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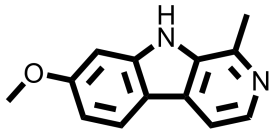
DYRK1A Inhibitor - Harmine

Chemical Name: 7-methoxy-1-methyl-9H-pyrido[3,4-b]indole



Molecular Weight:	212.25
Formula:	$C_{13}H_{12}N_2O$
Purity:	≥98%
CAS#:	442-51-3
Solubility:	DMSO up to 100 mM
Storage	Powder: 4 °C 1 year DMSO: 4 °C 3 months -20 °C 1 year

Biological Activity:

Harmine is a potent, selective and orally bioavailable DYRK1A inhibitor with IC_{50} of 80 nM. It inhibits phosphorylation of tau directly by DYRK1A (IC_{50} ~700 nM). It has >10-fold selectivity over DYRK3 and DYRK2 (IC_{50} ~800 nM and 900 nM respectively. Harmine is also a unique regulator of PPARγ expression that acts by inhibiting the Wnt signalling pathway in a cell-specific manner. It attenuates inflammatory gene expression (TNFα, IL-1β, iNOS) and macrophage accumulation in adipose tissue. Administration of harmine (30 mg/kg) to obese db/db mice resulted in reduced blood glucose, free fatty acids, and triglyceride levels, delayed hyperglycemia, and improved insulin sensitivity. Being function as a new class of human beta cell mitogenic compound, by using three different mouse and human islet in vivo-based models, harmine is able to induce beta cell proliferation, increase islet mass and improve glycemic control. The nuclear factors of activated T cells (NFAT) family of transcription factors are defined as likely mediators of human beta cell proliferation and differentiation.

How to Use:

In vitro: Harmine was used at 10 μM final concentration in various in vitro assays.

In vivo: Harmine was dosed orally to obese db/db mice at 30 mg/kg. Harmine was dosed by intraperitoneal injection at 10 mg/kg in mouse partial pancreatectomy model (PPX), Euglycemic human islet transplantation model and diabetic marginal mass human islet transplantation model.

Reference:

1. Bain J, et al. The selectivity of protein kinase inhibitors: a further update. (2007) Biochem J. 408(3):297-315.
2. Waki H, et al. The small molecule harmine is an antidiabetic cell-type-specific regulator of PPARgamma expression. (2007) Cell Metab. 5(5):357-70.
3. Egusa H, et al. The small molecule harmine regulates NFATc1 and Id2 expression in osteoclast progenitor cells. (2011) Bone. 49(2):264-74.
4. Smith B, et al. Recent advances in the design, synthesis, and biological evaluation of selective DYRK1A inhibitors: a new avenue for a disease modifying treatment of Alzheimer's? (2012) ACS Chem Neurosci. 3(11):857-72.
5. Wang P, at al. A high-throughput chemical screen reveals that harmine-mediated inhibition of DYRK1A increases human pancreatic beta cell replication. (2015) Nat Med. In press.