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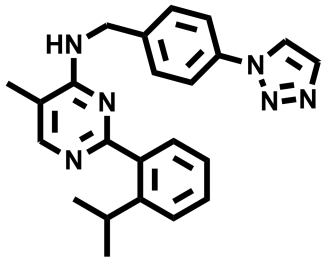
USP1-UAF1 Inhibitor – ML323

Chemical Name: N-(4-(1H-1,2,3-triazol-1-yl)benzyl)-2-(2-isopropylphenyl)-5-methylpyrimidin-4-amine



Molecular Weight:	384.48
Formula:	$C_{23}H_{24}N_6$
Purity:	≥98%
CAS#:	1572414-83-5
Solubility:	DMSO up to 50 mM
Storage	Powder: 4 °C 1 year DMSO: 4 °C 3 months -20 °C 1 year

Biological Activity:

ML323 is a potent, selective and reversible inhibitor of the USP1-UAF1 deubiquitinase complex with IC_{50} ~76 nM in the Ub-Rho assay. It has excellent selectivity against human DUBs, deSUMOylase, deneddylase and unrelated proteases, showed little to no inhibition against other USPs tested, including USP2, USP5, USP7, USP8, USP10, USP11, USP14 and USP21. Inhibition mechanism and HDX studies suggest that ML323 binds away from the USP1 active site. ML323 inhibits the deubiquitination of PCNA and FANCD2. Inhibition of USP1–UAF1 by ML323 impairs homologous recombination and sister chromatid exchange in U2OS cells. Moreover, ML323 potentiates cisplatin cytotoxicity in non-small cell lung cancer and osteosarcoma cells. A notable feature of ML323 is that it simultaneously targets two major DNA damage response pathways (TLS and FA) by inhibiting a common deubiquitinase.
USP1-UAF1 could be a key regulator of the DNA damage response and a target for overcoming resistance to the platinum-based anticancer drugs.

How to Use:

In vitro: ML323 was used at 10-30 μM in vitro and cellular assays.

In vivo: n/a

Reference:

1. Liang Q, et al. A selective USP1-UAF1 inhibitor links deubiquitination to DNA damage responses. (2014) Nat Chem Biol. 10(4):298-304.

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