Doramapimod

Cat. No.: HY-10320

CAS No.: 285983-48-4

Molecular Formula: $C_{31}H_{37}N_5O_3$

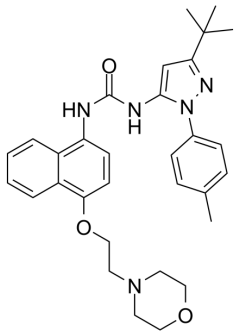
Molecular Weight: 527.66

Target: p38 MAPK; Raf; Autophagy

Pathway: MAPK/ERK Pathway; Autophagy

Storage:

Powder	-20°C	3 years
	4°C	2 years
In solvent	-80°C	6 months
	-20°C	1 month



SOLVENT & SOLUBILITY

In Vitro

DMSO : 125 mg/mL (236.89 mM; Need ultrasonic)
Ethanol : 33.33 mg/mL (63.17 mM; Need ultrasonic)

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	1.8952 mL	9.4758 mL	18.9516 mL
5 mM	0.3790 mL	1.8952 mL	3.7903 mL
10 mM	0.1895 mL	0.9476 mL	1.8952 mL

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

In Vivo

1. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (4.74 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: ≥ 2.08 mg/mL (3.94 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: 2.08 mg/mL (3.94 mM); Suspended solution; Need ultrasonic

BIOLOGICAL ACTIVITY

Description

Doramapimod (BIRB 796) is an orally active, highly potent p38 MAPK inhibitor, which has an IC_{50} for p38α=38 nM, for p38 β=65 nM, for p38γ=200 nM, and for p38δ=520 nM. Doramapimod has picomolar affinity for p38 kinase (K_d=0.1 nM). Doramapimod also inhibits B-Raf with an IC_{50} of 83 nM[1][2].

IC_{50} & Target

p38α	p38β	p38δ	p38γ
38 nM (IC_{50})	65 nM (IC_{50})	520 nM (IC_{50})	200 nM (IC_{50})

	B-Raf 83.4 nM (IC_{50})	Abl 14600 nM (IC_{50})	p38 MAP kinase 0.1 nM (Kd)

In Vitro

Doramapimod (BIRB 796) is usually associated with inflammation because of its role in T-cell proliferation and cytokine production[1].

Doramapimod (BIRB 796) blocks the stress-induced phosphorylation of the scaffold protein SAP97, further establishing that this is a physiological substrate of SAPK3/p38γ. The binding of Doramapimod to the p38 MAPKs or JNK1/2 is impairing their phosphorylation by the upstream kinase MKK6 or MKK4[3].

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

In Vivo

The mean xenograft weigh of Doramapimod (BIRB 796) is lighter than control. The inhibition rate of Doramapimod is 1.93% [4].

The Doramapimod (BIRB 796) treatment slightly reduces blood pressure (166±7 mm Hg at week 7; P<0.05), whereas SD rats are normotensive (123±3 mm Hg). Despite the reduction in blood pressure, untreated and Doramapimod-treated dTGRs have similar heart weight and cardiac hypertrophy indices (heart-to-tibia ratio), which are significantly higher compare with nontransgenic SD rats (310±6 versus 307±6 versus 206±5 mg/cm, respectively; P<0.05)[5].

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PROTOCOL

Cell Assay [3]

Human embryonic kidney (HEK) 293 and HeLa cells are exposed to 0.5 M sorbitol for 30 min or 100 ng/mL EGF for 10 min and then lysed in buffer A (50 mM Tris-HCl, pH 7.5, 1 mM EGTA, 1 mM EDTA, 1 mM sodium orthovanadate, 10 mM sodium fluoride, 50 mM sodium β-glycerophosphate, 5 mM pyrophosphate, 0.27 M sucrose, 0.1 mM phenylmethylsulfonyl fluoride, 1% (v/v) Triton X-100) plus 0.1% (v/v) 2-mercaptoethanol and Complete proteinase inhibitor mixture. Lysates are centrifuged at 18,000× g for 5 min at 4°C, and the supernatants are removed, quick-frozen in liquid nitrogen, and stored at -20°C until use. When required, cells are preincubated for 1 h without or with 10 μM SB 203580 or 10 μM PD 184352 or with different concentrations of Doramapimod for the times indicated in the figures[3].

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Animal Administration [4][5]

Mice[4]

Athymic nude mice (BALB/c-nu/nu), 6 to 8 weeks of age and weighing 18 to 24 g, are used. The mice are treated with Doramapimod (10 mg/kg p.o., every 3 days×5). The body weights of the animals and the two perpendicular tumor diameters (A and B) are recorded every 3 days, and the tumor volume (V) is estimated.

Rats[5]

Male transgenic dTGRs (RCC Ltd) and age-matched nontransgenic Sprague-Dawley (SD) rats (MDC) are use. 2 different protocols are performed. In protocol 2, untreated dTGR (n=15), dTGR+BIRB796 (30 mg/kg per day in the diet for 3 weeks; n=11), and SD (n=8 each group) rats are analyzed. Systolic blood pressure is measured weekly by tail cuff. Twenty-four-hour urine samples are collected in metabolic cages from weeks 5 to 7. Serum is collected at week 7. Serum creatinine and cystatin C are measured by clinical routine assays. Urinary rat albumin is determined by enzyme-linked immunosorbent assay. The aim of protocol 2 is to focus on electrophysiological alterations and mortality. Untreated dTGR (n=10), dTGR+BIRB796 (n=10), and SD (n=10) rats are studied up to week 8.

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

CUSTOMER VALIDATION

- Nature. 2019 Jul;571(7763):127-131.
- Cell Res. 2020 Jul;30(7):574-589.
- Sci Transl Med. 2018 Jul 18;10(450):eaaq1093.

- Dev Cell. 2021 Dec 20;56(24):3334-3348.e6.
- Anal Chem. 2021 Nov 4.

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REFERENCES

[1]. Dietrich J, et al. The design, synthesis, and evaluation of 8 hybrid DFG-out allosteric kinase inhibitors. Bioorg Med Chem. 2010 Aug 1;18(15):5738-48

[2]. Cicenas J, et al. JNK, p38, ERK, and SGK1 Inhibitors in Cancer. Cancers (Basel). 2017 Dec 21;10(1). pii: E1.

[3]. Kuma Y, et al. BIRB796 inhibits all p38 MAPK isoforms in vitro and in vivo. J Biol Chem, 2005, 280(20), 19472-19479.

[4]. He D, et al. BIRB796, the inhibitor of p38 mitogen-activated protein kinase, enhances the efficacy of chemotherapeutic agents in ABCB1 overexpression cells. PLoS One. 2013;8(1):e54181.

[5]. Park JK, et al. p38 mitogen-activated protein kinase inhibition ameliorates angiotensin II-induced target organ damage. Hypertension. 2007 Mar;49(3):481-9.

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