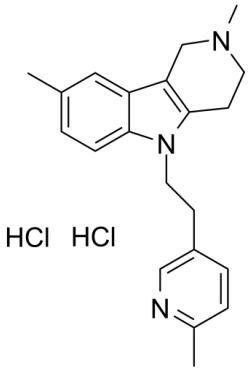
Data Sheet

Product Name:	Latrepirdine (dihydrochloride)
Cat. No.:	CS-5771
CAS No.:	97657-92-6
Molecular Formula:	$C_{21}H_{27}Cl_2N_3$
Molecular Weight:	392.37
Target:	5-HT Receptor; Adrenergic Receptor; Amyloid-β; Autophagy; Histamine Receptor
Pathway:	Autophagy; GPCR/G Protein; Immunology/Inflammation; Neuronal Signaling
Solubility:	DMSO : 6.4 mg/mL (16.31 mM; Need warming); H2O : 100 mg/mL (254.86 mM; Need ultrasonic)



BIOLOGICAL ACTIVITY:

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. IC50 & 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]. **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].

PROTOCOL (Extracted from published papers and Only for reference)

Cell Assay: Latrepirdine is dissolved directly into culture media to the desired concentration[1].[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]. **Animal Administration:** Latrepirdine is dissolved into 0.9% saline (vehicle) at a final concentration of 3.5 mg/mL (made fresh every 2 days) [1].[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.

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.

CAIndexNames:

1H-Pyrido[4,3-b]indole, 2,3,4,5-tetrahydro-2,8-dimethyl-5-[2-(6-methyl-3-pyridinyl)ethyl]-, hydrochloride (1:2)

SMILES:

CN(C1)CCC2=C1C3=CC(C)=CC=C3N2CCC4=CN=C(C)C=C4.Cl.Cl

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