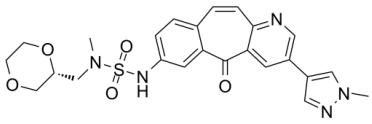
Data Sheet

Product Name:	MK-2461
Cat. No.:	CS-5537
CAS No.:	917879-39-1
Molecular Formula:	C24H25N5O5S
Molecular Weight:	495.55
Target:	c-Met/HGFR
Pathway:	Protein Tyrosine Kinase/RTK
Solubility:	DMSO : ≥ 31 mg/mL (62.56 mM)



BIOLOGICAL ACTIVITY:

MK-2461 is a novel ATP-competitive multitargeted inhibitor of activated c-Met with a mean IC50 of 2.5 nM. IC50 value: 2.5 nM [1] Target: c-Met in vitro: MK-2461 inhibits the kinase activity of human c-Met with a mean IC50 of 2.5 nM in the presence of 50 μM ATP. Ron (IC50 = 7 nM) and Flt1 (IC50 = 10 nM) are inhibited by MK-2461 with similar potencies to c-Met (IC50 = 2.5 nM), whereas nine other kinases, including FGFR1, FGFR2, FGFR3, PDGFRβ, KDR, Flt3, Flt4, TrkA, and TrkB, are found to be 8- to 30-fold less sensitive to MK-2461 than c-Met. [1] in vivo: MK-2461 inhibits c-Met signaling and tumor growth in tumor xenograft models in mice.[1]

PROTOCOL (Extracted from published papers and Only for reference)

Kinase assay [1] c-Met-catalyzed phosphorylation of N-biotinylated peptide (EQEDEPEGDYFEWLE-CONH2) was measured using a time-resolved fluorescence resonance energy transfer assay adapted from Park and colleagues. To evaluate kinase selectivity, a single concentration (1 μM) of MK-2461 was tested using 216 kinases, which also determined the MK-2461 IC50 for DRAK1, DYRK2, IRAK1, IRAK4, MELK, and MLK1. The MK-2461 IC50 for Ron, Mer, Flt1, Flt3, Flt4, KDR, PDGFRβ, FGFR1, FGFR2, FGFR3, TrkA, and TrkB were determined using time-resolved fluorescence resonance energy transfer assays similar to the c-Met kinase assay. Cell assay [1] The cells were cultured for six passages in DMEM containing heavy arginine and heavy lysine (13C6-Arg and 13C6-Lys) or DMEM containing light (12C6) arginine and lysine. Heavy-labeled cells were treated for 2 h with 1 μM MK-2461, whereas the light-labeled cells were treated with the vehicle. c-Met was immunoprecipitated from a 1:1 mixture of the heavy- and light-labeled cell lysates, gel-purified, tryptic digested, and subjected to liquid chromatography tandem mass spectrometry (LC-MS/MS) analysis. As a "self-to-self" control, a 1:1 mixture of lysates of vehicle-treated, heavy-labeled and vehicle-treated, light-labeled cells was subjected to the same procedures. The effect of MK-2461 on the abundance of a phosphotyrosine residue(s) of interest was gauged from ion-intensity ratio of the heavy (MK-2461-treated)- and light (vehicle-treated)-labeled tryptic peptide containing the phosphotyrosine(s). The ratio was normalized using the heavy/light ratio of the self-to-self control. Animal administration [1] TL-16 cells or c-Met mutant-transformed NIH3T3 cells were inoculated s.c. into the flank of female nude CD-1 nu/nu mice. When mean tumor size reached a predetermined range, the mice were randomized and given vehicle or MK-2461 by p.o. gavage once or twice daily. Tumor volumes were determined using calipers. The percentage increase in the volume of a xenograft tumor on day n versus day 0 (the day when dosing of MK-2461 began) was calculated as (tumor volume on day n - tumor volume on day 0) / tumor volume on day 0 × 100. The mean percentage of tumor growth inhibition in each MK-2461-treated group relative to the vehicle-treated group was calculated as (1 - ,mean percent increase of tumor volume in the MK-2461-treated group/mean percent increase of the tumor volume in the vehicle-treated group) × 100.

References:

[1]. Pan BS, et al. MK-2461, a novel multitargeted kinase inhibitor, preferentially inhibits the activated c-Met receptor. Cancer Res. 2010 Feb 15;70(4):1524-33.

CAIndexNames:

Sulfamide, N-[(2R)-1,4-dioxan-2-ylmethyl]-N-methyl-N'-[3-(1-methyl-1H-pyrazol-4-yl)-5-oxo-5H-benzo[4,5]cyclohepta[1,2-b]pyridin-7-yl]-

SMILES:

O=S(N(C)C[C@H]1OCCOC1)(NC2=CC=C3C=CC(C(C(C3=C2)=O)=C4)=NC=C4C5=CN(N=C5)C)=O

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