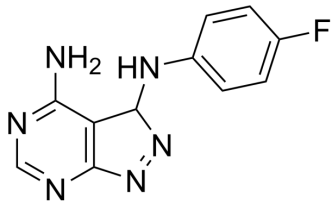
CGP 57380

Cat. No.:	HY-10520
CAS No.:	522629-08-9
Molecular Formula:	$C_{11}H_9FN_6$
Molecular Weight:	244.23
Target:	MNK; Apoptosis
Pathway:	MAPK/ERK Pathway; 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 : 6 mg/mL (24.57 mM; Need ultrasonic and warming)

H_2O : < 0.1 mg/mL (ultrasonic;warming;heat to 60°C) (insoluble)

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	4.0945 mL	20.4725 mL	40.9450 mL
5 mM	0.8189 mL	4.0945 mL	8.1890 mL
10 mM	0.4095 mL	2.0473 mL	4.0945 mL

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

In Vivo

1. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: ≥ 2.5 mg/mL (10.24 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.5 mg/mL (10.24 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

CGP 57380 is a cell-permeable pyrazolo-pyrimidine compound that acts as a selective inhibitor of Mnk1 with IC_{50} of 2.2 μM, but has no inhibitory activity against p38, JNK1, ERK1/2, PKC, or Src-like kinases.

IC_{50} & Target

MNK1

2.2 μM (IC_{50})

In Vitro

CGP57380 inhibits phosphorylation of eIF4E in cellular assays with an IC_{50} of about 3 μM. CGP57380 causes dephosphorylation of eIF4E, and induces a further increase in the cap-dependent reporter in 293 cells[1]. CGP57380 results in dose-dependent decreases in Ang II-stimulated phosphorylation of eIF4E, protein synthesis, and VSMC hypertrophy[2].

	CGP57380 sensitizes wild-type cells for serum-withdrawal induced apoptosis in mouse embryo fibroblasts (MEFs)[3]. CGP57380 prevents the serial replating function of BC progenitors[4]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	CGP57380 (40 mg/kg/d i.p.) potently extinguishes the ability of BC CML cells to serially transplant-immunodeficient mice and function as LSCs[4]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Kinase Assay [1]	Recombinant p38 isoforms are activated by Mkk6(E) under the following conditions: p38 (100 ng/mL), Mkk6(E) (30 ng/mL), ATP (100 mM) are mixed in kinase buffer (25 mM Hepes, 25 mM b-glycerophosphate, 0.1 mM sodium orthovanadate, 25 mM $MgCl_2$, 2.5 mM DTT, pH 7.4) and incubated for 30 min at 30°C. A typical assay reaction for Mnk1 activity contained Mnk1 (2 ng/mL), HA-eIF4E (10 ng/mL), ATP (300 mM) in kinase buffer. The reaction is started by addition of activated p38 (0.03-3 ng/mL) and stopped after 30 min at 30°C by addition of SDS loading buffer. Inhibitors of Mnk1 are identified under the same assay conditions, except that Mnk1 is pre-activated using active p38a before exposure to the substrate and inhibitors. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [4]	$CD34^+$ cells (5×10^5) or GMPs (1×10^5) are resuspended in 25 μL 1% FBS/PBS solution and injected into the right femur of 8- to 10-wk-old sublethally irradiated (200 cGy) female mice (n=5 mice per group). Mice injected with 1% FBS/PBS solution serve as a sham control for each experiment. Beginning at 4 wk posttransplantation, mice are monitored for engraftment of human cells by flow cytometry. At 6 wk after transplantation, engrafted mice are treated with vehicle alone, dasatinib (5 mg/kg/d) by gavage, or CGP57380 (40 mg/kg/d) intraperitoneally for 3 wk (n=5 mice per group). At the end of treatment, mice are euthanized, and $CD45^+$ cells are isolated from BM and spleen by using anti-human CD45-specific immunomagnetic microbeads. An aliquot of 1×10^5 human $CD45^+$ cells is seeded into methylcellulose for the colony forming cell (CFC) assay, and colonies are enumerated after 2 wk. All of the remaining human cells from each primary transplant recipient are then transplanted by intrafemoral injection into secondary recipients, and human engraftment is monitored at 2-wk intervals beginning at 4 wk. At the end of 16 wk, all mice are euthanized. Engraftment in BM and blood is assessed by flow cytometry, and BCR-ABL1 transcripts are detected by RT-PCR. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Cell Rep. 2022 Nov 22;41(8):111707.
- Int J Biol Macromol. 2023 Jan 9;230:123191.
- Viruses. 2018 Nov 1;10(11). pii: E601.
- Harvard Medical School LINCS LIBRARY

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REFERENCES

[1]. Knauf U, et al. Negative regulation of protein translation by mitogen-activated protein kinase-interacting kinases 1 and 2. Mol Cell Biol. 2001 Aug;21(16):5500-11.

[2]. Ishida M, et al. Mnk1 is required for angiotensin II-induced protein synthesis in vascular smooth muscle cells. Circ Res. 2003 Dec 12;93(12):1218-24. Epub 2003 Nov 6

[3]. Chrestensen CA, et al. Loss of MNK function sensitizes fibroblasts to serum-withdrawal induced apoptosis. Genes Cells. 2007 Oct;12(10):1133-40.

[4]. Lim S, et al. Targeting of the MNK-eIF4E axis in blast crisis chronic myeloid leukemia inhibits leukemia stem cell function. Proc Natl Acad Sci U S A. 2013 Jun 18;110(25):E2298-307

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