GSK-3 inhibitor 4

Cat. No.: HY-154852

CAS No.: 2227279-83-4

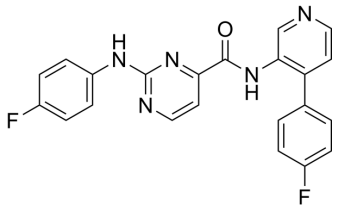
Molecular Formula: $C_{22}H_{15}F_2N_5O$

Molecular Weight: 403.38

Target: GSK-3; CDK

Pathway: PI3K/Akt/mTOR; Stem Cell/Wnt; Cell Cycle/DNA Damage

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



BIOLOGICAL ACTIVITY

Description

GSK-3 inhibitor 4 is an orally active and brain-penetrant inhibitor of GSK-3, CDK2, and CDK5, with IC_{50} values of 0.56 nM (GSK-3β), 0.45 nM (GSK-3α), 0.47 μM, and 0.68 μM, respectively. GSK-3 inhibitor 4 effectively reduces the phosphorylation level of Tau protein. GSK-3 inhibitor 4 can be used in Alzheimer's disease (AD) studies[1].

IC_{50} & Target

GSK-3α	GSK-3β	CDK2	CDK5
0.45 nM (IC_{50})	0.56 nM (IC_{50})	0.47 μM (IC_{50})	0.68 μM (IC_{50})

In Vitro

GSK-3 inhibitor 4 (compound 40) exhibits excellent selectivity against CDK2 (840-fold, IC_{50} = 0.47 μM), CDK5 (1200-fold, IC_{50} = 0.68 μM), GSK-3β (IC_{50} = 0.56 nM), and GSK-3α (IC_{50} = 0.45 nM)[1].

GSK-3 inhibitor 4 has good permeability and exhibits a high ability to bind to plasma proteins and brain tissue due to its lipophilic nature[1].

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

In Vivo

GSK-3 inhibitor 4 (10 mg/kg, p.o.) produce a 37% reduction in pTau396, when administered orally as a nanosuspension at a dose of 10 mg/kg[1].

GSK-3 inhibitor 4 (2 mg/kg, i.v.; 10 mg/kg, p.o.) exhibite low-moderate clearance ranging from 15.8 to 23.3 mL/min/kg and are well-absorbed when administered orally as a solution[1].

Pharmacokinetic Parameters of GSK-3 Inhibitor 4 (compound 40) in Mice. [1]

□□□□ GSK-3 Inhibitor 4 (compound 40) □□□□□□□□[1]

	IV PK parameters			oral PK parameters		
CL (mL min^{-1} kg^{-1})	V_{dss} (L/kg)	MRT (h)	$t_{1/2}$ (h)	AUC_{tot} (μM•h)	C_{max} (μM)	F%
18.9	2.6	2.3	2.8	11.7	1.5	53

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Animal Model:	3xTg mice were bred onto the C57BL6 background and bred as homozygotes. Male animals between the ages of five to seven months were used for the study[1].
Dosage:	10 mg/kg
Administration:	Oral gavage (p.o.)
Result:	Produced a 37% reduction in pTau396, when administered orally as a nanosuspension at a dose of 10 mg/kg.

Animal Model:	male C57BL6 mice (Pharmacokinetic assay)[1]
Dosage:	2 mg/kg, 10 mg/kg.
Administration:	Kept for 8 h fasting prior to formulation administration. intravenous and oral routes of administration to mice at a dose of 2 and 10 mg/kg, respectively.
Result:	Exhibited clearance ranging from 15.8 to 23.3 mL /min/kg , halflives ranging from 2.5 to 2.9 h and were readily orally bioavailable (F% = 53).

REFERENCES

[1]. Hartz RA, et al. Discovery of 2-(Anilino)pyrimidine-4-carboxamides as Highly Potent, Selective, and Orally Active Glycogen Synthase Kinase-3 (GSK-3) Inhibitors. J Med Chem. 2023 Jun 8;66(11):7534-7552.

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