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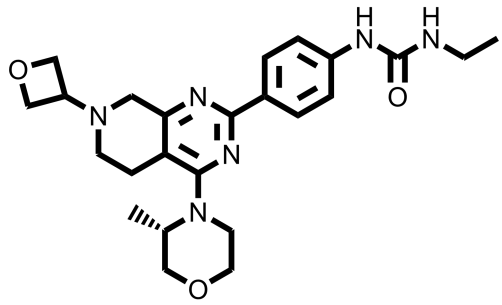
mTOR Inhibitor GDC-0349

Chemical Name: (S)-1-ethyl-3-(4-(4-(3-methylmorpholino)-7-(oxetan-3-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-2-yl)phenyl)urea



Molecular Weight:	452.55
Formula:	$C_{24}H_{32}N_6O_3$
Purity:	≥98%
CAS#:	1207360-89-1
Solubility:	DMSO up to 50 mM
Storage	Powder: 4 °C 1 year DMSO: 4 °C 3 month -20 °C 1 year

Biological Activity:

GDC-0349 is a potent and selective ATP-competitive inhibitor of mTOR with IC_{50} ~3.8 nM. It has remarkable selectivity over 266 kinases, including all isoforms of PI3K (less than 25% inhibition when tested at 1 μM against Invitrogen kinase panel). GDC-0349 demonstrates pathway modulation and dose-dependent efficacy in mouse xenograft cancer models. When dosed orally once daily in athymic mice in a MCF7-neo/Her2 tumor xenograft model (PI3K mutation), GDC-0349 inhibited tumor growth in a dose-dependent manner. It was also efficacious in other xenograft models, including PC3 (PTEN null) and 786-0 (VHL mutant). GDC-0349 inhibited downstream markers of mTOR, including phospho-4EBP1 and phospho-Akt(S473) in an in vivo PK/PD study in mouse, consistent with an inhibition of both mTORC1 and mTORC2 complexes. Currently GDC-0349 is in Phase I clinical trials to evaluate the safety and tolerability in patients with locally advanced or metastatic solid tumors or Non-Hodgkin's lymphoma.

How to Use:

In vitro: GDC-0349 was used at 1 μM in vitro and in cellular assays.

In vivo: GDC-0349 was orally dosed to mice at 30-80 mg/kg once per day.

Reference:

1. Zhonghua Pei, et al. Discovery and Biological Profiling of Potent and Selective mTOR Inhibitor GDC-0349 (2013) ACS Med. Chem. Lett., 4 (1), pp 103–107