For Research Use Only

Doramapimod

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Catalog Number: CM00223

产品信息

Catalog Number:
CM00223

CAS号:
285983-48-4

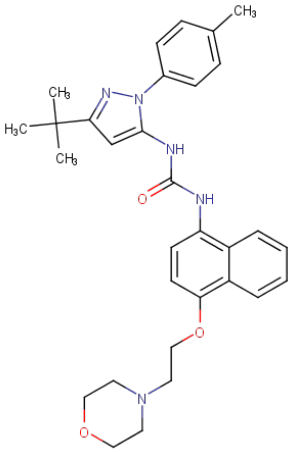
分子式:
$C_{31}H_{37}N_5O_3$

主要靶点:
Autophagy|Raf|p38 MAPK

主要通路:
自噬|MAPK信号通路

分子量:
527.66

溶解度:
DMSO:52.8 mg/mL (100 mM),Ethanol:26.4 mg/mL (50 mM)



靶点活性

p38 MAPK:0.1 nM (Kd, cell free)

体外活性

Doramapimod (BIRB796) is a highly potent inhibitor of p38 MAPK (Kd: 0.1 nM) that blocks TNF α release in LPS-stimulated THP-1 cells (IC50: 18 nM) [1]. BIRB796 also inhibits the activity and the activation of SAPK3/p38gamma. BIRB796 blocks the stress-induced phosphorylation of the scaffold protein SAP97 [2]. BIRB 796 inhibited Hsp27 phosphorylation induced by 17-AAG plus bortezomib, thereby enhancing cytotoxicity. In bone marrow stromal cells (BMSC), BIRB 796 inhibited phosphorylation of p38 MAPK and secretion of IL-6 and vascular endothelial growth factor triggered by either tumour necrosis factor-alpha or tumour growth factor-beta1. BIRB 796 also inhibited IL-6 secretion induced in BMSCs by adherence to MM cells, thereby inhibiting tumour cell proliferation [3].

体内活性

Systolic blood pressure of untreated dTGRs was 204 mm Hg, but partially reduced after BIRB796 (30 mg/kg per day) treatment (166 mm Hg), whereas Sprague-Dawley rats were normotensive. The beta-myosin heavy chain expression of BIRB796-treated hearts was significantly lower in BIRB796 compared with dTGRs. BIRB796 treatment significantly reduced cardiac fibrosis, connective tissue growth factor, tumor necrosis factor-alpha, interleukin-6, and macrophage infiltration [4].

动物实验

We studied male transgenic dTGRs and age-matched nontransgenic Sprague–Dawley (SD) rats (MDC). Local authorities approved the studies, and American Physiological Society guidelines for animal care were followed. We performed 2 different protocols. 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 were analyzed. Systolic blood pressure was measured weekly by tail cuff. Twenty-four–hour urine samples were collected in metabolic cages from weeks 5 to 7. Serum was collected at week 7. Serum creatinine and cystatin C were measured by clinical routine assays. Urinary rat albumin was determined by enzyme-linked immunosorbent assay. The aim of protocol 2 was to focus on electrophysiological alterations and mortality. Untreated dTGR (n=10), dTGR+BIRB796 (n=10), and SD (n=10) rats were studied up to week 8. Cardiac magnetic field mapping (CMFM) was performed at week 7 under isoflurane anesthesia. Echocardiography was performed as described earlier [4].

细胞实验

Human embryonic kidney (HEK) 293 and HeLa cells were cultured in Dulbecco's modified Eagle's medium at 37 °C, supplemented with 10% fetal calf serum, 50 μg/ml streptomycin, and 2 mM glutamine. Mouse embryonic fibroblasts were cultured as described previously, and C2C12 myoblasts were cultured. Cells were 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 from Roche Applied Science. Lysates were centrifuged at 18,000 × g for 5 min at 4 °C, and the supernatants were removed, quick-frozen in liquid nitrogen, and stored at –20 °C until use. When required, cells were preincubated for 1 h without or with 10 μM SB 203580 or 10 μM PD 184352 or with different concentrations of BIRB796 for the times indicated in the figures [2].

描述

Doramapimod is a highly potent inhibitor of p38 MAPK (Kd: 0.1 nM), but weakly inhibits c-RAF, Fyn, Lck, ERK-1, SYK, IKK2, and ZAP-70.

储存

Powder: -20°C for 3 years | In solvent: -80°C for 2 years