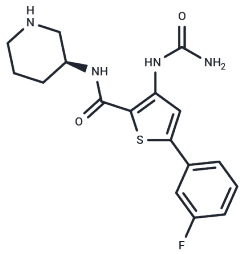
Data Sheet (Cat.No.T6093)

TargetMol

AZD-7762

Chemical Properties



CAS No. : 860352-01-8

Formula: C17H19FN4O2S

Molecular Weight: 362.42

Appearance: no data available

Storage: Powder: -20°C for 3 years | In solvent: -80°C for 1 year

Biological Description

Description	AZD-7762, an effective and specific inhibitor of Chk1(IC50=5 nM), is equally potent against Chk2 and less potent against CAM, Yes, Fyn, Lyn, Hck and Lck.
Targets(IC50)	Chk
In vitro	AZD7762, a more selective Chk1 inhibitor, inhibits Chk1 phosphorylation of a cdc25C peptide by reversibly binding to the ATP-binding site of Chk1, with IC50 of 5 nM and Ki of 3.6 nM. AZD7762 induces cell arrest with EC50 of 0.620 μM, and significantly abrogates the camptothecin induced G2 arrest with an EC50 of 10 nM, by blocking the chk1 dependent degradation of Cdc25A and activation of Cyclin A. AZD7762 (300 nM) enhances the antitumor efficacy of gemcitabine against SW620 and topotecan against MDA-MB-231 by reducing the GI50 values from 24.1 nM and 2.25 μM to 1.08 nM and 0.15 μM, respectively. [1] AZD7762 shows cytotoxicity against a variety of neuroblastoma cell lines bearing p53 wild type, p53 mutation, Mdm2 amplification or p14 deletion with IC50 values ranging from 82.6-505.9 nM. [2]
In vivo	AZD7762 alone at 25 mg/kg shows little antitumor activity in the H460-DNp53 xenograft mice and SW620 xenograft mice, but when administrated in combination with gemcitabine (60 mg/kg), AZD7762 shows significant antitumor efficacy in the two xenografts mice with a log cell kill of 0.9 or percent treated/control (%T/C) of 26 even at low dose of 12.5 mg. Dosing of AZD7762 in combination with gemcitabine (10 mg/kg) in the H460-DNp53 xenograft rat inhibits the tumor volume in a dose-dependent manner with the %T/C values of 48 and 32 for 10 and 20 mg/kg AZD7762, respectively. AZD7762 (25 mg/kg) in combination with irinotecan (25 or 50 mg/kg) causes complete tumor regression in the SW620 xenograft mice with the %T/C increasing significantly to -66% and -67%, respectively. [1]
Kinase Assay	Chk1 Kinase Assay: Recombinant human Chk1 is expressed as a glutathione S-transferase fusion in insect cells using a baculovirus vector and purified by glutathione affinity chromatography. A synthetic peptide substrate (N-biotinylaminohexanoyl-KKVSRSGLYRSPMPENLNRPR) for Chk1 is synthesized. Final assay concentrations of peptide and ATP (cold + 40 nCi [33P]ATP) are 0.8 and 1 μM, respectively. Different concentrations of AZD7762, buffer containing peptide and chk1 kinase and ATP, are added sequentially to a 384-well assay plate. The plate is incubated for 2 hours, reaction is stopped by the addition of buffer containing EDTA and scintillation proximity assay beads, and plates are read using a TopCount reader. Data analysis is carried out to determinate a dose response (IC50).

Cell Research	For the checkpoint abrogation assay, HT29 cells are treated for 2 hours with camptothecin (topoisomerase I inhibitor; 0.07 μg/mL) to induce the G2 checkpoint. Cells are then treated for 20 hours with a 12-point titration of AZD7762 (12.5 μM to 6 nM) plus nocodazole. Cells are fixed with 3.7% formaldehyde for 1 hour, permeabilized with PBS containing 0.05% Triton X, and incubated with anti-phH3 antibody for 1 hour followed by Alexa Fluor 488 anti-rabbit and Hoechst stain for 1 hour. Mitotic index is determined on the ArrayScan and expressed as the percentage of cells undergoing mitosis. For the potentiation assays, SW620 or MDA-MB-231 cells are dosed for 24 hours with a 9-point titration of gemcitabine ranging from 0.01 to 100 nM with a constant dose of AZD7762 (300 nM). After 24 hours, medium is removed and AZD7762 alone is added back to the wells for an additional 24 hours. Cells are then incubated in AZD7762-free medium for an additional 72 hours. The effect on cell proliferation is determined by MTT.(Only for Reference)

Solubility Information

Solubility	Ethanol: < 1 mg/mL (insoluble or slightly soluble), DMSO: 47 mg/mL (129.68 mM),Sonication is recommended. H2O: < 1 mg/mL (insoluble or slightly soluble), (< 1 mg/ml refers to the product slightly soluble or insoluble)

Preparing Stock Solutions

	1mg	5mg	10mg
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
50 mM	0.0552 mL	0.2759 mL	0.5518 mL

Please select the appropriate solvent to prepare the stock solution, according to the solubility of the product in different solvents. Please use it as soon as possible.

Reference

Zabludoff SD, et al. Mol Cancer Ther, 2008, 7(9), 2955-2966.
Mooser C, Symeonidou I E, Leimbacher P A, et al. Treacle controls the nucleolar response to rDNA breaks via TOPBP1 recruitment and ATR activation. Nature Communications. 2020 Jan 8;11(1):123
Zhu H, Rao Z, Yuan S, et al. One therapeutic approach for triple-negative breast cancer: Checkpoint kinase 1 inhibitor AZD7762 combination with neoadjuvant carboplatin. European Journal of Pharmacology. 2021: 174366.
Mooser C, Symeonidou I E, Leimbacher P A, et al. Treacle controls the nucleolar response to rDNA breaks via TOPBP1 recruitment and ATR activation[J]. Nature Communications. 2020, 11(1): 1-16.