Ganetespib

Cat. No.: HY-15205

CAS No.: 888216-25-9

Molecular Formula: $C_{20}H_{20}N_4O_3$

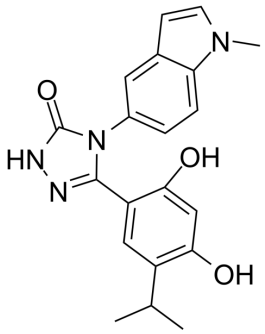
Molecular Weight: 364

Target: HSP; Apoptosis

Pathway: Cell Cycle/DNA Damage; Metabolic Enzyme/Protease; Apoptosis

Storage:

Powder	-20°C	3 years
	4°C	2 years
In solvent	-80°C	1 year
	-20°C	6 months



SOLVENT & SOLUBILITY

In Vitro

DMSO : ≥ 100 mg/mL (274.73 mM)

* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions	Concentration / Solvent / Mass	1 mg	5 mg	10 mg
	1 mM	2.7473 mL	13.7363 mL	27.4725 mL
	5 mM	0.5495 mL	2.7473 mL	5.4945 mL
	10 mM	0.2747 mL	1.3736 mL	2.7473 mL

Please refer to the solubility information to select the appropriate solvent.

In Vivo

1. Add each solvent one by one: 15% Cremophor EL >> 85% Saline
   Solubility: 10 mg/mL (27.47 mM); Suspended solution; Need ultrasonic
2. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: ≥ 2.5 mg/mL (6.87 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.5 mg/mL (6.87 mM); Clear solution
4. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (6.87 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Ganetespib (STA-9090) is a heat shock protein 90 (HSP90) inhibitor which exhibits potent cytotoxicity in a wide variety of hematological and solid tumor cell lines. Ganetespib has antiangiogenic effects in colorectal cancer mediated through inhibition of HIF-1α and STAT3[1][2][3][4][5][6].

IC_{50} & Target	HSP90
In Vitro	Ganetespib causes depletion of receptor tyrosine kinases, extinguishing of downstream signaling, inhibition of proliferation and induction of apoptosis with IC_{50} values ranging 2-30 nM in genomically-defined NSCLC cell lines. Ganetespib is also approximately 20-fold more potent in isogenic Ba/F3 pro-B cells rendered IL-3 independent by expression of EGFR and ERBB2 mutants[1]. Ganetespib exhibits potent in vitro cytotoxicity in a range of solid and hematologic tumor cell lines, induces the degradation of known Hsp90 client proteins, displays superior potency to the ansamycin inhibitor 17-allylamino-17-demethoxygeldanamycin (17-AAG)[2]. Ganetespib is a potent HSP90 inhibitor, and shown to kill canine tumor cell lines in vitro[3]. Ganetespib possesses superior JAK/STAT inhibitory activity to both P6 and 17-AAG in terms of potency or duration of response in the HEL92.1.7 cells[4]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	Ganetespib (125 mg/kg, i.v.) accumulates in tumors relative to normal tissues and displays greater in vivo efficacy than 17-AAG without increased toxicity and inhibits proliferation and induces apoptosis in parallel with EGFR depletion in NCI-H1975 xenografts[1]. Ganetespib (100, 125, 150 mg/kg, i.v.) shows potent antitumor efficacy in solid and hematologic xenograft models of oncogene addiction, as evidenced by significant growth inhibition and/or regressions[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Kinase Assay [1]	Exponentially growing cells are processed in lysis buffer (20 mM HEPES, pH 7.4, 1 mM EDTA, 5 mM $MgCl_2$, 100 mM KCl) and incubated with increasing concentrations of 17-AAG or ganetespib for 30 min at 4°C, and incubated with biotin-GM linked to Dynabeads MyOne Streptavidin T1 magnetic beads for 1 h at 4°C. Beads are washed three times in lysis buffer and heated for 5 min at 95°C in SDS-PAGE sample buffer. Samples are resolved on 4-12% Bis-Tris gradient gel and Western blots are performed using an anti-HSP90 antibody. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Cell Assay [2]	Cells are grown in 96-well plates based on optimal growth rates determined empirically for each line. Twenty-four hours after plating, cells are treated with the indicated compounds or controls for 72 hours. AlamarBlue is added (10% v/v) to the cells, and the plates are incubated for 3 hours and, then, subjected to fluorescence detection. For the comparative viability/apoptosis assay, NCI-H1975 cells are treated with escalating concentrations of ganetespib for the indicated time periods and subjected to viability analysis via CellTiter Fluor and apoptosis via Caspase Glo 3/7. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1]	Mice: NCI-H1975 or HCC827 cells are cultured as above and $0.5\text{-}1\times10^7$ cells are mixed with 50% RPMI 1640/50% Matrigel and subcutaneously injected into the flanks of SCID mice. For efficacy studies, animals with 100-200 mm^3 tumors are then randomized into treatments groups of eight. Tumor volumes (V) are calculated by the equation V=0.5236×L×W×T (Length, width, and thickness). Animals are treated by intravenous bolus tail vein injection at 10 mL/kg with ganetespib formulated in 10/18 DRD (10% DMSO, 18% Cremophor RH 40, 3.6% dextrose and 68.4% water). As a measurement of in vivo efficacy, the relative size of treated and control tumors [(%T/C) value] is determined from the change in average tumor volumes of each drug-treated group relative to the vehicle-treated group, or itself in the case of tumor regression. Body weights are monitored daily. For biomarker studies, mice bearing NCI-H1975 xenografts are treated with either a single dose of vehicle or ganetespib, or with 5 daily doses of vehicle or ganetespib, in groups of 3 or 8, and harvested at various time points. Tumors are excised and flash frozen in liquid nitrogen for preparation of protein lysates or fixed in 10% neutral buffered formalin for immunohistochemistry. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Cancer Cell. 2018 Sep 10;34(3):411-426.e19.
- Nat Commun. 2020 Aug 7;11(1):3946.
- Theranostics. 2020 Jul 9;10(18):8415-8429.
- Theranostics. 2020 Jul 9;10(18):8415-8429.
- Theranostics. 2019 Aug 12;9(20):5769-5783.

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REFERENCES

[1]. Shimamura T, et al. Ganetespib (STA-9090), a Non-Geldanamycin HSP90 Inhibitor, has Potent Antitumor Activity in In Vitro and In Vivo Models of Non-Small Cell Lung Cancer. Clin Cancer Res. 2012 Jul 17.

[2]. Ying W, et al. Ganetespib, a unique triazolone-containing Hsp90 inhibitor, exhibits potent antitumor activity and a superior safety profile for cancer therapy. Mol Cancer Ther. 2012 Feb;11(2):475-84.

[3]. London CA, et al. Phase I evaluation of STA-1474, a prodrug of the novel HSP90 inhibitor ganetespib, in dogs with spontaneous cancer. PLoS One. 2011;6(11):e27018.

[4]. Proia DA, et al. Multifaceted intervention by the Hsp90 inhibitor ganetespib (STA-9090) in cancer cells with activated JAK/STAT signaling. PLoS One. 2011 Apr 14;6(4):e18552.

[5]. Stewart E, et al. Identification of Therapeutic Targets in Rhabdomyosarcoma through Integrated Genomic, Epigenomic, and Proteomic Analyses. Cancer Cell. 2018 Sep 10;34(3):411-426.e19.

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