Product Data Sheet

Product Name: TH-Z827 diTFA
Cat. No.: GC81859

Chemical Properties

Cas. No.

Formula	$C_{34}H_{40}F_6N_6O_5$	M.Wt	726.71
Solubility	DMSO: 100 mg/mL (137.61 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

Product Data Sheet

Background

TH-Z827 diTFA is a selective KRAS G12D inhibitor that exhibits activity against GDP-bound and GMPPNP-bound KRAS G12D, but shows no activity against KRAS (WT) and KRAS G12C. TH-Z827 diTFA blocks the KRAS G12D -CRAF interaction with a IC_{50} value of 42 μM. TH-Z827 diTFA can be used for the research of pancreatic cancer [1] [2].

In Vivo, TH-Z827 (10-30 mg/kg; i.p.; Days 38, 41, 44, 47, 50, 53, 56, 59, 62) diTFA reduces pancreatic tumor volumes in a dose-dependent manner in BALB/c nude mice, with the 30 mg/kg intraperitoneal dose achieving greater tumor volume reduction than the 10 mg/kg dose[1]. TH-Z827 (10 mg/kg; i.p.) diTFA reduces pancreatic tumor volumes in C57BL/6 mice, and exhibits synergistic antitumor activity when combined with anti-PD-1 antibody[1]. TH-Z827 diTFA synergizes with an anti-PD-1 antibody to reduce tumor volume in C57BL/6 mice bearing KPC pancreatic cancer xenografts[2].

In Vitro, TH-Z827 (10 min) diTFA potently inhibits SOS-catalyzed nucleotide exchange of GDP-bound KRASG12D with an IC_{50} of 3.1 μM, and displays nearly 10-fold selectivity for KRASG12D over KRASG12C[1]. TH-Z827 (800 μM) diTFA binds to both GDP-bound and GMPPNP-bound KRASG12D with similar affinities (Kd of 6.52 μM and 7.01 μM, respectively), and does not bind to KRASWT or KRASG12C[1]. TH-Z827 diTFA blocks the KRASG12D-CRAF interaction with an IC_{50} of 42 μM, without affecting interactions involving KRAS(WT) or KRASG12C[1]. TH-Z827 diTFA potently inhibits SOS-catalyzed GDP/GDP exchange of purified GDP-bound KRASG12D protein with an IC_{50} of 3.1 μM[2]. TH-Z827 diTFA exhibits selective binding and inhibition for purified KRASG12D protein over KRAS WT and KRASG12C proteins, with no measurable binding to the latter two variants[2]. TH-Z827 (24 h) diTFA inhibits proliferation of KRASG12D-mutant PANC-1 and Panc 04.03 pancreatic cancer cells with IC_{50} values of 4.4 μM and 4.7 μM, respectively [1]. TH-Z827 (1-20 μM; 3 h) diTFA inhibits MAPK and PI3K/mTOR signaling in KRASG12D-mutant PANC-1 and Panc 04.03 pancreatic cancer cells by reducing pERK and pAKT levels following 3 h of treatment[1].

References:

[1]. Mao Z, et al. KRAS(G12D) can be targeted by potent inhibitors via formation of salt bridge. Cell

discovery. 2022 Jan 25;8(1):5.
[2]. Mao Z, et al. KRAS G12D can be targeted by potent salt-bridge forming inhibitors[J]. bioRxiv, 2021: 2021.12. 13.472365.