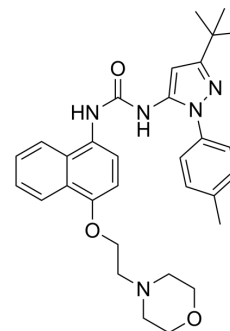


## Doramapimod

<b>Cat. No.:</b>	HY-10320		
<b>CAS No.:</b>	285983-48-4		
<b>Molecular Formula:</b>	C <sub>31</sub> H <sub>37</sub> N <sub>5</sub> O <sub>3</sub>		
<b>Molecular Weight:</b>	527.66		
<b>Target:</b>	p38 MAPK; Raf; Autophagy		
<b>Pathway:</b>	MAPK/ERK Pathway; Autophagy		
<b>Storage:</b>	Powder	-20°C	3 years
		4°C	2 years
	In solvent	-80°C	1 year
		-20°C	6 months



### 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 Concentration	Mass		
		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

- Add each solvent one by one: 10% DMSO >> 90% corn oil  
Solubility: ≥ 2.5 mg/mL (4.74 mM); Clear solution
- 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
- 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<sub>50</sub> for p38α=38 nM, for p38β=65 nM, for p38γ=200 nM, and for p38δ=520 nM. Doramapimod has picomolar affinity for p38 kinase (K<sub>d</sub>=0.1 nM). Doramapimod also inhibits B-Raf with an IC<sub>50</sub> of 83 nM<sup>[1][2]</sup>.

#### IC<sub>50</sub> & Target

p38α 38 nM (IC <sub>50</sub> )	p38β 65 nM (IC <sub>50</sub> )	p38δ 520 nM (IC <sub>50</sub> )	p38γ 200 nM (IC <sub>50</sub> )
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	B-Raf 83.4 nM (IC <sub>50</sub> )	Abl 14600 nM (IC <sub>50</sub> )	p38 MAP kinase 0.1 nM (Kd)
<b>In Vitro</b>	<p>Doramapimod (BIRB 796) is usually associated with inflammation because of its role in T-cell proliferation and cytokine production<sup>[1]</sup>.</p> <p>Doramapimod (BIRB 796) blocks the stress-induced phosphorylation of the scaffold protein SAP97, further establishing that this is a physiological substrate of SAPK3/p38<math>\gamma</math>. The binding of Doramapimod to the p38 MAPKs or JNK1/2 is impairing their phosphorylation by the upstream kinase MKK6 or MKK4<sup>[3]</sup>.</p> <p>MCE has not independently confirmed the accuracy of these methods. They are for reference only.</p>		
<b>In Vivo</b>	<p>The mean xenograft weigh of Doramapimod (BIRB 796) is lighter than control. The inhibition rate of Doramapimod is 1.93% [4].</p> <p>The Doramapimod (BIRB 796) treatment slightly reduces blood pressure (166±7 mm Hg at week 7; P&lt;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&lt;0.05)<sup>[5]</sup>.</p> <p>MCE has not independently confirmed the accuracy of these methods. They are for reference only.</p>		

## PROTOCOL

<b>Cell Assay</b> <sup>[3]</sup>	<p>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 <math>\beta</math>-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<math>\times</math> 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 <math>\mu</math>M SB 203580 or 10 <math>\mu</math>M PD 184352 or with different concentrations of Doramapimod for the times indicated in the figures<sup>[3]</sup>.</p> <p>MCE has not independently confirmed the accuracy of these methods. They are for reference only.</p>
<b>Animal Administration</b> <sup>[4][5]</sup>	<p>Mice<sup>[4]</sup></p> <p>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<math>\times</math>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.</p> <p>Rats<sup>[5]</sup></p> <p>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.</p> <p>MCE has not independently confirmed the accuracy of these methods. They are for reference only.</p>

## 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):eaq1093.

- Exp Mol Med. 2021 Sep 21.
- Dev Cell. 2021 Dec 20;56(24):3334-3348.e6.

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## REFERENCES

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- [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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