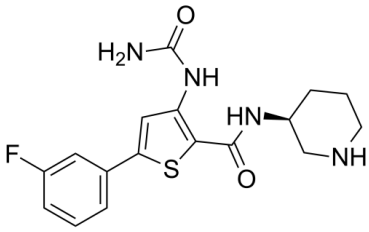
Data Sheet

Product Name:	AZD-7762
Cat. No.:	CS-0025
CAS No.:	860352-01-8
Molecular Formula:	$C_{17}H_{19}FN_4O_2S$
Molecular Weight:	362.4217632
Target:	Checkpoint Kinase (Chk)
Pathway:	Cell Cycle/DNA Damage
Solubility:	DMSO : 100 mg/mL (275.92 mM; Need ultrasonic)



BIOLOGICAL ACTIVITY:

AZD-7762 is a potent ATP-competitive checkpoint kinase (**Chk**) inhibitor in with an **IC_{50}** of 5 nM for Chk1. IC50 & Target: IC50: 5 nM (ChK1), 5 nM (ChK2)[1] ***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]. ***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].

PROTOCOL (Extracted from published papers and Only for reference)

Cell Assay: AZD-7762 (AZD7762) is dissolved in DMSO and stored, and then diluted with appropriate media (DMSO 0.1%) before use[1].[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]. **Animal Administration:** AZD-7762 (AZD7762) is formulated in 11.3% hydroxyproplyl-β-cyclodextrin (Mice and Rats)[1].;AZD7762 (Medchem Express) is prepared in 10.3% -hydroxypropyl-β-cyclodextrin in 0.9% saline (Mice)[2].[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.

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.

CAIndexNames:

2-Thiophenecarboxamide, 3-[(aminocarbonyl)amino]-5-(3-fluorophenyl)-N-(3S)-3-piperidinyl-

SMILES:

O=C(N[C@@H]1CNCCC1)C2=C(C=C(S2)C3=CC=CC(F)=C3)NC(N)=O

Tel: 610-426-3128 Fax: 888-484-5008 E-mail: sales@ChemScene.com

Address: 1 Deer Park Dr, Suite Q, Monmouth Junction, NJ 08852, USA