AZD-7762

Cat. No.: HY-10992

CAS No.: 860352-01-8

Molecular Formula: $C_{17}H_{19}FN_4O_2S$

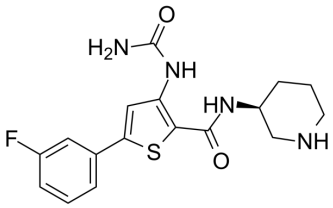
Molecular Weight: 362.42

Target: Checkpoint Kinase (Chk)

Pathway: Cell Cycle/DNA Damage

Storage:

Powder	-20°C	3 years
	4°C	2 years
In solvent	-80°C	1 year
	-20°C	6 months



SOLVENT & SOLUBILITY

In Vitro

DMSO : 100 mg/mL (275.92 mM; Need ultrasonic)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	2.7592 mL	13.7961 mL	27.5923 mL
	5 mM	0.5518 mL	2.7592 mL	5.5185 mL
	10 mM	0.2759 mL	1.3796 mL	2.7592 mL

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

In Vivo

1. Add each solvent one by one: 10% HP-β-CD
   Solubility: 10 mg/mL (27.59 mM); Clear solution; Need ultrasonic
2. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: ≥ 2.5 mg/mL (6.90 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.5 mg/mL (6.90 mM); Clear solution
4. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (6.90 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

AZD-7762 is a potent ATP-competitive checkpoint kinase (Chk) inhibitor in with an IC_{50} of 5 nM for Chk1.

IC_{50} & Target

Chk1	Chk2
5 nM (IC_{50})	5 nM (IC_{50})

In Vitro	AZD-7762 (AZD7762) is an equally potent inhibitor of Chk1 and Chk2 in vitro. AZD-7762 potently inhibits Chk1 and Chk2, abrogates DNA damage-induced S and G_2 checkpoints, enhances the efficacy of NSC 613327 and SKF 104864A, and modulates downstream checkpoint pathway proteins. AZD-7762 potently inhibits Chk1 phosphorylation of a cdc25C peptide with an IC_{50} of 5 nM as measured by a scintillation proximity assay. The K_i for AZD-7762 is determined to be 3.6 nM. Kinetic characterization suggests that AZD-7762 binds in the ATP-binding site of Chk1 and is thought to compete directly for ATP binding in a reversible manner. AZD-7762 is shown to abrogate the G_2 arrest induced by Camptothecin with an average EC_{50} of 10 nM (n=12) and maximal abrogation in the range of 100 nM[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	In the rat H460-DNp53 xenograft study, AZD-7762 (AZD7762) potentiates the antitumor activity of NSC 613327 in a dose-dependent manner by a decrease in %T/C with increasing dose (48% and 32%, 10 and 20 mg/kg AZD-7762, respectively). In the mouse xenograft study in combination with CPT-11, SW620 established tumors are treated with vehicle, CPT-11 alone, AZD-7762 alone, or AZD-7762 in combination with CPT-11. AZD-7762 dosed alone shows insignificant antitumor activity, whereas CPT-11 alone displays striking and significant activity (%T/C with increasing dose is 9 and 1, respectively). In combination with AZD-7762, %T/C increases significantly to -66% and -67%, respectively[1]. AZD7762 combination with CX-5461 induces cancer cell death of Tp53-null ($Tp53^{-/-}$) Eμ-Myc lymphoma cells in vitro and in vivo[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Cell Assay [1]	SW620 (5.5×10^3 per well) or MDA-MB-231 (5×10^3 per well) cells are seeded in 96-well plates and incubated overnight. Cells are dosed for 24 h with a 9-point titration of NSC 613327 ranging from 0.01 to 100 nM with or without a constant dose of AZD-7762 (300 nM). Control wells are dosed with vehicle alone (0.1% DMSO) or 300 nM AZD-7762. After 24 h, medium is removed and AZD-7762 alone is added back to the wells treated previously with AZD-7762 for an additional 24 h. Cells are then incubated in drug-free medium for an additional 72 h. The effect on cell proliferation is determined by MTS assay[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1][2]	Mice and Rats[1] Male NCr mice and male rnu rats are used. For xenograft models in mice, tumor cells are harvested, pelleted by centrifugation for 5 min, and resuspended in sterile PBS. Cells (3×10^3-6×10^6) are implanted s.c. into the right flank of the mice in a volume of 0.1 to 0.2 mL using a 25-gauge needle. Tumors are allowed to grow to the designated size of 100 to 200 mm^3 before the administration of compound. For xenograft models in rats, Cells are harvested, pelleted by centrifugation for 5 min, and resuspended in 50% sterile PBS and 50% Matrigel. Rats receive a 5 Gy whole-body radiation dose 5 days before cell implantation to improve tumor growth. H460-DNp53 cells (1×10^7) are implanted s.c., into the right flank of the rats in a volume of 0.2 mL using a 25-gauge needle. Tumors are allowed to grow to the designated size of 100 to 200 mm^3 before the administration of AZD-7762. AZD-7762 (10 and 20 mg/kg) is administered by i.v. injection via the tail vein. Cyclic schedules are used and treatment ranged from three to five cycles. Each cycle includes administration of a standard agent (NSC 613327 or CPT-11) every 3 days follow by delivery of AZD-7762. Tumor volumes are measured with electronic calipers and calculated. Mice [2] C57Bl/6 mice are intravenously injected with 2×10^5 Eμ-Myc B-lymphoma cells in PBS and treated with pharmacological inhibitors from 8 days post-injection. Treatment of mice is continued until an ethical end-point is reached; hunched posture, ruffled fur, enlarged lymph nodes, laboured breathing, weight loss greater than 20% of start body weight and limited mobility or paralysis. AZD7762 is delivered intraperitoneally in 10.3% -hydroxypropyl-β-cyclodextrin in 0.9% saline at 20 mg/kg daily on weekdays. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Nat Nanotechnol. 2021 Jul;16(7):830-839.
- Cell Metab. 2022 Feb 7;34(3):424-440.e7.
- Sci Transl Med. 2021 Jan 20;13(577):eaba7401.
- Sci Transl Med. 2018 Jul 18;10(450):eaaq1093.
- Nat Commun. 2023 Nov 22;14(1):7631.

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REFERENCES

[1]. Zabludoff SD, et al. AZD7762, a novel checkpoint kinase inhibitor, drives checkpoint abrogation and potentiates DNA-targeted therapies. Mol Cancer Ther. 2008 Sep;7(9):2955-66.

[2]. Quin J, et al. Inhibition of RNA polymerase I transcription initiation by CX-5461 activates non-canonical ATM/ATR signaling. Oncotarget. 2016 Aug 2;7(31):49800-49818.

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