SAG (Smoothened Agonist) is a chlorobenzothiophene-containing compound which acts as an activator of the G protein-coupled receptor Smoothened (SMO, \( EC_{50} = 3 \text{ nM}; \) Chen et al.) SMO is a component of the Hedgehog signaling pathway, which is translocated to the primary cilium after stimulation of the Patched receptor by Hedgehog family ligands, leading to pathway activation. SAG activates SMO via direct binding to the heptahelical bundle (\( K_d = 59 \text{ nM} \)), stabilizing a specific conformation of SMO in cilia and leading to increased downstream gene expression (Rohatgi et al.). SAG abrogates cyclopamine inhibition of SMO, indicating that it acts downstream of cyclopamine (Chen et al.; Frank-Kamenetsky et al.; Lewis & Krieg).

**Structure:**

![Chemical structure of SAG](image)

**Properties**

**Physical Appearance:** A crystalline solid

**Storage:**

Product stable at -20°C as supplied. Protect from prolonged exposure to light.

Stable as supplied for 12 months from date of receipt.

**Solubility:**

- DMSO \( \leq 40 \text{ mM} \)
- Absolute ethanol \( \leq 40 \text{ mM} \)

For example, to prepare a 10 mM stock solution in DMSO, resuspend 1 mg in 204 \( \mu \text{L} \) of DMSO.

Prepare stock solution fresh before use. Information regarding stability of small molecules in solution has rarely been reported, however, as a general guide we recommend storage in DMSO at -20°C. Aliquot into working volumes to avoid repeated freeze-thaw cycles. The effect of storage of stock solution on compound performance should be tested for each application.

Compound has low solubility in aqueous media. For use as a cell culture supplement, stock solution should be diluted into culture medium immediately before use. Avoid final DMSO concentration above 0.1% due to potential cell toxicity.
Published Applications

MAINTENANCE AND SELF-RENEWAL
- Induces proliferation and survival of neuronal and glial precursors in vitro and in vivo (Bragina et al.).
- Prevents glucocorticoid neurotoxicity in Math1-Cre, SmoM2 transgenic mice (Heine et al.).
- Rescues cerebellar size and behavioral phenotypes in the Ts65Dn mouse model of Down syndrome (Das et al.).

DIFFERENTIATION
- Improves neuronal differentiation of human induced pluripotent stem cells (Mak et al.).

References


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