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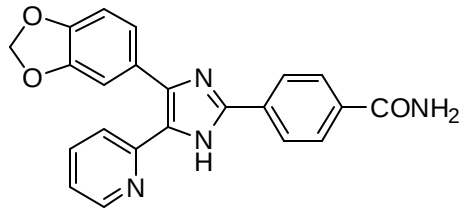
ProductInformation

SB 431542 hydrate

Product Number **S4317**
Store at –20 °C

Cas #: 301836-41-9 (anhydrous)
Chemical Name: 4-[4-(1,3-Benzodioxol-5-yl)-5-(2-pyridinyl)-1H-imidazol-2-yl]-benzamide; 4-[4-(3,4-Methylenedioxyphenyl)-5-(2-pyridyl)-1H-imidazol-2-yl]-benzamide; 4-(5-benzol[1,3]dioxol-5-yl-4-pyridin-2-yl-1H-imidazol-2-yl)-benzamide hydrate



Product Description
Molecular Formula: $C_{22}H_{16}N_4O_3 \cdot H_2O$
Molecular Weight: 384.4

SB 431542 is a potent and selective inhibitor of TGF-β Type 1 receptor kinases (Activin Receptor-Like kinases, ALK-4, -5, -7).

Transforming growth factor β1 (TGF-β1) is a member of a large superfamily of pleiotropic cytokines that are involved in many biological activities, including growth, differentiation, migration, cell survival, and adhesion in diseased and normal states. Nearly 30 members have been identified in this superfamily. These are considered to fall into two major branches: TGFβ/Activin/Nodal and BMP/GDF (Bone Morphogenetic Protein/Growth and Differentiation Factor). They have very diverse and often complementary functions. Some are expressed only for short periods during embryonic development and/or only in restricted cell types (e.g. anti-Mullerian hormone, AMH, Inhibin) while others are widespread during embryogenesis and in adult tissues (e.g. TGFβ1 and BMP4). TGF-β1 is a potent regulator in the synthesis of the extracellular matrix (fibrotic factor) and plays a role in wound healing.

TGFβ signaling involves complex but by no means unusual mechanisms. Ligand binding induces receptor complex formation consisting of receptor type I and II, both of which are serine/threonine kinases. The type II receptor phosphorylates and activates the type I receptor within the complex. Seven type I receptors have been identified to date (Activin Receptor-Like Kinases, ALKs 1-7), and five mammalian type II receptors (TGF-β RII, Act RII, Act RIIB, BMP RII, and AMH RII). The relationship between different TGFβ family ligands and usage of receptor types I and II has been reviewed.[1] Downstream signal transduction takes place when the phosphorylated type I receptor phosphorylates transcription factors, R-Smad or Smad substrates for receptors (Smads 1-8). In general ALK-4, -5, and -7, corresponding to the TGFβ/Activin/Nodal branch, phosphorylates Smad-2 and -3, while Smad-1, -5, and -8 are substrates for ALK-1, -2, -3, and -6 corresponding to the BMP/GDF branch. These phosphorylated Smads then interact with the co-Smad, Smad 4, at high affinity. The Smad complexes that accumulate in the nucleus are required for the assembly of transcriptional apparatus and directly interacts with target genes.[1] Aberrant signaling has been implicated in a number of human diseases: cancer, hereditary hemorrhagic telangiectasia, atherosclerosis, fibrotic disease of kidney, liver, and lung.

SB 431542 inhibits the acitivity of transforming growth factor β1 (TGF-β1) activin receptor-like kinases (ALKs). It is a selective and potent inhibitor of the phylogenetically related subset of ALK-4 (activin type I receptor), ALK-5 (TGFβ type I receptor), and ALK-7 (nodal type I receptor). SB 431542 inhibits endogenous activin and TGF-β signaling but is without effect on the more divergent ALK-1, -2, -3, and -6 and hence BMP signaling.[2, 3] Phosphorylation of Smad2 by ectopically expressed constitutively active ALK-4, ALK-5, and ALK-7 in transfected NIH 3T3 cells is completely abolished by SB 431542 at 10 μM.[3] In addition, the compound inhibits ligand dependent activation of wild type ALK-4 and endogenous ALK-5 with an IC_{50} of approximately 0.25 μM.[3]

In a surprise finding by another group of authors, SB 431542 was shown to inhibit TGFβ1 stimulated proliferation of MG63, a human osteosarcoma cell line expressing ALK-1, which is another TGFβ type I receptor predominantly present in vascular endothelial cells.[4] This observation remains to be reconciled with earlier results on constitutively active ALK-1 and the phosphorylation of Smad1.[3]

It has been demonstrated that SB 431542 stimulates proliferation, differentiation, and sheet formation of ESC (embryonic stem cells)-derived endothelial cells and selectively upregulates the expression of claudin-5, an endothelial specific component of tight junctions.[5] SB 413542 may become clinically useful as a regulator of vascular permeability, in modulating bioavailability of drugs, for the production of endothelial cells in cellular therapy, and as well as a potential research tool in affecting embryonic vasculogenesis.[5] Regardless of its definitive ALK inhibition profile, SB 431542 is a promising tool and drug candidate based on its effects in TGF/Activin/Nodal signaling.

References

1. Massague, J., et al., Cell, **103,** 295 (2000).
2. Laping, N.J., et al., Mol. Pharmacol., **62**, 58 (2002).
3. Inman, G.J., et al., Mol. Pharmacol., **62**, 65 (2002).
4. Matsuyama, S., et al., Cancer Res., **63**, 7791 (2003)
5. Watabe, T., et al., J. Cell Biol., **163**, 1303 (2003).

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