Product Data Sheet

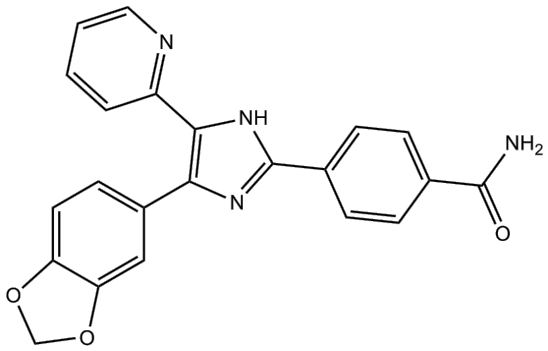
Product Name: SB 431542

Cat. No.: GC11545

Chemical Properties

Cas No.	301836-41-9		
化学名	4-[4-(1,3-benzodioxol-5-yl)-5-pyridin-2-yl-1H-imidazol-2-yl]benzamide		
Canonical SMILES	C1OC2=C(O1)C=C(C=C2)C3=C(NC(=N3)C4=CC=C(C=C4)C(=O)N)C5=CC=CC=N5		
分子式	$C_{22}H_{16}N_4O_3$	分子量	384.39
溶解度	≥ 19.2mg/mL in DMSO, ≥ 10.06 mg/mL in EtOH with ultrasonic	储存条件	Store at -20°C
General tips	For obtaining a higher solubility , please warm the tube at 37 ℃ and shake it in the ultrasonic bath for a while.Stock solution can be stored below -20℃ for several months.		
Shipping Condition	Evaluation sample solution : ship with blue ice All other available size: ship with RT , or blue ice upon request.		

Structure



Protocol

Kinase experiment [1]:

Preparation Method	The kinase domain without the GS region was cloned and expressed as a GST fusion protein. Expressing the protein without the GS domain, which has been shown to regulate the kinase activity, creates a constitutively active kinase that is able to phosphorylate GST-Smad3. Test the effects of SB-431542 on ALK5 and ALK4 kinase activity with GST-Smad3 as substrate.
Reaction Conditions	The Kinase assays were performed with 65 nM GSTALK5 and 184 nM GST-Smad3 in 50 mM HEPES, 5 mM MgCl2, 1 mM CaCl2, 1 mM dithiothreitol, and 3 μM ATP. Reactions were incubated with 0.5 μCi of [33P]γATP for 3 h at 30°C.
Applications	SB-431542 is a selective ALK5 inhibitor with little activity against p38 MAPK. SB-431542 also inhibits ALK4 activity. Which is consistent with the degree of homology between these kinases, such that ALK4 is the closest related kinase to ALK5. This data clearly demonstrated that SB-431542 is a potent and selective inhibitor of ALK5 and ALK4, with slightly higher selectivity for ALK5.

Cell experiment [1]:

Cell lines	Renal proximal tubule epithelial cells (RPTEC)

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Preparation Method	Cells were grown in Earle's minimum essential medium supplemented with 10% fetal calf serum, penicillin (5 units/ml), and streptomycin (5 ng/ml). Cells were serum-starved for 24 h before treatment.
Reaction Conditions	Cells were treated with TGF-β1 (5 ng/ml) plus increasing concentrations of SB-431542 (50, 250, 500, and 700 nM).
Applications	SB-431542 could be used to evaluate whether ALK5 activity is required for TGF-β1-induced translocation of Smad3. SB-431542 at a concentration of 1 μM significantly reduced the TGF-β1-induced nuclear accumulation of Smad proteins. Thus, SB-431542 selectively inhibits TGF-β1–induced Smad translocation without affecting BMP-induced Smads.
Animal experiment [2]:	
Animal models	Male Sprague-Dawley rats aged 5 weeks, weighing 200-220 g
Preparation Method	Rats lived in air served as control groups, and rats lived in an air condition incubator containing 10% O2 to simulate chronic hypoxia animal model, and served as model groups. Model groups were treated with daily intraperitoneal injections of the SB-431542 for 28 days.
Dosage form	10 mg/kg; 20 mg/kg
Applications	SB-431542 inhibited the proliferative activity as a function of exposure time and concentration. Treated rats with SB-431542 caused more pathological changes in vascular adventitia, and the severity of the changes varied from slight to moderate depending on concentrations. In addition, the pulmonary arteries in the hypoxia-induced model groups had greater amounts of collagen fibers than that of the control groups. In comparison, collagen fibers were significantly reduced after treatment with SB-431542 ($P < 0.01$).

References:
[1]. Laping NJ, et al. Inhibition of transforming growth factor (TGF)-beta1-induced extracellular matrix with a novel inhibitor of the TGF-beta type I receptor kinase activity: SB-431542. Mol Pharmacol. 2002 Jul;62(1):58-64.
[2]. Yuan W, et al. SB-431542, a specific inhibitor of the TGF-β type I receptor inhibits hypoxia-induced proliferation of pulmonary artery adventitial fibroblasts. Pharmazie. 2016 Feb;71(2):94-100.

Background

SB-431542, a small molecule inhibitor of the type I TGF-β receptor, blocks intracellular mediators of TGF-1 signaling, which leads to decreased TGF-β1–mediated proliferation, cytokines and collagen expression. In clinical settings, SB-431542 is widely used to treat respiratory asthma, and inhibits proliferation and synthesis of adventitial fibro in the process of pulmonary vascular remodeling.[1]

In vitro study indicated that SB-431542 is able to inhibit ALK5 with an IC50 of 94 nM and other type I receptors, such as ALK4. Although SB-431542 inhibited ALK4 with an IC50 of 140 nM. Moreover, SB-431542 inhibited TGF-β1–induced collagen Iα1 and PAI-1 mRNA with IC50 values of 60 and 50 nM, respectively. In addition, SB-431542 inhibited TGF-β1–induced fibronectin mRNA and protein with IC50 values of 62 and 22 nM, respectively. These data demonstrate for the first time that ALK5 activity is required for TGF-β1 regulation of extracellular matrix markers FN, collagen Iα1, and PAI-1 mRNA.[1]

In vivo study demonstrated that SB-431542 has the capacity to inhibit TGF-β1-induced gene expression. SB-431542 is recognized as a important inhibitor of the TGF-β1 receptors in blocking TGF-β1/Smads signal pathways in vascular remodeling. Moreover, hypoxia-induced vascular remodeling can significantly increase the amount of cytokines and collagen in vascular adventitia. However, after the treatment of SB-431542, attenuation of the fibrosis promoting effects of TGF-β1, including TGF-β1-induced cell proliferation, cell motility, cell migration and cell synthesis were observed. Therefore, it is significant to the identify the potential of SB-431542 for the treatment of hypoxia-induced pulmonary hypertension.[2]

References:
[1]. Laping NJ, et al. Inhibition of transforming growth factor (TGF)-beta1-induced extracellular matrix with a novel

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SB-431542 是 I 型 TGF-β 受体的小分子抑制剂，可阻断 TGF-1 信号转导的细胞内介质，从而导致 TGF-β1 介导的增殖、细胞因子和胶原蛋白表达减少。在临床上，SB-431542被广泛用于治疗呼吸性哮喘，抑制肺血管重构过程中外膜纤维的增殖和合成。[1]

体外研究表明，SB-431542 能够以 94 nM 的 IC50 抑制 ALK5 和其他 I 型受体，例如 ALK4。尽管 SB-431542 以 140 nM 的 IC50 抑制 ALK4。此外，SB-431542 抑制 TGF-β1 诱导的胶原蛋白 Iα1 和 PAI-1 mRNA，IC50 值分别为 60 和 50 nM。此外，SB-431542 抑制 TGF-β1 诱导的纤连蛋白 mRNA 和蛋白质，IC50 值分别为 62 和 22 nM。这些数据首次表明，TGF-β1 对细胞外基质标志物 FN、胶原蛋白 Iα1 和 PAI-1 mRNA 的调节需要 ALK5 活性。[1]

体内研究表明，SB-431542 具有抑制 TGF-β1 诱导的基因表达的能力。 SB-431542 被认为是 TGF-β1 受体的重要抑制剂，可阻断血管重塑中的 TGF-β1/Smads 信号通路。此外，缺氧诱导的血管重塑可以显着增加血管外膜中细胞因子和胶原蛋白的数量。然而，在 SB-431542 处理后，观察到 TGF-β1 的纤维化促进作用减弱，包括 TGF-β1 诱导的细胞增殖、细胞运动、细胞迁移和细胞合成。因此，鉴定SB-431542治疗缺氧性肺动脉高压的潜力具有重要意义。[2]

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