Latrepirdine dihydrochloride

Cat. No.: HY-14537

CAS No.: 97657-92-6

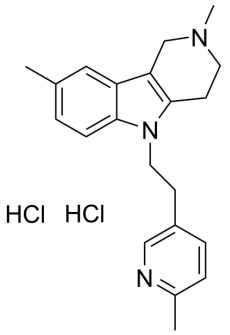
Molecular Formula: $C_{21}H_{27}Cl_2N_3$

Molecular Weight: 392.37

Target: Amyloid-β; Histamine Receptor; Adrenergic Receptor; 5-HT Receptor; Autophagy

Pathway: Neuronal Signaling; GPCR/G Protein; Immunology/Inflammation; Autophagy

Storage: 4°C, sealed storage, away from moisture
* In solvent : -80°C, 6 months; -20°C, 1 month (sealed storage, away from moisture)



SOLVENT & SOLUBILITY

In Vitro

H_2O : 100 mg/mL (254.86 mM; Need ultrasonic)
DMSO : 6.4 mg/mL (16.31 mM; Need warming)

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	2.5486 mL	12.7431 mL	25.4861 mL
5 mM	0.5097 mL	2.5486 mL	5.0972 mL
10 mM	0.2549 mL	1.2743 mL	2.5486 mL

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

In Vivo

1. Add each solvent one by one: PBS
   Solubility: 100 mg/mL (254.86 mM); Clear solution; Need ultrasonic
2. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: ≥ 0.5 mg/mL (1.27 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 0.5 mg/mL (1.27 mM); Clear solution
4. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 0.5 mg/mL (1.27 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Latrepirdine dihydrochloride is a neuroactive compound with antagonist activity at histaminergic, α-adrenergic, and serotonergic receptors. Latrepirdine stimulates amyloid precursor protein (APP) catabolism and amyloid-β (Aβ) secretion.

IC_{50} & Target

Amyloid-β (Aβ), Histaminergic receptor, α-adrenergic receptor, Serotonergic receptor[1]

In Vitro

Latrepirdine has been reported to possess several properties that are potentially relevant to the treatment of

neurodegenerative diseases: (1) protection of cultured cells from the cytotoxicity of amyloid-β (Aβ) peptide; (2) stabilization of mitochondrial function and calcium homeostasis; (3) modulation of Aβ release from cultured cells, isolated intact nerve terminals, and from hippocampal neurons in living mouse brain; and (4) promotion of neurogenesis in the murine hippocampus. Treatment of cultured mammalian cells with Latrepirdine leads to enhanced mTOR- and Atg5-dependent autophagy. Latrepirdine modulates Atg5-dependent autophagic activity in a dose-dependent manner and via the mTOR-signaling pathway. HeLa cells stably expressing LC3 fused are treated with EGFP (eGFP-LC3) for 3 or 6 hours in the absence or presence of 50 μM Latrepirdine. Treatment with Latrepirdine for 3 or 6 hours markedly enhances the number of eGFP-LC3 punctae, indicating that Latrepirdine induces formation of autophagosomes. Next, mouse N2a neuroblastoma cells are treated in the absence (vehicle) or presence of 5 nM, 500 nM or 50 μM Latrepirdine for 3 or 6 hours in order to determine the effects of acute drug treatment on the regulation of autophagy. A significant and dose-dependent increase is observed in LC3-II levels in N2a cells following 3- or 6-hour treatment with either 500 nM or 50 μM Latrepirdine. A significant decrease of p-mTOR and p-S6K from N2a cells treated with 50 μM Latrepirdine for 3 hours is observed, whereas the total mTOR and p70S6K levels remain relatively constant[1].

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

In Vivo

Latrepirdine treatment of TgCRND8 transgenic mice is associated with improved learning behavior and with a reduction in accumulation of Aβ42 and α-synuclein. Male, 90-day-old TgCRND8 mice or their wild-type littermates (nTg) receive 31 consecutive once daily i.p. injections of either 3.5 mg/kg Latrepirdine or 0.9% saline (vehicle). At the culmination of treatment, mice are tested for cued and contextual fear conditioning using a paradigm that has been widely accepted for evaluating learning and memory deficits in APP transgenic mice. A significant increase in cued memory only among Latrepirdine-versus vehicle-treated TgCRND8 mice (p=0.01) is observed. A weak, non-significant trend toward an improvement in contextual memory among Latrepirdine-versus vehicle-treated mice (p=0.099) is also observed[1].

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PROTOCOL

Cell Assay [1]

N2a cells, stable human cervical carcinoma (HeLa) cells expressing EGFP-LC3, and mouse embryonic fibroblasts (MEFs) derived from wildtype mice or ATG5$^{-/-}$ mice are maintained in “growth medium” (high glucose Dulbecco's modified Eagle's medium supplemented with 10% FBS and 100 units/mL Penicillin/Streptomycin) at 37°C, 5% CO_2. N2a cells stably transfected with APPK670N, M671L are maintained in growth medium supplemented with 0.2 mg/mL G418. Cells are washed 1× with ice cold PBS (pH 7.4) then incubated with either Latrepirdine (5 nM, 500 nM or 50 μM) or vehicle (growth medium). Following 3-, 6-, or 24-hour of treatment, cells are washed 1x with ice cold PBS, and collected in lysis buffer (50 mM Tris-HCl, 150 mM NaCl, 1 mM Pepstatin, 1 mM PMSF, 1% Triton X-100, EDTA-free mini-complete protease inhibitor cocktail tablet) then centrifuged (14,000 RPM) for 15 minutes at 4°C. For time-course experiments, cells are washed 2× with ice-cold PBS (pH 7.4) and incubated for the indicated time in serum-free DMEM containing 50 μg/mL CHX or 50 μg/mL Cycloheximide (CHX)+50 μg/mL Chloroquine (CQ). Baseline (T_0) samples are collected immediately prior to treatment[1].

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Animal Administration [1]

Mice[1]

Male 53-55-day-old TgCRND8 mice (N=25) are randomly distributed into either of the two treatment groups: Latrepirdine (n=13 TgCRND8) or vehicle (n=12 TgCRND8). Animals receive 21 consecutive once daily intraperitoneal injections of either 3.5 mg/kg Latrepirdine or 0.9% saline (vehicle). 90-day-old male TgCRND8 mice (N=28) or their wild-type littermates (N=56) are randomly distributed into either of two treatment groups: Latrepirdine (n=13 TgCRND8; n=21 nTg) or vehicle (n=15 TgCRND8; n=25 nTg). Following treatment, animals are sacrificed and transcardially perfused with ice-cold PBS (pH 7.4). Male 90-day-old (n=5 per genotype) or 120-day-old (n=6 per genotype) TgCRND8 mice or their non-transgenic littermates are sacrificed and transcardially perfused with ice-cold PBS (pH 7.4). One hemisphere from each mouse is post-fixed in 4% paraformaldeyhde in PBS (pH 7.4) for histological analysis and the other hemisphere is dissected and snap-frozen for biochemical analysis.

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

REFERENCES

[1]. Steele JW, et al. Latrepirdine improves cognition and arrests progression of neuropathology in an Alzheimer's mouse model. Mol Psychiatry. 2013 Aug;18(8):889-97.

Tel: 609-228-6898 Fax: 609-228-5909 E-mail: tech@MedChemExpress.com
Address: 1 Deer Park Dr, Suite Q, Monmouth Junction, NJ 08852, USA