For Research Use Only

DAPT

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Catalog Number: CM06386

产品信息

Catalog Number:
CM06386

CAS号:
208255-80-5

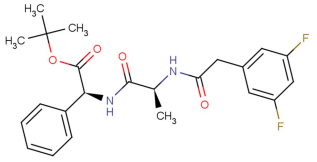
分子式:
$C_{23}H_{26}F_2N_2O_4$

主要靶点:
Autophagy|Beta Amyloid|Gamma-secretase|Apoptosis

主要通路:
蛋白酶体|凋亡|干细胞|自噬|神经科学

分子量:
432.46

溶解度:
H2O:Insoluble,DMSO:43.2 mg/mL (100 mM)



靶点活性

A β 42:200 nM (in human primary neuronal cultures)|A β :115 nM (in human primary neuronal cultures)|A β :20 nM (HEK 293 cells)

体外活性

DAPT presents the dose-dependent inhibition upon both total Ab and Ab42 production in human primary neuronal cultures. Both measures of Ab production are similarly inhibited with potencies (Ab total IC50: 115 nM, Ab42 IC50: 200 nM) of 5±10-fold lower than is observed in HEK 293 cells [1]. Although the application of the maximum dose of DAPT at 75 μ M had no obvious effect on cell survival, it substantially retarded CNE-2 cell proliferation in a dose-dependent manner. CNE-2 cells were treated with increasing concentrations of DAPT, and the γ -secretase-generated Notch 1 fragment Val1744-NICD was decreased after 48 h in a dose-dependent manner (P<0.01). The activation of γ -secretase was almost completely inhibited by DAPT at the concentration of 50 μ M [2].

体内活性

DAPT was administered to PDAPP mice (100 mg/kg s.c.) and the levels of DAPT and Ab were examined in the brain cortex. Peak DAPT levels of 490 ng/g were achieved in the brain 3 h after treatment and level greater than 100 ng/g (~200 nM) were sustained throughout the first 18 h. These brain concentrations of DAPT are in excess of its IC50 for lowering Ab in neuronal cultures (115 nM) and resulted in a robust and sustained pharmacodynamic effect in vivo [1]. DAPT could reduce the brain water content of ipsilateral hemispheres. In the sham-operated group, water content was 78.83 ± 0.35%. In DAPT group, brain water content was reduced compared with MCAO group (80.89 ± 0.51 vs. 83.84 ± 0.75%, P\0.05). These data indicated that DAPT protected the brain against brain ischemia damage at the early stage of cerebral ischemia [3].

动物实验

All studies were conducted with three- to four-month-old heterozygous PDAPP transgenic mice overexpressing the APPV717F a mutant form of the amyloid precursor protein. These animals have been previously shown to exhibit many of the neuropathological features of AD and to produce high levels of Ab in a regionally specific manner. Each treatment group (n=10) consisted of equal numbers of age-matched male and female animals that were fasted overnight prior to treatment. Both treatment and control groups were dosed at a volume of 10 mL/kg with compound formulated in corn oil, 5% (v/v) ethanol or vehicle alone. Tissues were processed and all Ab and APP measurements were made as described previously. After removal of the brain, the cortex from one hemisphere was homogenized, extracted with 5 M guanidine, 50 mM Tris ± pH 8.0, centrifuged, and the supernatant was used for Ab measurements. Cortex from the other hemisphere was snap frozen for analysis of compound levels. Ab levels were expressed as ng/g of wet tissue weight, and percentage reductions were calculated relative to the mean Ab level of tissue from vehicle-treated control animals. Data were analyzed with Mann± Whitney non-parametric statistics to assess significance [1].

细胞实验

Human embryonic kidney cells, transfected with the gene for APP751 (HEK 293) were used for routine Ab reduction assays. The Ab peptides secreted from these cells have been characterized previously. Cells were 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. For compound screening and dose±response testing, compounds were diluted from stock solutions in DMSO to yield a final concentration equal to 0.1% DMSO in media. Cells were pre-treated for 2 h at 378C with compounds, media were aspirated off and fresh compound solutions applied. After an additional 2-h treatment period, conditioned media were drawn off and analyzed by a sandwich ELISA (266±3D6) specific for total Ab. Reduction of Ab production was measured relative to control cells treated with 0.1% DMSO and expressed as percentage inhibition. Data from at least six doses in duplicate were fitted to a four-parameter logistical model using XLfit software in order to determine potency [1].

描述

DAPT is a novel γ -secretase inhibitor which reduces the A β production (IC50: 20 nM in HEK 293 cells) and A β 42 levels (IC50: 200 nM).

储存

Powder: -20°C for 3 years | In solvent: -80°C for 2 years