

Product Data Sheet

Product Name: AG-012986

Cat. No.: GC82119

Chemical Properties

Cas. No. 486414-35-1

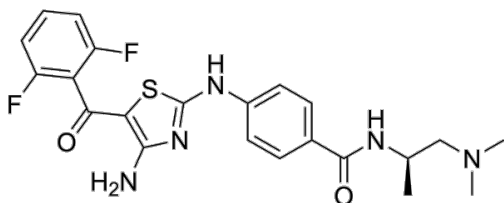
Formula $C_{22}H_{23}F_2N_5O_2S$ M.Wt 459.51

Solubility DMSO: 100 mg/mL (217.62 mM; Need ultrasonic) Storage Store at -20°C

General tips For obtaining a higher solubility, please warm the tube at 37 °C and shake it in the ultrasonic bath for a while. Stock solution can be stored below -20°C for several months.

Shipping Condition Evaluation sample solution: ship with blue ice All other available size: ship with RT, or blue ice upon request.

Structure



Background

AG-012986 is a pan- CDK inhibitor with K_i values of 44 nM (CDK1), 9.2 nM (CDK4), 94 nM (CDK2), and IC_{50} values of 22 nM (CDK5), 4 nM (CDK9). AG-012986 causes apoptosis of T-cells by targeting upstream kinases in the p38 Mitogen-activated protein kinase (MAPK) pathway and impairing cellular survival. AG-012986 induces cell cycle arrest, retinoblastoma protein

Caution: Product has not been fully validated for medical applications. For research use only.

Tel: (909) 407-4943 Fax: (626) 353-8530 E-mail: tech@glpbio.com

Address: 10292 Central Ave. #205, Montclair, CA, USA

Product Data Sheet

hypophosphorylation, and reduces Ki-67 expression. AG-012986 exerts antiproliferative activity in tumor cells, demonstrates antitumor efficacy in human xenograft models, and causes retinal and peripheral neurotoxicity, plus immune cell toxicity. AG-012986 can be used for the research of colon carcinoma, non-small cell lung carcinoma, lung carcinoma, breast carcinoma, ovarian tumor, pancreatic carcinoma, osteosarcoma, lymphoma, leukemia, retinotoxicity [1] [2] [3] [4].

In Vivo, AG-012986 (8.8-40 mg/kg; s.c.; daily, 12 days) shows >83% tumor growth inhibition (TGI) in 10 of the 11 tumor models tested^[1].

In Vitro, AG-012986 is a potent, selective pan-CDK inhibitor with nanomolar activity against CDK4/cyclin D3 ($K_i = 9.2$ nM), CDK1/cyclin B ($K_i = 44$ nM), CDK2/cyclin A ($K_i = 94$ nM), CDK9/cyclin T ($IC_{50} = 4$ nM), and CDK5/p35 ($IC_{50} = 22$ nM)^[1]. AG-012986 (0.837-2.44 μ M) has limited off-target activity against non-Kinase targets, with functional interactions at micromolar concentrations with the calcium type L ion channel, serotonin transporter, and histamine H3 receptor^[1]. AG-012986 (72 h) potently inhibits proliferation of 18 human tumor cell lines with an average IC_{50} of 120 nM, and displays IC_{50} values <100 nM in 13 of these cell lines, independent of p53 and Rb status^[1]. AG-012986 (60-240 nM; 8-24 h) induces dose-dependent hypophosphorylation of Rb Ser795 in HCT116 human colon cancer cells after 24 hours of treatment, with maximal effects at >120 nM, but shows minimal effect after 8 hours^[1]. AG-012986 (30 nM-1 μ M; 8-24 h) induces G1 phase arrest in HCT116 human colon cancer cells at 30 to 120 nM and G2-M phase arrest at ≥ 240 nM after 24 hours of treatment, but does not induce cell cycle arrest with <8 hours of exposure^[1]. AG-012986 (30-240 nM; 8-24 h) induces apoptosis in HCT116 human colon cancer cells with an IC_{50} of ≈ 160 nM after 24 hours of treatment, but shows no apoptotic effect after 8 hours^[1]. AG-012986 (10-1000 nM; 8-320 h) shows time-dependent cytotoxicity in SW620 human colon carcinoma cells, with minimal activity after 8 hours, moderate activity ($IC_{50} = 300$ nM) after 24 hours, and substantial cytotoxicity ($IC_{50} < 100$ nM) after ≥ 72 hours^[1]. AG-012986 exhibits binding inhibition of multiple CDK isoforms in a cell-free KINOMEScan assay, with similar IC_{50} values to non-neurotoxic NVP-2 for CDK11, CDK16, and CDK17^[2]. AG-012986 (200-500 nM; 24 h) induces dose-dependent cytotoxicity in human MIO-M1 Müller cells, with significant decreases in cell viability and increases in cell death observed at 200 nM and maximal effects at 500 nM after 24 h of incubation^[2]. AG-012986 (250 nM; 16 h) induces rapid

Caution: Product has not been fully validated for medical applications. For research use only.

Tel: (909) 407-4943 Fax: (626) 353-8530 E-mail: tech@glpbio.com

Address: 10292 Central Ave. #205, Montclair, CA, USA

Product Data Sheet

apoptosis/necrosis in primary human PBMCs, with 80% of cells showing dual PI/Annexin-V positivity^[3]. AG-012986 (50 nM-1 μ M; 8-48 h) activates caspase-3/7 in primary human PBMCs in vitro in a dose-dependent manner, with peak activity occurring 16-24 h after treatment with 50 nM, 200 nM, or 1 μ M^[3]. AG-012986 (50 nM-200 nM; 8 h) induces cleavage of caspase-3 and PARP in primary human PBMCs following 8 h treatment with 50 nM or 200 nM, confirming caspase-mediated apoptosis^[3]. AG-012986 (10 nM-500 nM; 16 h) exhibits greater cytotoxicity in primary human PBMCs than staurosporine after 16 h treatment with 10-500 nM, as measured by reduced ATP content and increased caspase-3/7 activity^[3]. AG-012986's (50 nM-250 nM; 20 min) toxicity profile is altered by acute stimulation of T cells^[3]. AG-012986 (20 nM-500 nM) inhibits α -CD3-induced proliferation in purified primary human T cells pretreated by AG-012986 followed by 24 h α -CD3 antibody stimulation, while α -CD3 stimulation decouples this antiproliferative activity from AG-012986-induced toxicity^[3]. AG-012986 (20 nM-500 nM; 48 h) inhibits α -CD3-induced IL-2 production in purified primary human T cells in a dose-dependent manner, with a fivefold reduction observed at 20 nM^[3]. AG-012986 (50-250 nM; 20 min pretreatment) inhibits both basal and α -CD3-induced p38 phosphorylation in purified primary human T cells pretreated with 50 nM or 250 nM for 20 min followed by 16 h incubation with or without stimulation^[3]. AG-012986 (250 nM; 16 h) causes rapidly apoptosis in PBMCs and occurs independently of any cell division^[4]. AG-012986 (50-200 nM; 8 h) induced the presence of p17 and p19 and the cleaved form of PARP^[4].

References:

- [1]. Zhang C, et al. Pharmacologic properties of AG-012986, a pan-cyclin-dependent kinase inhibitor with antitumor efficacy. *Mol Cancer Ther.* 2008 Apr;7(4):818-28.
- [2]. Wright P, et al. Differential expression of cyclin-dependent kinases in the adult human retina in relation to CDK inhibitor retinotoxicity. *Arch Toxicol.* 2019;93(3):659-671.
- [3]. Lee DU, et al. Off-target immune cell toxicity caused by AG-012986, a pan-CDK inhibitor, is associated with inhibition of p38 MAPK phosphorylation. *J Biochem Mol Toxicol.* 2012 Mar;26(3):101-8.

Caution: Product has not been fully validated for medical applications. For research use only.

Tel: (909) 407-4943 Fax: (626) 353-8530 E-mail: tech@glpbio.com

Address: 10292 Central Ave. #205, Montclair, CA, USA