48h in the presence or absence of HDL (100μg/ml), Avasimibe (2μg/ml) or HDL and Avasimibe (2μg/ml). In addition, the appearance of [^{14}C]FC was determined by first incubation of HMMs with RPMI medium containing agacLDL (100μg protein/ml) in ethanol spray (final concentration of 0.1%) for 24h. The ag-acLDL was radiolabeled using [4-^{14}C]FC (0.5μCi/ml). The medium was removed and the cells were washed 3 times using RPMI medium and then treated with control RPMI medium for 4-48h in the presence or absence of Avasimibe (1-10μg/ml). At each time point, the medium was aspirated, centrifuged, and unadhered cells were pelleted. The appearance of [^{14}C]FC was determined by liquid scintillation spectroscopy. Extract cellular lipids using hexane:isopropanol (3:2, v/v) for 1 hr. Cellular radiolabeled cholesterol distribution was determined by thin-layer chromatography using a solvent system of petroleum ether:hexane:glacial acetic acid (85:15:2, v/v) after cellular extracts and aliquots of FC and EC standards. The FC exclusion percentage was calculated by the following equation: medium [^{14}C]FC dpm/cell [^{14}C] dpm × 100. FC and TC masses were measured by gas-liquid chromatography using dystroglycan (1mg/ml) as an internal standard. The EC amount was calculated as the difference between TC and FC.

Animal Experiment	
Animal Models	Male crab-eating monkey
Formulation	Sterile 0.9% NaCl solution
Dosage	30mg/kg
Administration Method	Oral administration, once daily for 3 weeks

- References:

1. Lee HT, et al. J Med Chem, 1996, 39(26), 5031-5034.
2. Ramharack R, et al. Atherosclerosis, 1998, 136(1), 79-87.
3. Wilcox LJ, et al. Arterioscler Thromb Vasc Biol, 1999, 19(4), 939-949.
4. Rodriguez A, et al. Atherosclerosis, 2002, 161(1), 45-54.
5. Castillo U, et al. FEMS Microbiol Lett, 2003, 224(2), 183-190.
6. Bemlih S, et al. Cancer Biol Ther, 2010, 9(12), 1025-1032.
7. Huttunen HJ, et al. J Neuropathol Exp Neurol, 2010, 69(8), 777-788.

Packing List:

Item	Component	Quantity
SD7212-10mM	Avasimibe (P450 Inhibitor)	10mM×0.2ml
SD7212-5mg	Avasimibe (P450 Inhibitor)	5mg
SD7212-25mg	Avasimibe (P450 Inhibitor)	25mg
Manual	—	1 copy

Storage Conditions:

Store at -20ºC, valid for at least 1 year. SD7212-5mg and SD7212-25mg can also be stored at room temperature for at least 6 months. If dissolved in non-DMSO solvents, it is recommended to store aliquots at -80ºC, valid for 6 months.

Precautions:

- This product is for R&D only. Not for drug, household, or other uses.
- For your safety and health, please wear a lab coat and disposable gloves during the operation.

Instructions for Use:

1. Upon receipt, store this product immediately under recommended storage conditions. Before use, centrifuged at 2,000-10,000×*g* briefly to collect liquid or powder at the bottom of the tube.
2. The 10mM stock solution can be used directly after dilution. For the powdered product, please prepare a high-concentration stock solution with the appropriate solvent according to the solubility of this product and the experimental purpose.
3. The optimal working concentration should be determined for different cells, tissues, and experimental purpose by referring to relevant literature or by exploring through experiments.
4. Please refer to the following website for the equivalent dose conversion table for different experimental animals based on body surface area http://www.beyotime.com/support/animal-dose.htm

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