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DAPT

Cat. No.: HY-13027

CAS No.: 208255-80-5

Molecular Formula: $C_{23}H_{26}F_2N_2O_4$

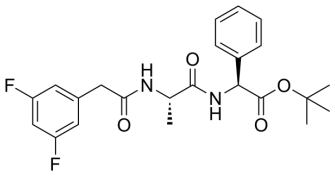
Molecular Weight: 432.46

Target: γ-secretase; Autophagy; Apoptosis; Amyloid-β; Notch; Organoid

Pathway: Neuronal Signaling; Stem Cell/Wnt; Autophagy; Apoptosis

Storage:

Powder	-20°C	3 years
	4°C	2 years
In solvent	-80°C	2 years
	-20°C	1 year



SOLVENT & SOLUBILITY

In Vitro

DMSO : 62.5 mg/mL (144.52 mM; Need ultrasonic)
Ethanol : 10 mg/mL (23.12 mM; Need ultrasonic)

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	2.3124 mL	11.5618 mL	23.1235 mL
5 mM	0.4625 mL	2.3124 mL	4.6247 mL
10 mM	0.2312 mL	1.1562 mL	2.3124 mL

Please refer to the solubility information to select the appropriate solvent.

In Vivo

1. Add each solvent one by one: corn oil
   Solubility: 10 mg/mL (23.12 mM); Suspended solution; Need ultrasonic
2. Add each solvent one by one: 50% PEG300 >> 50% saline
   Solubility: 5 mg/mL (11.56 mM); Suspended solution; Need ultrasonic
3. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: ≥ 2.5 mg/mL (5.78 mM); Clear solution
4. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: 2.5 mg/mL (5.78 mM); Suspended solution; Need ultrasonic
5. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (5.78 mM); Clear solution
6. Add each solvent one by one: 10% EtOH >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: ≥ 1 mg/mL (2.31 mM); Clear solution

BIOLOGICAL ACTIVITY

Description	DAPT (GSI-IX) is a potent and orally active γ-secretase inhibitor with IC_{50}s of 115 nM and 200 nM for total amyloid-β (Aβ) and $Aβ_{42}$, respectively. DAPT inhibits the activation of Notch 1 signaling and induces cell differentiation. DAPT also induces autophagy and apoptosis. DAPT has neuroprotection activity and has the potential for autoimmune and lymphoproliferative diseases, degenerative disease and cancers treatment[1][2].
IC_{50} & Target	IC50: 115 nM (Aβ), 200 nM (Aβ42)[5]
In Vitro	DAPT inhibits Aβ production over 90%, effects only a modest reduction in APPβ in the culture media. Although APPβ is reduced by about 30% by DAPT treatment, this effect is not concentration-dependent and is reversed by the removal of DAPT[1]. CNE-2 cells are treated with increasing concentrations of DAPT (0, 25, 50 and 75 μM), and the γ-secretase-generated Notch 1 fragment Val1744-NICD is decreased after 48 h in a dose-dependent manner ($P<0.01$). The activation of γ-secretase is almost completely inhibited by DAPT at the concentration of 50 μM[3]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	DAPT is administered to PDAPP mice (100 mg/kg s.c.) and the levels of DAPT and Aβ are examined in the brain cortex. Peak DAPT levels of 490 ng/g are achieved in the brain 3 h after treatment, and levels greater than 100 ng/g (~200 nM) are sustained throughout the first 18 h. These brain concentrations of DAPT are in excess of its IC_{50} for lowering Aβ in neuronal cultures (115 nM), and results in a robust and sustains pharmacodynamic effect[1]. DAPT protects brain against cerebral ischemia by down-regulating the expression of Notch 1 and Nuclear factor kappa B in rats. Western blot analyses also show a significant decrease of Notch 1 and NF-κB expression in DAPT (0.03 mg/kg) group ($P<0.05$ vs. MCAO group)[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Cell Assay [1]	Human embryonic kidney cells, transfected with the gene for APP_{751} (HEK 293) are used for routine Aβ reduction assays. Cells are plated in 96-well plates and allowed to adhere overnight in Dulbecco's modified Eagle medium (DMEM) supplemented with 10% heat-inactivated fetal bovine serum. Cells are pre-treated for 2 h at 37°C with DAPT (0, 0.4, 2, 10, 50 and 250 nM), media are aspirated off and fresh compound solutions applied. After an additional 2-h treatment period, conditioned media are drawn off and analyzed by a sandwich ELISA (266-3D6) specific for total Aβ. Reduction of Aβ production is measured relative to control cells treated with 0.1% DMSO and expressed as a percentage inhibition. Data from at least six doses in duplicate are fitted to a four-parameter logistical model using XLfit software in order to determine potency[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1][3]	Mice[1] The three- to four-month-old heterozygous PDAPP transgenic mice overexpressing the APP_{V717F} mutant form of the amyloid precursor protein. Each treatment group (n=10) consists of equal numbers of age-matched male and female animals that are fasted overnight prior to treatment. Both treatment and control groups are dosed at a volume of 10 mL/kg with DAPT or vehicle alone. Tissues are processed and all Aβ and APP measurements are made. After removal of the brain, the cortex from one hemisphere is homogenized, centrifuged, and the supernatant is used for Aβ measurements. Cortex from the other hemisphere is snap frozen for analysis of compound levels. Aβ levels are expressed as ng/g of wet tissue weight, and percentage reductions are calculated relative to the mean Aβ level of tissue from vehicle-treated control animals. Data are analyzed with Mann-Whitney non-parametric statistics to assess significance. Rats[3] Male Sprague-Dawley rats (260-290 g) are used. DAPT solution is stereotactically injected into the lateral cerebral ventricle (LV) immediately after MCAO. The stereotactic injections into the LVs are performed at coordinates −0.8 mm anteroposterior, ±1.5 mm mediolateral and −4.5 mm dorsoventral from the bregma. 30 rats are randomly assigned to three operating groups (10 rats in each group): sham-operated group that receive equal volume of PBS without MCAO operation; MCAO group that receive equal volume PBS after MCAO (MCAO); and DAPT group that receive DAPT as 0.03 mg/kg after MCAO. 24 h after operation the first neurological function is assessed and then 48 h after operation the second neurological

	function is assessed. Meanwhile, brain water content and infarction volume are measured and compared among different groups. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Science. 2022 Dec 2;378(6623):eabo5503.
- Nat Biotechnol. 2023 Jan 16.
- Mil Med Res. 2020 Sep 6;7(1):42.
- Nat Commun. 2023 Oct 20;14(1):6669.
- Neuro Oncol. 2023 Apr 21;noad079.

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[2]. Zhou JX, et al. γ-secretase inhibition combined with NSC 119875 enhances apoptosis of nasopharyngeal carcinoma cells.Exp Ther Med. 2012 Feb;3(2):357-361.

[3]. Li S, et al. DAPT protects brain against cerebral ischemia by down-regulating the expression of Notch 1 and nuclear factor κB in rats. Neurol Sci. 2012 Dec;33(6):1257-64.

[4]. Tanimizu N, et al. Intrahepatic bile ducts are developed through formation of homogeneous continuous luminal network and its dynamic rearrangement in mice. Hepatology. 2016 Jul;64(1):175-88.

[5]. Michael T. Chang, et al. Notch Drives Proliferation And Radiation Resistance Of Cancer Stem Cells In Adenoid Cystic Carcinoma. Yale University. January 2016.

[6]. Majumder S, et al. Shifts in podocyte histone H3K27me3 regulate mouse and human glomerular disease. J Clin Invest. 2018 Jan 2;128(1):483-499.

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