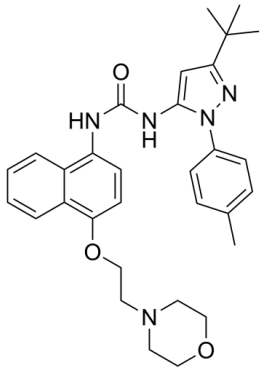
Data Sheet

Product Name:	Doramapimod
Cat. No.:	CS-0219
CAS No.:	285983-48-4
Molecular Formula:	$C_{31}H_{37}N_5O_3$
Molecular Weight:	527.66
Target:	Autophagy; p38 MAPK; Raf
Pathway:	Autophagy; MAPK/ERK Pathway
Solubility:	DMSO : 125 mg/mL (ultrasonic);Ethanol : 33.33 mg/mL (ultrasonic)



BIOLOGICAL ACTIVITY:

Doramapimod (BIRB 796) is an orally active, highly potent **p38 MAPK** inhibitor, which has an **IC_{50}** 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_d**=0.1 nM). Doramapimod also inhibits **B-Raf** with an **IC_{50}** of 83 nM[1][2]. IC50 & Target: IC50: 4 nM (p38α), 83 nM (B-Raf)[1] ***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]. ***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].

PROTOCOL (Extracted from published papers and Only for reference)

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]. **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.

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.

CAIndexNames:

Urea, N-[3-(1,1-dimethylethyl)-1-(4-methylphenyl)-1H-pyrazol-5-yl]-N'-[4-[2-(4-morpholinyl)ethoxy]-1-naphthalenyl]-

SMILES:

O=C(NC1=CC(C(C)(C)C)=NN1C2=CC=C(C)C=C2)NC3=C4C=CC=CC4=C(OCCN5CCOCC5)C=C3

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