Product Datasheet

PHA-408

Catalog No. **BP-02075** · CAS **503555-55-3** · Form **free base** · Physical state **solid** · Color **Off-white to light yellow** · Version **1.0** · Revision **2026-09-14**

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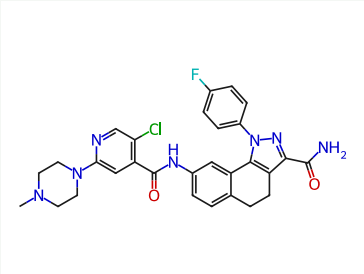
Target	Research area
IKK; TNF Receptor; NF-κB	**Neurological Disease; Inflammation/Immunology**

Molecular formula	$C_{29}H_{27}ClFN_7O_2$
Molecular weight	**560.0220**

STRUCTURE



DESCRIPTION

PHA 408 (PHA-408) is a potent, selective and orally active IκB kinase-2 (IKK-2) inhibitor. PHA 408 is a powerful anti-inflammatory agent against lipopolysaccharide (LPS)- and cigarette smoke (CS)-mediated lung inflammation.

BIOLOGICAL ACTIVITY

In Vitro

PHA-408 (2 μM; 6 days co-treatment with TNF-α) prevents TNF-α-induced premature senescence in HUVECs, as evidenced by reduced p16 and p21 expression, restored Ki-67 levels, and decreased senescence-associated secretory phenotype (SASP) markers including E-selectin, ICAM-1, IL-6, and IL-8.

PHA-408 (0-10000 nM) inhibits recombinant human IKK-2 homodimer and IKK-2/IKK-1 heterodimer with IC50 values of 10-40 nM, weakly suppresses IKK-1 (IC50 = 14 μM, > 350-fold selectivity), and displays no obvious activity against a panel of 30 tyrosine and serine/threonine kinases except PIM1, with a 15-fold selectivity over PIM1 relative to IKK-2.

PHA-408 (0.001-3 μM; 1 h preincubation; 20 min LPS stimulation) suppresses LPS-induced IKK-2 activity in immunoprecipitated IKK complexes from PBMCs and blocks LPS-triggered IκBα phosphorylation as well as p65 phosphorylation at Ser536 in PBMCs.

PHA-408 (0.001-3 μM; 1 h preincubation; 18 h LPS stimulation) inhibits LPS-induced TNF-α, IL-6 and IL-8 production in PBMCs and human whole blood in a concentration-dependent manner.

PHA-408 (0.001-3 μM; 1 h preincubation; 18 h IL-1β stimulation) inhibits IL-1β-induced IL-8, PGE2 production, and NF-κB-dependent SEAP reporter activity in RASFs without affecting cell viability.

PHA-408 (0.001-3 μM; 1 h preincubation; 45 min IL-1β stimulation) shows no effect on IL-1β-induced JNK and p38 MAPK pathways in RASFs.

PHA-408 (10 μM; 1 h preincubation; 20 min LPS stimulation) maintains inhibition of IKK-2 activity for up to 4 h following extensive washing of PBMCs.

PHA-408 (20 μM; 6 h) increases cytosolic IκB-α expression and reduces nuclear p65 expression in freshly isolated

adult mdx costal diaphragm.
PHA-408 (20 μM; 52 h) reduces nuclear p65 immunofluorescence intensity in cultured mdx myotubes.
PHA-408 (1, 10 μM; 6 h) shows no significant effect on cytosolic IκB-α or nuclear p65 expression at lower concentrations in freshly isolated adult mdx costal diaphragm.

In Vivo
PHA-408 (15 and 45 mg/kg; p.o.; once daily for 3 days) dose-dependently reduces LPS- and cigarette smoke-induced lung inflammation in male Sprague-Dawley rats (280 g), including neutrophil influx and elevated CINC-1, IL-6, TNF-α, IL-1β, and GM-CSF levels in BAL fluid/lung homogenates, and suppresses NF-κB activation (IκBα degradation, p65 nuclear translocation, and NF-κB DNA binding) in lung tissues at 1 h post-exposure.
PHA-408 (0.5-50 mg/kg; p.o.; single dose) inhibits LPS-induced serum TNF-α production, with an EC50 of approximately 27-29 mg/kg and an IC50 of approximately 2-3.4 μM based on plasma concentration in male Lewis rats.
PHA-408 (10 mg/kg; p.o.; t.i.d. for 11 days) reduces paw swelling, suppresses IKK-2 activity in immunoprecipitates from paw tissues and blocks bone destruction in streptococcal cell wall (SCW)-induced chronic arthritis in female Lewis rats (125-140 g).
PHA-408 (15-60 mg/kg/day; p.o.; t.i.d. for 14 days) exhibits good tolerability at efficacious doses with an ED90 of 30 mg/kg/day and a corresponding NOAEL of 30 mg/kg/day, induces mild and reversible adverse responses including transient body weight loss, neutrophilia, reduced liver enzyme levels and lymphoid depletion (45-60 mg/kg/day) in female Lewis rats (approximately 200 g).
PHA-408 (50 mg/kg; p.o.; once daily for 30 days) in mdx mice (1 month old, male) slightly increases cytosolic IκB-α expression in costal diaphragm, but does not significantly reduce nuclear p65 expression.
PHA-408 (100 mg/kg; p.o.; single dose) in mdx mice shows no reduction in nuclear p65 expression at 5 h post-administration.
PHA-408 (0.8 mg/kg/day; i.p.; twice daily for 30 days) in mdx mice (1 month old, male) significantly reduces nuclear p65 expression by approximately 50% in costal diaphragm.

SOLUBILITY

Soluble in DMSO : 50 mg/mL

REFERENCES

[1]. Khan SY, et al. Premature senescence of endothelial cells upon chronic exposure to TNFα can be prevented by N-acetyl cysteine and plumericin. Sci Rep. 2017 Jan 3;7:39501.

[2]. Rajendrasozhan S, et al. Anti-inflammatory effect of a selective IkappaB kinase-beta inhibitor in rat lung in response to LPS and cigarette smoke. Pulm Pharmacol Ther. 2010 Jun;23(3):172-81.

[3]. Mbalaviele G, et al. A novel, highly selective, tight binding IkappaB kinase-2 (IKK-2) inhibitor: a tool to correlate IKK-2 activity to the fate and functions of the components of the nuclear factor-kappaB pathway in arthritis-relevant cells and animal models. J Pharmacol Exp Ther. 2009 Apr;329(1):14-25.

[4]. Carlson CG, et al. The effect of specific IKKβ inhibitors on the cytosolic expression of IκB-α and the nuclear expression of p65 in dystrophic (MDX) muscle. Am J Transl Res. 2015 Apr 15;7(4):670-82.