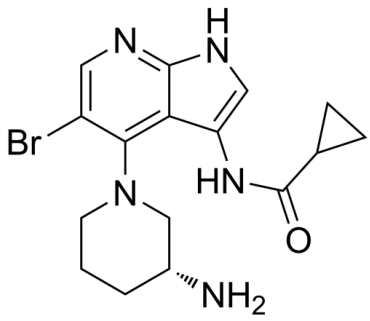
Data Sheet

Product Name:	GDC-0575
Cat. No.:	CS-0043591
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
Solubility:	DMSO : 100 mg/mL (264.36 mM; Need ultrasonic); H2O : < 0.1 mg/mL (insoluble)



BIOLOGICAL ACTIVITY:

GDC-0575 (ARRY-575, RG7741) is a highly-selective oral small-molecule **Chk1** inhibitor with an **IC_{50}** of 1.2 nM. IC50 & 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]. ***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].

PROTOCOL (Extracted from published papers and Only for reference)

Cell Assay: GDC-0575 (100 μM) are stored at −20 °C and used at a final concentration of 100 nM.[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]. **Animal Administration:** GDC-0575 is prepared in 0.5% w/v methylcellulose and 0.2%v/v Tween 80[1].[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].

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.

CAIndexNames:

Cyclopropanecarboxamide, N-[4-[(3R)-3-amino-1-piperidinyl]-5-bromo-1H-pyrrolo[2,3-b]pyridin-3-yl]-

SMILES:

O=C(C1CC1)NC2=CNC3=NC=C(Br)C(N4C[C@H](N)CCC4)=C32

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