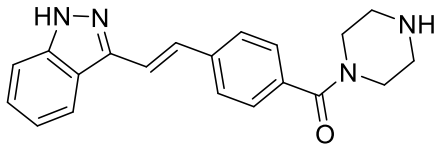
Product data sheet

MedKoo Cat#: 206213 Name: KW-2449 CAS#: 1000669-72-6 Chemical Formula: $C_{20}H_{20}N_4O$ Exact Mass: 332.16371 Molecular Weight: 332.4	
Product supplied as:	Powder
Purity (by HPLC):	≥ 98%
Shipping conditions	Ambient temperature
Storage conditions:	Powder: -20°C 3 years; 4°C 2 years.
	In solvent: -80°C 3 months; -20°C 2 weeks.

1. Product description:
KW-2449 is a novel multikinase inhibitor, which suppresses the growth of leukemia cells with FLT3 mutations or T315I-mutated BCR/ABL translocation. Recent research showed that HDACIs increase KW-2449 lethality in Bcr/Abl(+) cells in association with inhibition of Bcr/Abl, generation of ROS, and induction of DNA damage. This strategy preferentially targets primary Bcr/Abl(+) hematopoietic cells and exhibits enhanced in vivo activity. Combining KW-2449 with HDACIs warrants attention in IM-resistant Bcr/Abl(+) leukemias. (source: Clin Cancer Res. 2011 May 15;17(10):3219-32. Epub 2011 Apr 7.).

2. CoA, QC data, SDS, and handling instruction
SDS and handling instruction, CoA with copies of QC data (NMR, HPLC and MS analytical spectra) can be downloaded from the product web page under "QC And Documents" section. Note: copies of analytical spectra may not be available if the product is being supplied by MedKoo partners. Whether the product was made by MedKoo or provided by its partners, the quality is 100% guaranteed.

3. Solubility data

Solvent	Max Conc. mg/mL	Max Conc. mM
DMSO	49.0	147.41

4. Stock solution preparation table:

Concentration / Solvent Volume / Mass	1 mg	5 mg	10 mg
1 mM	3.01 mL	15.04 mL	30.08 mL
5 mM	0.60 mL	3.01 mL	6.02 mL
10 mM	0.30 mL	1.50 mL	3.01 mL
50 mM	0.06 mL	0.30 mL	0.60 mL

5. Molarity Calculator, Reconstitution Calculator, Dilution Calculator
Please refer the product web page under section of "Calculator"

6. Recommended literature which reported protocols for in vitro and in vivo study
In vitro study

1. Shiotsu Y, Kiyoi H, Ishikawa Y, Tanizaki R, Shimizu M, Umehara H, Ishii K, Mori Y, Ozeki K, Minami Y, Abe A, Maeda H, Akiyama T, Kanda Y, Sato Y, Akinaga S, Naoe T. KW-2449, a novel multikinase inhibitor, suppresses the growth of leukemia cells with FLT3 mutations or T315I-mutated BCR/ABL translocation. Blood. 2009 Aug 20;114(8):1607-17. doi: 10.1182/blood-2009-01-199307. Epub 2009 Jun 18. PMID: 19541823.
2. Nguyen T, Dai Y, Attkisson E, Kramer L, Jordan N, Nguyen N, Kolluri N, Muschen M, Grant S. HDAC inhibitors potentiate the activity of the BCR/ABL kinase inhibitor KW-2449 in imatinib-sensitive or -resistant BCR/ABL+ leukemia cells in vitro and in vivo. Clin Cancer Res. 2011 May 15;17(10):3219-32. doi: 10.1158/1078-0432.CCR-11-0234. Epub 2011 Apr 7. PMID: 21474579; PMCID: PMC3096723.

In vivo study

1. Shiotsu Y, Kiyoi H, Ishikawa Y, Tanizaki R, Shimizu M, Umehara H, Ishii K, Mori Y, Ozeki K, Minami Y, Abe A, Maeda H, Akiyama T, Kanda Y, Sato Y, Akinaga S, Naoe T. KW-2449, a novel multikinase inhibitor, suppresses the growth of leukemia cells with FLT3 mutations or T315I-mutated BCR/ABL translocation. Blood. 2009 Aug 20;114(8):1607-17. doi: 10.1182/blood-2009-01-199307. Epub 2009 Jun 18. PMID: 19541823.

2. Nguyen T, Dai Y, Attkisson E, Kramer L, Jordan N, Nguyen N, Kolluri N, Muschen M, Grant S. HDAC inhibitors potentiate the activity of the BCR/ABL kinase inhibitor KW-2449 in imatinib-sensitive or -resistant BCR/ABL+ leukemia cells in vitro and in vivo. Clin Cancer Res. 2011 May 15;17(10):3219-32. doi: 10.1158/1078-0432.CCR-11-0234. Epub 2011 Apr 7. PMID: 21474579; PMCID: PMC3096723.

7. Bioactivity

Biological target:

KW-2449 is a multi-targeted kinase inhibitor of FLT3, ABL, ABLT315I and Aurora kinase with IC50s of 6.6, 14, 4 and 48 nM, respectively.

In vitro activity

KW-2449 inhibited the growth of human ALL cell line RS4;11, which expresses unphosphorylated wt-FLT3, with the GI50 value of 0.23 μM (Table 2). Because KW-2449 shows potent Aurora A and Aurora B kinase inhibition, it was evaluated whether the growth inhibitory effect on RS4;11 was induced by Aurora kinase inhibition. When the cell cycle was arrested in the M-phase by nocodazole, phosphorylated histone-H3 (P-HH3) was clearly observed in RS4;11, but it was decreased by the treatment with KW-2449 in a dose-dependent manner (Figure 6A). Cell cycle distribution analysis indicated that KW-2449 (0.60 μM) induced G2/M arrest and apparent increase of sub-G1 apoptotic cells after 24 hours and 48 hours of exposure, respectively (Figure 6B). Even at 0.30 μM, KW-2449 slightly decreased the population of S-phase cells from 49.0% to 40.6% after 72 hours (histogram data not shown). The increase of annexin V–positive (early apoptotic) cells was also observed at the GI50 value against RS4;11 cells (Figure 6C). These results suggested that KW-2449 has a growth inhibitory potency against leukemia cells even without activated FLT3 through the inhibition of Aurora kinase, although its potency was 5- to10-fold lower than that against those with activated FLT3 kinase.

Reference: Blood. 2009 Aug 20;114(8):1607-17. https://pubmed.ncbi.nlm.nih.gov/19541823/

In vivo activity

In vivo antileukemia activities of KW-2449 were evaluated using MOLM-13, FLT3-ITD AML, xenograft model. First, the concentrations of KW-2449 in both plasma and tumor after oral administration were sequentially examined in SCID mice bearing the subcutaneous MOLM-13 tumor. The tumor/plasma concentration ratio of KW-2449 tended to increase along with the time after administration and reached approximately 400, 24 hours after dosing (Figure 3A). The levels of P-FLT3 and P-STAT5 in the tumor were completely reduced from 4 to 12 hours after the administration of KW-2449 (Figure 3B). In the MOLM-13 tumor xenograft model, oral administration of KW-2449 for 14 days showed a potent and significant antitumor effect in a dose-dependent manner (Figure 4A). KW-2449 treatment at 2.5 and 5.0 mg/kg twice a day showed growth inhibition of tumors with the ratio of tumor volume in the treated to control mice minimum values (T/Cmin) of 0.57 and 0.29, respectively (Figure 4B). Furthermore, KW-2449 treatment at 10 mg/kg twice a day showed tumor regression with T/Cmin of 0.010 and treatment at 20 mg/kg twice a day completely eradicated tumors in all mice (Figure 4C).

Reference: Blood. 2009 Aug 20;114(8):1607-17. https://pubmed.ncbi.nlm.nih.gov/19541823