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Product Information

Geldanamycin from Streptomyces hygroscopicus

Catalog Number **G3381** Storage Temperature –20 °C

CAS RN 30562-34-6

Product Description

Molecular Formula: C₂₉H₄₀N₂O₉ Formula Weight: 560.64

Geldanamycin is a benzoquinone ansamycin antitumor antibiotic. ¹ Geldanamycin binds specifically to Hsp90 (Heat Shock Protein 90) ² and to its endoplasmic reticulum homologue GP96. ³ The Hsp90 chaperone is required for the activation of several families of eukaryotic protein kinases and nuclear hormone receptors, many of which are proto-oncogenic and play a prominent role in cancer. The geldanamycin antibiotic has antiproliferative and antitumor effects, as it binds to Hsp90, inhibits the Hsp90-mediated conformational maturation/refolding reaction, and results in the degradation of Hsp90 substrates. ² Hsp90 also plays a key role in regulating the physiology of cells exposed to environmental stress and thus, geldanamycin interferes with cellular stress response. ⁴

Geldanamycin was found to be a potent antibiotic active at nanomolar concentrations against 60 cell lines¹ as well as in mouse tumor models.⁵

It is an inhibitor of proto-oncogenic protein kinases, such as erbB22, ⁶ EFG receptor tyrosine kinases, ⁷ and non-receptor tyrosine kinases, such as v-src⁸ and Raf-1. ⁹ In addition, it is a potent inhibitor of the nuclear hormone receptor family including the estrogen and androgen hormone receptors. ^{10,11}

Precautions and Disclaimer

This product is for R&D use only, not for drug, household, or other uses. Please consult the Safety Data Sheet for information regarding hazards and safe handling practices.

Preparation Instructions

The product is soluble (5 mg/ml) in dichloromethane, yielding a clear yellow-orange solution. It is also soluble in DMSO (10 mg/ml) and insoluble in water

Storage/Stability

It is recommended the product be stored desiccated and protected from light at -20 °C. The product as supplied is stable for 5 years when stored properly.

Solutions in DMSO are stable for at least two weeks when stored at $-20~^{\circ}$ C. Geldanamycin decomposes in acidic solution.

Related product

17-(Allylamino)-17-demethoxygeldanamycin (17-AAG), Catalog Number A8476, which is a less toxic analog

References

- Supko, J.G. et al., Preclinical pharmacologic evaluation of geldanamycin as an antitumor agent. Cancer Chemother. Pharmacol., 36, 305-315 (1995).
- Whitesell, L. et al., Inhibition of heat shock protein HSP90-pp6Ov-src heteroprotein complex formation by benzoquinone ansamycins: Essential role for stress proteins in oncogenic transformation. *Proc. Natl. Acad. Sci. USA*, **91**, 8324-8328 (1994).
- Chavany C. et al., p185erbB2 binds to GRP94 in vivo. Dissociation of the p185erbB2/GRP94 heterocomplex by benzoquinone ansamycins precedes depletion of p185erbB2. J. Biol. Chem., 271, 4974-4977 (1996).
- 4. Schneider, C. et al., Pharmacologic shifting of a balance between protein refolding and degradation mediated by Hsp90. *Proc. Natl. Acad. Sci. USA*, **91**, 14536-14541 (1996).
- 5. Sasaki, K. et al., Growth inhibition of virus transformed cells *in vitro* and antitumor activity *in vivo* of geldanamycin and its derivatives. *J. Antibiot.* (Tokyo), **32**, 849-851 (1979).

- 6. Miller, P. et al., Depletion of the erbB-2 gene product p185 by benzoquinoid ansamycins. *Cancer Res.*, **54**, 2724-2730 (1994).
- 7. Murakami, Y. et al., Accelerated degradation of 160 kDa epidermal growth factor (EGF) receptor precursor by the tyrosine kinase inhibitor herbimycin A in the endoplasmic reticulum of A431 human epidermoid carcinoma cells. *Biochem. J.*, 301, 63-68 (1994).
- 8. June, C.H. et al., Inhibition of tyrosine phosphorylation prevents T-cell receptor-mediated signal transduction. *Proc. Natl. Acad. Sci. USA*, **87**, 7722-7726 (1990).
- 9. Schulte, T.W. et al., Disruption of the Raf-1-Hsp90 Molecular Complex Results in Destabilization of Raf-1 and Loss of Raf-1-Ras Association. *J. Biol. Chem.*, **270**, 24585-88 (1995).
- Whitesell, L., and Cook, P., Stable and specific binding of heat shock protein 90 by geldanamycin disrupts glucocorticoid receptor function in intact cells. *Mol. Endocrinol.*, **10**, 705-712 (1996).
- Smith, D.F. et al., Progesterone receptor structure and function altered by geldanamycin, an hsp90binding agent. *Mol. Cell Biol.*, 15, 6804-12 (1995).

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