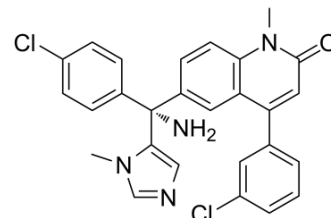


Tipifarnib

Cat. No.:	HY-10502		
CAS No.:	192185-72-1		
Molecular Formula:	C ₂₇ H ₂₂ Cl ₂ N ₄ O		
Molecular Weight:	489.4		
Target:	Farnesyl Transferase		
Pathway:	Metabolic Enzyme/Protease		
Storage:	Powder	-20°C	3 years
		4°C	2 years
	In solvent	-80°C	6 months
		-20°C	1 month



SOLVENT & SOLUBILITY

In Vitro

DMSO : 14.29 mg/mL (29.20 mM; Need ultrasonic)
 H₂O : < 0.1 mg/mL (insoluble)

Preparing Stock Solutions	Solvent Concentration	Mass		
		1 mg	5 mg	10 mg
	1 mM	2.0433 mL	10.2166 mL	20.4332 mL
	5 mM	0.4087 mL	2.0433 mL	4.0866 mL
	10 mM	0.2043 mL	1.0217 mL	2.0433 mL

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

In Vivo

- Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
 Solubility: ≥ 1.43 mg/mL (2.92 mM); Clear solution
- Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
 Solubility: 1.43 mg/mL (2.92 mM); Suspended solution; Need ultrasonic
- Add each solvent one by one: 10% DMSO >> 90% corn oil
 Solubility: ≥ 1.43 mg/mL (2.92 mM); Clear solution
- Add each solvent one by one: 5% DMSO >> 40% PEG300 >> 5% Tween-80 >> 50% saline
 Solubility: ≥ 2.5 mg/mL (5.11 mM); Clear solution
- Add each solvent one by one: 5% DMSO >> 95% (20% SBE-β-CD in saline)
 Solubility: ≥ 2.5 mg/mL (5.11 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Tipifarnib (IND 58359) binds to and inhibits farnesyltransferase (FTase) with an IC₅₀ of 0.86 nM. Antineoplastic activity^[1].

IC₅₀ & Target	IC50: 0.86 nM (FTase)
In Vitro	<p>Tipifarnib inhibits the growth of H-Ras-transformed NIH 3T3 cells with an impressive IC₅₀ value of 1.7 nM^[1]. Tipifarnib is a potent inhibitor of Trypanosoma Cruzi with the ED₅₀ of 4 nM^[1]. Combining Tipifarnib with 10 nM 4-OH-ICI 47699 in the presence of E2 reduces the IC₅₀ 8-fold from 400 to 50 nM^[2]. Tipifarnib inhibits isolated human farnesyltransferase for a lamin B peptide and for the K-RasB peptide with IC₅₀ of 0.86 nM and 7.9 nM, respectively^[3]. Tipifarnib shows inhibition of cell growth or angiogenesis, and induction of apoptosis in aggressive prostate cancer (PCa)^[4]. Tipifarnib shows a significant decrease in the concentration of exosomes in C4-2B cells both at 0.25 and 1 μM as well as in the PC-3 cells at 0.25 μM for 48 hours^[4]. Tipifarnib (1 μM) significantly inhibits the protein concentration of Alix, nSMase2, and Rab27a in C4-2B cells^[4]. Tipifarnib (0.25 μM) significantly inhibits the activation of p-ERK (downstream effector molecule of the Ras/Raf/ERK signaling pathway) but not total ERK in C4-2B and PC-3 cells but not in the normal RWPE-1 cells^[4]. Tipifarnib (0-250 nM) causes a dose-dependent decrease in Alix, nSMase2, and Rab27a in both C4-2B and PC-3 cells, but not in the RWPE-1 cells, Tipifarnib has the potential to be a potent inhibitor of exosome biogenesis and/or secretion^[4]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.</p>
In Vivo	<p>Combined therapy with ICI 47699 and Tipifarnib (50 mg/kg, p.o.) produces greater tumor growth inhibition when compared with either drug alone. E2 deprivation and Tipifarnib in combination results in greater growth inhibition than either E2 deprivation or Tipifarnib alone. The combination of ICI 47699 and Tipifarnib results in significantly lower Ki-67 compared with either ICI 47699 or Tipifarnib alone. Tipifarnib alone also reduces the CTI compared with control. The combination of ICI 47699 and Tipifarnib or Tipifarnib coupled with E2 withdrawal is most effective at lowering the CTI (0.8 and 0.7, respectively), which may account for the decrease in tumor volume^[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.</p>

PROTOCOL

Cell Assay ^[2]	<p>Steroid-depleted cells are seeded into 12-well plates at a density of appr 1×10⁴ cells per well or into 96-well plates at a density of 4,000 cells per well, in dextran-coated charcoal medium. After 24 h, monolayers are treated with E2 plus inhibitors either alone or in combination. The 12-well plates are treated for 6 days with daily changes. Cell number is then determined using a Z1 Coulter counter. The 96-well plates are treated with a single dose and left for 96 h at which time cell viability is measured using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide assay as described previously. The interaction between Tipifarnib and 4-OH-ICI 47699 is analyzed by the median effect plot method described by Chou and Talalay. Calculation of the combination index took into account a nonfixed drug ratio and is based on the assumption that the action of the two drugs is mutually nonexclusive for the strict detection of synergism. A combination index < 1 indicates synergism, combination index=1 indicates additivity, and a combination index > 1 indicates antagonism. Experiments are repeated thrice. MCE has not independently confirmed the accuracy of these methods. They are for reference only.</p>
Animal Administration ^[2]	<p>Female ovariectomized Ncr foxhead nude mice are kept under sterile conditions with free access to food and water. MCF-7 xenografts are initiated by implantation of 2-mm diameter tumor fragments from established tumors. Once tumors reach a diameter of appr 7 mm, mice are randomized to receive vehicle [20% w/v β-cyclodextrin (pH 2.5) for Tipifarnib, 50% PEG 300, 50% H₂O + 1 drop 1N HCl per 3 mL for ICI 47699], Tipifarnib (50 mg/kg twice daily), ICI 47699 (20 mg/kg), or a combination of both Tipifarnib and ICI 47699. Two further treatment arms are used to assess the effect of E2 withdrawal (removal of the E2 pellet) or E2 withdrawal combined with Tipifarnib (50 mg/kg twice daily). All drugs are given by oral gavage daily for 5 consecutive days followed by a 2-day rest period, for a total of 19 days. The experiment is done twice giving similar results; therefore, the growth data are combined for statistical analysis. There are six tumor-bearing animals in each group and all tumors are harvested on day 19. Tumor volumes are calculated using the formula $a \times b^2 \times \pi/6$, where a and b are orthogonal tumor diameters and expressed as a percentage of the volume at the start of treatment (relative tumor volume). Overall statistical difference is calculated using the Kruskal-Wallis test and statistical differences between individual treatment arms are calculated using the Mann-Whitney test. MCE has not independently confirmed the accuracy of these methods. They are for reference only.</p>

CUSTOMER VALIDATION

- Mol Plant Pathol. 2019 Sep;20(9):1264-1278.
- Patent. US20180263995A1.

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- [3]. End DW, et al. Characterization of the antitumor effects of the selective farnesyl protein transferase inhibitor R115777 in vivo and in vitro. Cancer Res. 2001 Jan 1;61(1):131-7
- [4]. Amrita Datta, et al. High-throughput screening identified selective inhibitors of exosome biogenesis and secretion: A drug repurposing strategy for advanced cancer. Sci Rep. 2018 May 25;8(1):8161.
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