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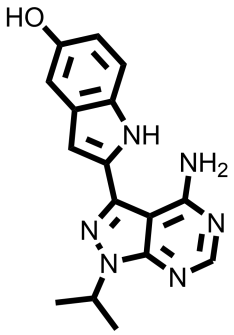
mTOR Inhibitor – PP242

Chemical Name: 2-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-1H-indol-5-ol



Molecular Weight:	308.34
Formula:	$C_{16}H_{16}N_6O$
Purity:	≥ 98%
CAS#:	1092351-67-1
Solubility:	DMSO up to 100 mM
Storage	Powder: 4°C 1 year DMSO: 4°C 3 month -20°C 1 year

Biological Activity:

PP242 is a highly potent, selective and ATP-competitive mTORC1/mTORC2 inhibitor (IC_{50} = 8 nM). It has > 10 folds selectivity over the other PI-3K family kinases (IC_{50} 0.102 μM, 0.408 μM, 1.27 μM, 1.96 μM and 2.2 μM for p110γ, DNA-PK, p110δ, p110α and p110β, respectively). Except some weak inhibitory activity against PKCα, JAK2, PKCβI, PKCβII and RET (0.05-0.22 μM), PP242 exhibits excellent selectivity over 215 other protein kinases. PP242 differentially inhibits insulin-stimulated phosphorylations of cellular proteins both in vitro and in vivo in a manner distinctly different from that seen in mTORC2-functional knockout SIN1-/- cells or in cultures treated with Rapamycin, which targets only mTORC1, but not mTORC2. Blockage of 4EBP1 T36/T45/S65 phosphorylation by PP242 upon insulin stimulation in primary MEFs correlates well with an enhanced 4EBP1 association with the cap-binding protein eIF4E, resulting in a selective inhibition of cap-dependent, but not cap-independent, protein translation.

How to Use:

In vitro: PP242 was used at 2.5 μM concentration in vitro and in cellular assays.

In vivo: PP242 was orally dosed to mice at 20-60 mg/kg once per day to inhibit tumor growth, or in combination with Dasatinib, Bortezomib or Imatinib for synergistic activity.

Reference:

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3. Hoang B, et al. Targeting TORC2 in multiple myeloma with a new mTOR kinase inhibitor. (2010) Blood. 116(22):4560-8.
4. Liu Q, et al. Kinome-wide selectivity profiling of ATP-competitive mammalian target of rapamycin (mTOR) inhibitors and characterization of their binding kinetics. (2012) J Biol Chem. 287(13):9742-52.
5. Hoang B, et al. The PP242 mammalian target of rapamycin (mTOR) inhibitor activates extracellular signal-regulated kinase (ERK) in multiple myeloma cells via a target of rapamycin complex 1 (TORC1)/eukaryotic translation initiation factor 4E (eIF-4E)/RAF pathway and activation is a mechanism of resistance. (2012) J Biol Chem. 287(26):21796-805.

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6. Zhang F, et al. Inhibition of the mTORC2 and chaperone pathways to treat leukemia. (2012) Blood. 119(25):6080-8.
7. Zeng Z, et al. Targeting of mTORC1/2 by the mTOR kinase inhibitor PP242 induces apoptosis in AML cells under conditions mimicking the bone marrow microenvironment. (2012) Blood. 120(13):2679-89.
8. Zhao L, et al. mTOR complex 2 is involved in regulation of Cbl-dependent c-FLIP degradation and sensitivity of TRAIL-induced apoptosis. (2013) Cancer Res. In press.