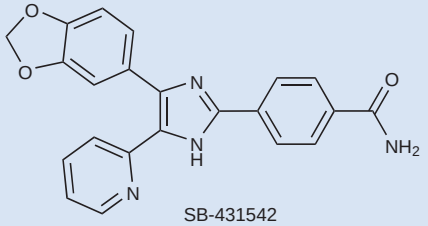
SB-431542: Potent and selective inhibitor of activin receptor-like kinase (ALK) receptors

Transforming growth factor β (TGF-β) is a member of a large superfamily of pleiotropic cytokines that are involved in many cellular activities, including growth, differentiation, migration, cell survival and adhesion. TGF-β family members signal through a receptor complex consisting of type I and type II receptors. Transforming growth factor β1 (TGF-β1) is responsible for the production of extracellular matrix, acting through the TGF-β type I and type II receptors and activating intracellular mediators such as Smad proteins, p38 MAPK (mitogen-activated protein kinase) and the extracellular signal-regulated kinase (ERK) pathway.

SB-431542 (Prod No. **S 4317**) inhibits the activity of transforming growth factor β1 (TGF-β1) superfamily activin receptor-like kinase (ALK) receptors. It is a selective and potent inhibitor of a subset of activin receptor-like kinase receptors, specifically ALK4, ALK5 and ALK7. Phosphorylation of Smad2 by ectopically expressed constitutively active ALK4, ALK5, ALK7 in transfected NH 3T3 cells is completely abolished by SB-431542 at 10 µM [3]. In addition, the compound inhibited ligand-dependent activation of wild type ALK4 and endogenous ALK5, displaying an IC_{50} value of 25 µM [3]. SB-431542 inhibits endogenous activin and TGF-β signaling, but has no effect on bone morphogenetic protein (BMP) signaling. SB-431542 will be a useful tool for studying the role of TGF-β, activin and various cellular processes.



SB-431542
(Prod. No. S 4317)

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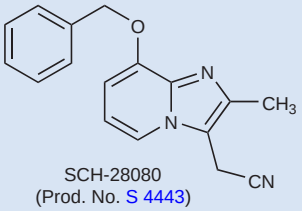
SCH-28080: Potent inhibitor of gastric H^+, K^+-ATPase

Parietal cells are present in the stomach and ileum and are responsible for the secretion of highly concentrated HCl into the lumen. They also recruit and recycle the transport protein H^+,K^+-ATPase, the primary gastric proton pump. An overactive pump may lead to ulcers and other gastrointestinal complications. Thus, developing gastric proton pump inhibitors has become a major target for researchers. Several compounds have been shown to effectively inhibit this pump, notably **omeprazole** (Prod. No. **O-104**), which binds irreversibly, thus blocking acid secretion, leading to anacidity, hyperplasia and hypergastremia [1].

Sigma-RBI is pleased to offer **SCH-28080** (Prod. No. **S 4443**), a potent, reversible inhibitor of gastric H^+,K^+-ATPase that competitively binds to the luminal K^+ high affinity site of H^+,K^+-ATPase. In contrast, SCH-28080 does not inhibit Na^+,K^+-ATPase. In addition, SCH-28080 inhibits renal ouabain-insensitive H^+,K^+-ATPase, but not colonic ouabain-sensitive H^+,K^+-ATPase [2]. The inhibition of ATPase activity by **ouabain** (Prod. No. **O 3125**) has been widely used as a marker of Na^+ pump activity *in vitro*, while inhibition by SCH-28080 has been used as a marker of H^+,K^+-ATPase activity [3], as the binding sites for these compounds differ between the ATPases. The binding site for SCH-28080 is located in the gastric H^+,K^+-ATPase α-subunit in the first extracellular loop between the M1 and M2 transmembrane segments [2], although further details are still to be elucidated [4,5].

SCH-28080 has been shown to possess both antisecretory and cytoprotective properties. The antisecretory ED_{50} values obtained in the pylorus-ligated rat were 3.7 mg/kg p.o. and 2.8 mg/kg i.p., which were 7 and 10 times more potent than the H_2 histamine receptor antagonist **cimetidine** (Prod. No. C 4502), respectively. In rats, the cytoprotective activity of SCH 28080 was demonstrated by inhibition of ethanol-induced gastric lesions in a dose-dependent manner (ED_{50} 3.0 mg/kg p.o.) [6]. In addition, SCH-28080 (1-30 mg/kg p.o. in rats) inhibited gastric ulcers provoked by aspirin, **aspirin** (Prod. No. **A 5376**) plus acid, **indomethacin** (Prod.No. **I 8280**) and stress [6].

Clearly, SCH-28080 will continue to be an indispensable tool for the study of gastric acid secretion and for differentiating the H^+,K^+ and Na^+, K^+-ATPases.



SCH-28080
(Prod. No. S 4443)

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New Product Highlight