GZD856 formic

Cat. No.: HY-101489A

CAS No.: 2804039-78-7

Molecular Formula: $C_{30}H_{29}F_3N_6O_3$

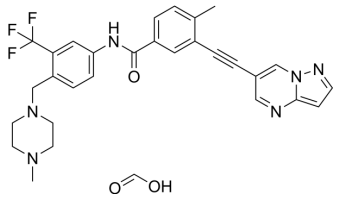
Molecular Weight: 578.58

Target: PDGFR; Bcr-Abl; Apoptosis

Pathway: Protein Tyrosine Kinase/RTK; Apoptosis

Storage: -20°C, sealed storage, away from moisture

* In solvent : -80°C, 6 months; -20°C, 1 month (sealed storage, away from moisture)



SOLVENT & SOLUBILITY

In Vitro

DMSO : 100 mg/mL (172.84 mM; Need ultrasonic)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	1.7284 mL	8.6418 mL	17.2837 mL
	5 mM	0.3457 mL	1.7284 mL	3.4567 mL
	10 mM	0.1728 mL	0.8642 mL	1.7284 mL

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

BIOLOGICAL ACTIVITY

Description

GZD856 formic is a potent and orally active PDGFRα/β inhibitor, with IC_{50}s of 68.6 and 136.6 nM, respectively. GZD856 formic is also a Bcr-Abl^{T315I} inhibitor, with IC_{50}s of 19.9 and 15.4 nM for native Bcr-Abl and the T315I mutant. GZD856 formic has antitumor activity[1][2]. GZD856 (formic) is a click chemistry reagent, it contains an Alkyne group and can undergo copper-catalyzed azide-alkyne cycloaddition (CuAAc) with molecules containing Azide groups.

IC_{50} & Target

PDGFRα	PDGFRβ	Bcr-Abl^{T315I}	Bcr-Abl
68.6 nM (IC_{50})	136.6 nM (IC_{50})	15.4 nM (IC_{50})	19.9 nM (IC_{50})

In Vitro

GZD856 (0.0032-10 μM, 72 h) exerts antiproliferative activity against a panel of lung cancer cells[1].

GZD856 (0.3-3 μM; 24-28 h) induces a dose-dependent G0/G1 phase arrest and apoptosis in H1703 but not A549 cells[1].

GZD856 (0.1-10 μM; 6 h) dose-dependently inhibits the PDGFRα/β phosphorylation and downstream signaling in H1703 and A549 cells[1].

GZD856 inhibits the proliferation of K562, K562R (Q252H) and murine Ba/F3 cells ectopically expressing Bcr-Abl^{WT} and Bcr-Abl^{T315I}, with IC_{50}s of 2.2, 67.0, 0.64 and 10.8 nM, respectively[2].

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

Cell Viability Assay[1]

Cell Line:	H1703, A549, Calu-6, 95-D, L-78, HCC827, SPCA-1, H1650, H1299, H522, H332 and H820 NSCLC cells
Concentration:	0.0032-10 μM
Incubation Time:	72 hours
Result:	Inhibited PDGFRα-overexpressing H1703 cells, with an IC_{50} of 0.25 μM.

Apoptosis Analysis[1]

Cell Line:	H1703 and A549 NSCLC cells
Concentration:	0.3, 1, 3 μM
Incubation Time:	24, 48 hours
Result:	Led to 54.1% apoptosis in H1703 cells at the concentration of 3.0 μM, whereas only 15.5% apoptotic A549 cells were observed under similar conditions. Decreased the CDK4, cyclin D2, CDK2 and Cyclin E protein levels and activated of PARP and Caspase-3 cleavage in H1703 cells.

Western Blot Analysis[1]

Cell Line:	H1703 and A549 NSCLC cells
Concentration:	0.1-10 μM
Incubation Time:	6 hours
Result:	Inhibited the phosphorylation of PDGFRα and PDGFRβ in a dose-dependent manner. Observed the activation of downstream AKT, ERK1/2 and STAT3, with no obvious effects on total protein levels.

In Vivo

GZD856 (10-30 mg/kg, p.o. once daily for 16 d) displays good antitumor activity in both H1703 and A549 lung cancer models and is well tolerated. GZD856 inhibits brain and liver metastasis of lung cancer cells in an A549-Luc orthotopic model[1].

GZD856 (10 mg/kg; p.o. once daily for 8 d) potently inhibits tumor growth in mouse bearing xenograft K562 and Ba/F3 cells expressing Bcr-Abl^{T315I}[2].

GZD856 (5 mg/kg; a single i.v.) exhibits a long half-life ($T_{1/2}$=19.97 h), optimal plasma exposure (C_{max}=934.38 μg/L) and a $AUC_{0-\infty}$ (8165.8 μg/L•h) in rats[1].

GZD856 (25 mg/kg; a single p.o.) exhibits a long half-life ($T_{1/2}$=22.2 h), optimal plasma exposure (C_{max}=899.5 μg/L) and a good oral bioavailability (BA=78%) in rats[1].

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

Animal Model:	Male CB17-SCID mice implanted with H1703 and A549 cancer cells[1]
Dosage:	10, 30 mg/kg
Administration:	Oral gavage once daily for 16 days
Result:	Displayed antitumor effects in H1703-xenograft mice, with tumor growth inhibition (TGI) values of 20.8% and 74.1% at dosages of 10 and 30 mg/kg, respectively. Displayed antitumor effects in A549-xenograft mice, with a TGI value of 51.1% at 30 mg/kg. Was well tolerated in all of the tested groups, with no mortality or significant loss of body weight.

Animal Model:	Sprague-Dawley (SD) rats (180-220 g)[1]
Dosage:	5 mg/kg for i.v.; 25 mg/kg for p.o. (Pharmacokinetic Analysis)
Administration:	A single intravenous injection and oral administration
Result:	I.v.: $T_{1/2}$=19.97 h; C_{max}=934.38 μg/L; $AUC_{0-\infty}$=8165.8 μg/L•h. P.o.: $T_{1/2}$=22.2 h; C_{max}=899.5 μg/L; BA=78%.

REFERENCES

[1]. Zhang Z, et, al. GZD856, a novel potent PDGFRα/β inhibitor, suppresses the growth and migration of lung cancer cells in vitro and in vivo. Cancer Lett. 2016 May 28;375(1):172-178.

[2]. Lu X, et, al. Synthesis and identification of GZD856 as an orally bioavailable Bcr-Abl T315I inhibitor overcoming acquired imatinib resistance. J Enzyme Inhib Med Chem. 2017 Dec;32(1):331-336.

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