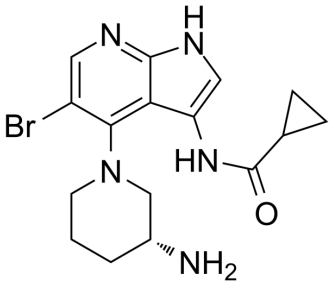
GDC-0575

Cat. No.:	HY-112167
CAS No.:	1196541-47-5
Molecular Formula:	$C_{16}H_{20}BrN_5O$
Molecular Weight:	378.27
Target:	Checkpoint Kinase (Chk)
Pathway:	Cell Cycle/DNA Damage
Storage:	Powder -20°C 3 years 4°C 2 years In solvent -80°C 2 years -20°C 1 year



SOLVENT & SOLUBILITY

In Vitro

DMSO : 100 mg/mL (264.36 mM; Need ultrasonic)
H_2O : < 0.1 mg/mL (insoluble)

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	2.6436 mL	13.2181 mL	26.4361 mL
5 mM	0.5287 mL	2.6436 mL	5.2872 mL
10 mM	0.2644 mL	1.3218 mL	2.6436 mL

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

In Vivo

1. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: ≥ 2.5 mg/mL (6.61 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.5 mg/mL (6.61 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

GDC-0575 (ARRY-575, RG7741) is a highly-selective oral small-molecule Chk1 inhibitor with an IC_{50} of 1.2 nM.

IC_{50} & Target

1.2 nM (Chk1)[1]

In Vitro

GDC-0575 is significantly more potent in promoting DNA damage, replication stress and cell death than V158411, LY2603618, and MK-8776 in a panel of melanoma cell lines[1]. GDC-0575 abrogates DNA damage-induced S and G2–M checkpoints, exacerbates DNA double-strand breaks and induces apoptosis in STS cells. GDC-0575 has a synergistic or additive effect together with gemcitabine[2]. CHK1 inhibitor GDC-0575 in combination with AraC enhances the killing of primary acute myeloid leukemia cells ex vivo by inducing apoptosis[3].

	MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	GDC-0575 is active at 25 mg/kg as a single agent, but the efficacy is improved at the higher drug dose. GDC-0575 effectively blocks tumor growth in the D20 and C002 xenografts, and the effect is maintained for at least 10 days after the final dose is administered[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Cell Assay [3]	AML cell lines are seeded at 1×10^4 cells/well in 96-well plates in triplicate, and subjected to different treatment conditions. After 24 h of incubation with GDC-0575, cell proliferation is measured with the XTT Cell Proliferation Kit II[3]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1]	Mice[1] Female nude BALB/c mice are injected with $2\text{-}3\times10^6$ melanoma cells in Matrigel by subcutaneous injection on the hind flank. Once tumors reach approximately 100 mm^3, mice are treated with GDC-0575 (25 mg/kg, 50 mg/kg) or vehicle (0.5% w/v methylcellulose and 0.2%v/v Tween 80) by oral gavage for 3 cycles where one cycle is three consecutive days of treatment followed by four rest days. Tumor size is measured three times per week using calipers. Mice are sacrificed at up to 6 weeks after terminating the treatment or when tumor size measured >1 cm^3[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Nat Commun. 2020 Jan 8;11(1):123.
- Neurotherapeutics. 2022 Mar;19(2):570-591.
- Mol Cancer Res. 2020 Jan;18(1):91-104.
- bioRxiv. 2023 Feb 7.

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REFERENCES

[1]. Oo ZY, et al. Endogenous Replication Stress Marks Melanomas Sensitive to CHEK1 Inhibitors In Vivo. Clin Cancer Res. 2018 Mar 13. doi: 10.1158/1078-0432.CCR-17-2701.

[2]. Laroche-Clary A, et al. CHK1 inhibition in soft-tissue sarcomas: biological and clinical implications. Ann Oncol. 2018 Apr 1;29(4):1023-1029.

[3]. Di Tullio A, et al. The combination of CHK1 inhibitor with G-CSF overrides cytarabine resistance in human acute myeloid leukemia. Nat Commun. 2017 Nov 22;8(1):1679.

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