A-971432

Cat. No.: HY-110291

CAS No.: 1240308-45-5

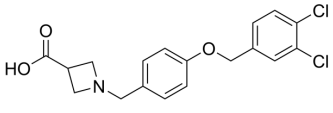
Molecular Formula: $C_{18}H_{17}Cl_2NO_3$

Molecular Weight: 366.24

Target: Others

Pathway: Others

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



BIOLOGICAL ACTIVITY

Description

A-971432 is a potent, selective and orally active sphingosine-1-phosphate (S1P) receptor 5 agonist with IC_{50}s of .362, >10, 0.006 μM for S1P1, S1P3, S1P5 respectively. A-971432 protects blood–brain barrier (BBB) homeostasis. A-971432 reverses age-related cognitive decline. A-971432 has the potential for the research of alzheimer's disease or multiple sclerosis [1][2].

IC_{50} & Target

S1P5[1][2]

In Vitro

A-971432 (compound 29) (0-10 μM) shows selectivity with IC_{50}s of 0.362, >10, 0.006 μM for S1P1, S1P3, S1P5 respectively[1].
A-971432 (0.1-1000 nM) induces full agonism with an EC_{50}s of 5.7 nM and 4.1 nM for HEK cells and CHO cells, respectively[1].
MCE has not independently confirmed the accuracy of these methods. They are for reference only.

In Vivo

A-971432 (1, 2 mg/kg; p.o.) shows excellent PK characteristics and oral bioavailability[1].
A-971432 (0.1 mg/kg; P.o.; daily for 21 days) shows pro-cognitive impact in a dose-dependent manner[1].
A-971432 (11 weeks R6/2 mice; 0.1 mg/kg; i.p.) increases the phosphorylation of AKT and ERK and significantly incremented the levels of BDNF in the cortex[2].
A-971432 (0.1 mg/kg; i.p.) attenuates the classic progressive BBB leakage and therefore the FITC-albumin extravasation in striatal parenchyma, and protects blood–brain barrier (BBB) homeostasis and suppresses aggregation of mHtt in the CNS blood vessels[2].
A-971432 (0.1 mg/kg; i.p.; daily for 4 weeks) prevents the worsening of motor deficit in symptomatic R6/2 mice by chronic infusion[2].
Pharmacokinetic Parameters of A-971432 in Balb/C mice, SD rat, beagle dog, cyno monkey[1].

				IV				PO				
species	dose (mg/kg)	sample analyzed)	protein binding (%)	$t_{1/2}$ (h)	AUC (ng.h/mL)	VL (L/h/kg)	V_{ss}(L/kg)	$t_{1/2}$ (h)	t_{max} (h)	C_{max} (ng/mL)	AUC (ng.h/mL)	F(%)
BALB/C mouse	2	plasma	93	7.6	8500	0.24	1.9	7.4	2.0	300	4800	57
BALB/C	2	brain	nd	9.8	3200 (C	nd	nd	10	2-24	43	1600	56

mouse					$_{max}$=133 ng/nL)							
SD rat	1	plasm	93	9.0	6400	0.16	1.3	14	4.3	400	8700	>100
SD rat	2	brain	99.5	nd	nd	nd	nd	15	8	120	3100	nd
beagle dog	1	plasma	96	9.3	12000	0.09	1.2	10	1.5	690	11000	92
cyno monkey	1	plasma	97	3.5	6400	0.16	0.82	6.7	1.7	650	5500	86

Balb/C mice, SD rat, beagle dog, cyno monkey; p.o. or i.v.; 2 mg/kg for Balb/C mice, SD rat; 1mg/kg for SD rat, beagle dog, cyno monkey[1].

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

Animal Model:	Balb/C mice, SD rat, beagle dog, cyno monkey[1]
Dosage:	1, 2 mg/kg
Administration:	P.o. or i.v.
Result:	Showed high oral bioavailability, high exposure, low clearance, a long half-life.

Animal Model:	Male C57BL6J mice[1]
Dosage:	0.1 mg/kg
Administration:	P.o.; daily for 21 days
Result:	Showed pro-cognitive impact in a dose-dependent manner.

Animal Model:	7-week R6/2 mice[2]
Dosage:	0.1 mg/kg
Administration:	I.p.; daily for 4 weeks
Result:	Restored normal motor function within the first week of treatment, and preserved them from the gradual motor deficit, classically occurring during the disease, for the entire period of the treatment.

Animal Model:	4-week R6/2 mice[2]
Dosage:	0.1 mg/kg
Administration:	I.p., daily for 2 weeks
Result:	Preserved BBB integrity and delayed the onset of motor symptoms in R6/2 mice and suppressed aggregation of mHtt in the CNS blood vessels.

REFERENCES

[1]. 1Hobson AD,et al. Discovery of A-971432, An Orally Bioavailable Selective Sphingosine-1-Phosphate Receptor 5 (S1P5) Agonist for the Potential Treatment of Neurodegenerative Disorders. J Med Chem. 2015 Dec 10;58(23):9154-70.

[2]. Di Pardo A, et al. Stimulation of S1PR5 with A-971432, a selective agonist, preserves blood-brain barrier integrity and exerts therapeutic effect in an animal model of Huntington's disease. Hum Mol Genet. 2018 Jul 15;27(14):2490-2501.

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