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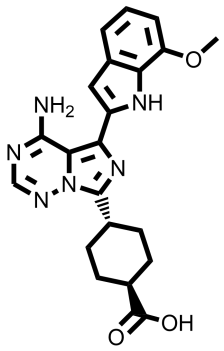
mTOR Inhibitor - OSI-027

Chemical Name: (1r,4r)-4-(4-amino-5-(7-methoxy-1H-indol-2-yl)imidazo[5,1-f][1,2,4]triazin-7-yl)cyclohexanecarboxylic acid



Molecular Weight:	406.44
Formula:	$C_{21}H_{22}N_6O_3$
Purity:	≥98%
CAS#:	936890-98-1
Solubility:	DMSO up to 50 mM
Storage	Powder: 4 °C 1 year DMSO: 4 °C 3 month -20 °C 1 year

Biological Activity:

OSI-027 is a selective and potent dual inhibitor of mTORC1 and mTORC2 with IC_{50} of 22 nM and 65 nM, respectively. It shows more than 100-fold selectivity for mTOR relative to PI3Kα, PI3Kβ, PI3Kγ, and DNA-PK. It inhibits phosphorylation of the mTORC1 substrates 4E-BP1 and S6K1 as well as the mTORC2 substrate AKT in diverse cancer models in vitro and in vivo. OSI-027 shows robust antitumor activity in several different human xenograft models representing various histologies. In COLO 205 and GEO colon cancer xenograft models, OSI-027 showed superior efficacy compared with rapamycin. OSI-027 is currently in Phase I clinical trials in patients with advanced solid tumors or lymphoma.

How to Use:

In vitro: OSI-027 was used at 1-10 μM in vitro and in cellular assays.

In vivo: OSI-027 was orally dosed to mice at 50-65 mg/kg once per day.

Reference:

1. Vakana E, et al. Induction of autophagy by dual mTORC1-mTORC2 inhibition in BCR-ABL-expressing leukemic cells. (2010) Autophagy. 6(7):966-7.
2. Carayol N,et al. Critical roles for mTORC2- and rapamycin-insensitive mTORC1-complexes in growth and survival of BCR-ABL-expressing leukemic cells. (2010) Proc Natl Acad Sci USA. 107(28):12469-74.
3. Falcon BL, et al. Reduced VEGF production, angiogenesis, and vascular regrowth contribute to the antitumor properties of dual mTORC1/mTORC2 inhibitors. (2011) Cancer Res. 71(5):1573-83.
4. Altman JK, et al. Dual mTORC2/mTORC1 targeting results in potent suppressive effects on acute myeloid leukemia (AML) progenitors. (2011) Clin Cancer Res. 17(13):4378-88.
5. Bhagwat SV, et al. Preclinical characterization of OSI-027, a potent and selective inhibitor of mTORC1 and mTORC2: distinct from rapamycin. (2011) Mol Cancer Ther. 10(8):1394-406.
6. Gupta M, et al. Dual mTORC1/mTORC2 inhibition diminishes Akt activation and induces Puma-dependent apoptosis in lymphoid malignancies. (2012) Blood. 119(2):476-87.