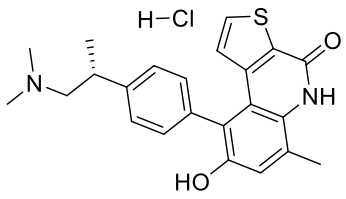
Product data sheet

MedKoo Cat#: 206191 Name: OTS964 HCl CAS#: 1338545-07-5 (HCl) Chemical Formula: $C_{23}H_{25}ClN_2O_2S$ Molecular Weight: 428.98	
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:

OTS964 is a potent and selective TOPK inhibitor with potential anticancer activity. OTS964 inhibits TOPK kinase activity with high affinity and selectivity. Similar to the knockdown effect of TOPK small interfering RNAs (siRNAs), this inhibitor causes a cytokinesis defect and the subsequent apoptosis of cancer cells in vitro as well as in xenograft models of human lung cancer. Although administration of the free compound induced hematopoietic adverse reactions (leukocytopenia associated with thrombocytosis), the drug delivered in a liposomal formulation effectively caused complete regression of transplanted tumors without showing any adverse reactions in mice. (Sci Transl Med. 2014 Oct 22;6(259):259ra145.)

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	30.0	69.9

4. Stock solution preparation table:

Concentration / Solvent Volume / Mass	1 mg	5 mg	10 mg
1 mM	2.33 mL	11.66 mL	23.31 mL
5 mM	0.47 mL	2.33 mL	4.66 mL
10 mM	0.23 mL	1.17 mL	2.33 mL
50 mM	0.05 mL	0.23 mL	0.47 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. Lin A, Giuliano CJ, Palladino A, John KM, Abramowicz C, Yuan ML, Sausville EL, Lukow DA, Liu L, Chait AR, Galluzzo ZC, Tucker C, Sheltzer JM. Off-target toxicity is a common mechanism of action of cancer drugs undergoing clinical trials. Sci Transl Med. 2019 Sep 11;11(509):eaaw8412. doi: 10.1126/scitranslmed.aaw8412. PMID: 31511426; PMCID: PMC7717492.
2. Sugimori M, Hayakawa Y, Koh M, Hayashi T, Tamura R, Kuroda S. Targeting the T-Lak cell originated protein kinase by OTS964 shrinks the size of power-law coded heterogeneous glioma stem cell populations. Oncotarget. 2017 Dec 9;9(3):3043-3059. doi: 10.18632/oncotarget.23077. PMID: 29423027; PMCID: PMC5790444.

In vivo study

1. Matsuo Y, Park JH, Miyamoto T, Yamamoto S, Hisada S, Alachkar H, Nakamura Y. TOPK inhibitor induces complete tumor regression in xenograft models of human cancer through inhibition of cytokinesis. Sci Transl Med. 2014 Oct 22;6(259):259ra145. doi: 10.1126/scitranslmed.3010277. PMID: 25338756.

7. Bioactivity

Biological target:

Product data sheet

OTS964 hydrochloride is a TOPK (T-lymphokine-activated killer cell-originated protein kinase) inhibitor with an IC_{50} of 28 nM. OTS964 hydrochloride is also a potent inhibitor of the cyclin-dependent kinase CDK11, which binds to CDK11B with a K_d of 40 nM.

In vitro activity

This study next determined the cellular effects of OTS964 treatment and CDK11 ablation with CRISPR. In cell competition assays, cancer cells transduced with guide RNAs specific for either CDK11A or CDK11B exhibited minimal dropout. However, guides designed to recognize both isoforms exhibited substantial dropout in every cell line that was tested, including pancreatic cancer and triple-negative breast cancer (Fig. 4G and fig. S17A). Flow cytometry revealed that cells transduced with pan-CDK11 guides accumulated in G2/M with 4C DNA content, suggesting that CDK11 function is required for mitotic progression (fig. S17B). To test whether OTS964 phenocopied the CDK11 guide RNAs, this study arrested A375 cells expressing the chromosomal marker H2B-mCherry at G1/S with a double-thymidine block, and then released them into normal medium or medium containing OTS964. Cells treated with a low concentration of OTS964 exhibited delayed nuclear envelope breakdown and progressed slowly through mitosis (Fig. 4H, fig. S17C, and movies S1–2). Cells treated with a lethal concentration of OTS964 arrested in G2, before mitotic entry (movie S3). OTS964 treatment did not perturb DNA replication, as the arrested cells displayed 4C DNA content and did not accumulate 53BP1-foci, a marker of DNA damage (fig. S17D–E). Introducing the G579S substitution into A375 cells rescued normal mitotic entry and progression in the presence of a lethal concentration of OTS964 (fig. 4H–I, fig. S17C, and movie S4). These results establish CDK11 activity as necessary for mitosis in human cancer and suggest that CDK11 is the key in cellulo target of OTS964.

Reference: Sci Transl Med. 2019 Sep 11; 11(509): eaaw8412. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7717492/

In vivo activity

When this study administered free OTS964 intravenously at 40 mg/kg on days 1, 4, 8, 11, 15, and 18 to mice bearing LU-99 lung cancer cells, this study observed a TGI of 44% on day 22 (Fig. 4A) without any body weight loss (Fig. 4B). Similar to observation with OTS514, OTS964 treatment also enhanced the differentiation of HSCs to a megakaryocyte population (fig. S7A). Furthermore, both compounds resulted in a reduction of STAT5 (signal transducer and activator of transcription 5) protein (fig. S7B). When this study administered liposomal OTS964 at 40 mg/kg on days 1, 4, 8, 11, and 15 to mice bearing LU-99 lung cancer cells after the tumor size reached about 150 mm^3 (instead of 200 mm^3 as in Fig. 4A, to allow longer monitoring of the rapidly growing LU-99 tumors; see Materials and Methods for details), this study observed a TGI of 110% on day 22. The tumors continued shrinking even after the treatment and finally revealed complete regression in five of six mice examined (three mice on day 25 and two mice on day 29) (Fig. 4C) without any body weight loss (Fig. 4D). Most strikingly, this liposomal formulation did not cause any hematopoietic toxicity (Fig. 4E). Further preclinical toxicity studies in rats did not show any histopathological changes in the liver after treatment with liposomal OTS964 (fig. S8).

Reference: Sci Transl Med. 2014 Oct 22;6(259):259ra145. https://pubmed.ncbi.nlm.nih.gov/25338756/

Note: The information listed here was extracted from literature. MedKoo has not independently retested and confirmed the accuracy of these methods. Customer should use it just for a reference only.