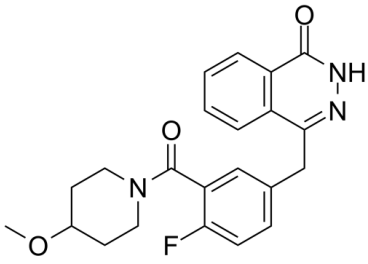
Data Sheet

Product Name:	AZD-2461
Cat. No.:	CS-1402
CAS No.:	1174043-16-3
Molecular Formula:	C22H22FN3O3
Molecular Weight:	395.43
Target:	PARP
Pathway:	Cell Cycle/DNA Damage; Epigenetics
Solubility:	DMSO : ≥ 100 mg/mL (252.89 mM)



BIOLOGICAL ACTIVITY:

AZD-2461 is a potent **PARP** inhibitor, with **IC_{50}**s of 5 nM, 2 nM and 200 nM for PARP1, PARP2 and PARP3, respectively. IC50 & Target: IC50: 5 nM (PARP1), 2 nM (PARP2), 200 nM (PARP3)[1] **In Vitro:** AZD-2461 is a potent PARP inhibitor, with IC_{50}s of 5 nM, 2 nM and 200 nM for PARP1, PARP2 and PARP3, respectively. AZD-2461 (500 nM) shows inhibitory activity against DNA single-strand break repair in human A459 cells. AZD-2461 cuases resistance and high P-gp expression levels in BRCA2-deficient mouse breast cancer line KB2P3.4 [1]. AZD-2461 is cytotoxic to BT-20 cells (5-50 μM), increases the proportions of S- and G2-phase BT-20 cells (5-20 μM), and weakly affects the progression of cell cycle in SKBr-3 cells (5-20 μM)[2]. **In Vivo:** AZD-2461 (10 mg/kg, p.o.) enhances the antitumor activity of temozolomide in a mouse colorectal xenograft and exhibits low effect on mouse bone marrow cells. However, the increased bone marrow tolerability of AZD-2461 is not seen in rat models[1]. AZD-2461 (0.5% v/w HPMC, p.o.) increases the survival of mice bearing KB1P tumors after short-term treatment, and long-term treatment is well tolerated, but can not lead to tumor eradication[3].

PROTOCOL (Extracted from published papers and Only for reference)

Cell Assay: AZD-2461 is dissolved in DMSO.[2]**BT-20** and **SKBr-3 human primary breast cancer cell lines** are used in the assay. SKBr-3 cells are cultivated in DMEM medium with 10% FCS and BT-20 in RPMI medium under an atmosphere containing 5% CO_2. Twenty four hours after plating (at 60-70% confluence), the cells are treated with the PARP-1 inhibitors NU1025, **AZD-2461**, iniparib, olaparib, and rucaparib at concentrations ranging from 50 to 200 μM, **5 to 50 μM**, 5 to 50 μM, 1 to 10 μM, and 0.3 to 10 μM, respectively, for durations indicated in figures 1-7[2]. **Animal Administration:** AZD-2461 is diluted in 0.5% w/v hydroxypropyl methylcellulose in deionized water to a concentration of 10 mg/mL.[3]Starting from 2 weeks after transplantation into **mice**, tumor size is monitored at least 3 times a week. All treatments are started when tumors reach a size of approximately 200 mm^3. Olaparib (50 mg/kg intraperitoneally) and **AZD-2461 (100 mg/kg per os) are given for 28 consecutive days**, unless otherwise indicated. If tumors do not shrink below 50% of the initial volume, treatment is continued for another 28 days; otherwise, a new treatment cycle of 28 days is started when the relapsing tumor reaches a size of 100% of the original volume. **AZD-2461 is diluted in 0.5% w/v hydroxypropyl methylcellulose in deionized water to a concentration of 10 mg/mL**[3].

References:

[1]. Oplustil O'Connor L, et al. The PARP Inhibitor AZD2461 Provides Insights into the Role of PARP3 Inhibition for Both Synthetic Lethality and Tolerability with Chemotherapy in Preclinical Models. Cancer Res. 2016 Oct 15;76(20):6084-6094. Epub 2016 Aug 22.

[2]. Węsierska-Gądek J, et al. Differential Potential of Pharmacological PARP Inhibitors for Inhibiting Cell Proliferation and Inducing Apoptosis in Human Breast Cancer Cells. J Cell Biochem. 2015 Dec;116(12):2824-39.

[3]. Jaspers JE, et al. Loss of 53BP1 causes PARP inhibitor resistance in Brca1-mutated mouse mammary tumors. Cancer Discov. 2013 Jan;3(1):68-81.

CAIndexNames:

1(2H)-Phthalazinone, 4-[[4-fluoro-3-[(4-methoxy-1-piperidinyl)carbonyl]phenyl]methyl]-

SMILES:

O=C1NN=C(CC2=CC=C(F)C(C(N3CCC(OC)CC3)=O)=C2)C4=C1C=CC=C4

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