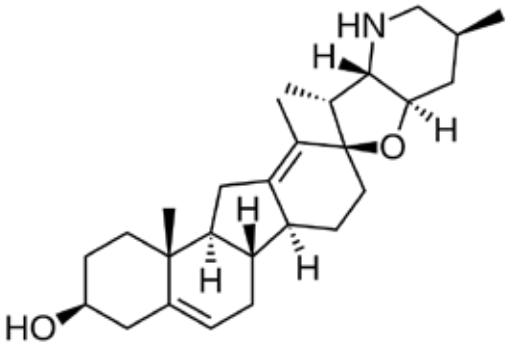
Cyclopamine

Cyclopamine (C9710) is a steroidal alkaloid isolated from the corn lily (*Veratrum californicum*) known for its inhibitory action on Hedgehog (Hh) signaling pathways. Across a variety of studies, cyclopamine exhibits several biological activities, including anticancer and anti-inflammatory properties.

The Hh signaling pathway regulates cell growth and differentiation, playing a significant role in embryonic development and tissue regeneration. Hh proteins bind and inhibit the Patched receptor, allowing levels of neighboring transmembrane receptor Smoothened (Smo) to increase and suppress cleavage (inactivation) of downstream transcription factors; the end result of this signaling cascade is gene activation. Signaling initiated by Hh proteins appears to be overactive in several types of cancer, potentially allowing unchecked cell growth[1-3].

Inhibition of proteins in the Hh signaling pathway shows benefit in the treatment of cancer in preclinical models. Mutations in Patched or Smo may result in constitutively active signaling. Gain-of-function mutations allow Smo to signal for gene transcription without input from upstream proteins and receptors; these mutations have been linked to the development of basal cell carcinoma and colorectal cancer[4-5].



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Cyclopamine directly inhibits Smo, preventing Hh binding and the induction of gene transcription[6]. In one study, cyclopamine induces apoptosis in colorectal adenoma cells and colorectal carcinoma cells[7]. In a cellular model of cholangiocarcinoma, cyclopamine inhibits the epithelial-to-mesenchymal transition as well as cell migration, invasion, and proliferation[8]. Similarly, cyclopamine administered to animal models increases cell necrosis and inhibits tumor growth.

Cyclopamine also displays other biological activities. In an animal model of cholestasis due to hepatic ischemia/reperfusion injury, administration of cyclopamine decreases Akt and ERK activation, reduces neutrophil infiltration, and lowers levels of pro-inflammatory cytokines and fibrosis biomarkers; it also reduces overall histological damage[9]. In separate models of kidney fibrosis, this compound decreases levels of fibronectin and collagen I, preventing the development of interstitial fibrosis after obstructive injury[10].

References:
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