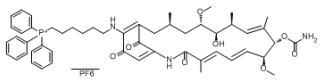
Gamitrinib TPP hexafluorophosphate

Cat. No.:	HY-102007A		
CAS No.:	1131626-47-5		
Molecular Formula:	$C_{52}H_{65}F_6N_3O_8P_2$		
Molecular Weight:	1036.03		
Target:	Others		
Pathway:	Others		
Storage:	Powder	-20°C	3 years
		4°C	2 years
	In solvent	-80°C	6 months
		-20°C	1 month



BIOLOGICAL ACTIVITY

Description	Gamitrinib TPP hexafluorophosphate is a **Gamitrinib (GA) mitochondrial matrix** inhibitor.
IC_{50} & Target	GA mitochondrial matrix[1].
In Vitro	Gamitrinib TPP (Gamitrinib^{TPP}, G-TPP), a small molecule that combines the Hsp90 ATPase inhibitory module of 17-allylamino geldanamycin (17-AAG) with the mitochondrial-targeting moiety of triphenylphosphonium. Gamitrinib TPP is selectively delivered to mitochondria and does not affect Hsp90 homeostasis outside the organelle. Within a 16-hour exposure, concentrations of Gamitrinib TPP of 15-20 μM indistinguishably kill patient-derived and cultured glioblastoma cell lines. This cell death response has the hallmarks of mitochondrial apoptosis, with loss of organelle inner membrane potential, release of cytochrome c in the cytosol, activation of initiator caspase-9 and effector caspase-3 and caspase-7, and cellular reactivity for annexin V[1].
In Vivo	Whether the combination of TRAIL plus Gamitrinib TPP (Gamitrinib^{TPP}, G-TPP) has activity against glioblastoma in vivo is studied. Luciferase-expressing U87 glioblastoma cells implanted in the right cerebral striatum of immunocompromised mice give rise to rapidly growing tumors by bioluminescence imaging, and treatment of these mice with vehicle, stereotactic delivery of TRAIL, or systemic administration of suboptimal concentrations of Gamitrinib TPP does not affect tumor growth in vivo. Similarly, systemic monotherapy with Gamitrinib TPP at concentrations (20 mg/kg as daily i.p. injections) that inhibit subcutaneous xenograft tumor growth in mice has no effect on orthotopic glioblastoma growth. In contrast, 2 cycles of intracranial TRAIL combined with systemic Gamitrinib TPP suppresses the growth of established glioblastomas, with no significant animal weight loss throughout treatment[1].

PROTOCOL

Cell Assay [1]	Human glioblastoma cell lines **LN229** (p53 mutant; PTEN, WT), **U87** (p53 WT; PTEN mutant), **U251** (p53 mutant), prostate adenocarcinoma **PC3**, breast adenocarcinoma **MCF-7**, and human epithelial kidney (**HEK**) **293T** are seeded in triplicate onto 96-well plates at 2×103 cells/well, treated with vehicle, **Gamitrinib TPP (5, 10, 15, and 20 uM)**, or nontargeted 17-AAG (**0-20 μM**) for up to 24 h, and quantified for metabolic activity by a MTT colorimetric assay with

	absorbance at 405 nm. For determination of apoptosis, control or treated tumor cell types (1×10^6) are labeled for annexin V and propidium iodide (PI) and analyzed by multiparametric flow cytometry. For Gamitrinib TPP-TRAIL combination studies, tumor cell types are simultaneously incubated with suboptimal concentrations of **Gamitrinib TPP** at **5 μM** and TRAIL depending on the cell type at 100 ng/mL (U87), 20 ng/mL (U251), 40 ng/mL (PC3, MCF-7, FHAS), or 200 ng/mL (LN229), and analyzed after 16 h for cell viability by MTT[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1]	Mice[1] U87 glioblastoma cells stably transfected with a luciferase expression plasmid (U87-Luc) are suspended in sterile PBS, pH 7.2, and stereotactically implanted (1×10^5) in the right cerebral striatum of immunocompromised **nude mice**. Animals with established tumors are randomized in 4 groups (4 animals/group) and started on sterile vehicle (cremophor), TRAIL alone, Gamitrinib TPP alone, or the combination of TRAIL plus Gamitrinib TPP. In all animal groups, TRAIL is injected stereotactically in the right cerebral striatum (2 ng on days 7 and 10 after implantation), and **Gamitrinib TPP is given systemically** (**10 mg/kg as daily i.p. injections on days 6, 7, 9, and 10 after implantation**). Treatment is suspended on day 10 after tumor implantation, and tumor growth is assessed weekly by bioluminescence imaging after i.p injection of 110 mg/kg D-luciferin. In some experiments, nude mice carrying established U87-Luc intracranial glioblastomas are treated with systemic **Gamitrinib TPP monotherapy at 20 mg/kg as daily i.p. injections** and monitored for tumor growth by bioluminescence imaging. Animal survival is calculated per group[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

REFERENCES

[1]. Markus D. Siegelin, et al. Exploiting the mitochondrial unfolded protein response for cancer therapy in mice and human cells. J Clin Invest. 2011 Apr 1; 121(4): 1349–1360.

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