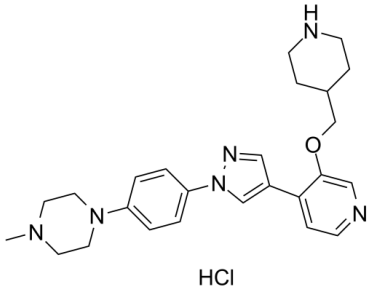
Data Sheet

Product Name:	MELK-8a (hydrochloride)
Cat. No.:	CS-6237
CAS No.:	2096992-20-8
Molecular Formula:	C25H33ClN6O
Molecular Weight:	469.02
Target:	MELK
Pathway:	PI3K/Akt/mTOR
Solubility:	DMSO : 8.6 mg/mL (18.34 mM; Need ultrasonic and warming); H2O : ≥ 100 mg/mL (213.21 mM)



BIOLOGICAL ACTIVITY:

MELK-8a hydrochloride is a novel maternal embryonic leucine zipper kinase (**MELK**) inhibitor with an **IC_{50}** of 2 nM. IC50 & Target: IC50: 2 nM (MELK)[1] **In Vitro:** MELK-8a remains very potent (IC_{50}=140 nM) when the ATP concentration in the biochemical assay is shifted from 20 μM to 2 mM. Its potency is well tracked between full-length MELK versus catalytic domain construct (5 nM versus 2 nM). It only inhibits seven off-target kinases in addition to MELK with >85% inhibition of binding at 1 μM demonstrating great selectivity. The compound is at least 90-fold more selective in targeting MELK in all cases. MELK-8a is fairly soluble (0.22 g/L at pH 6.8) and shows a good permeability in the Caco-2 assay. MELK-8a inhibits the growth of MDA-MB-468 cells and MCF-7 cells with an IC_{50} of approximately 0.06 and 1.2 μM, respectively[1]. **In Vivo:** Subcutaneous administration of MELK-8a at 30 mg/kg in C57BL/6 mice results in good plasma exposure. The compound adsorption into the systemic circulation is rapid (T_{max}=0.4 h) and peak plasma concentration reaches 6.6 μM. An ascending dose PK study in female athymic nude mice shows that the rate of compound release is maximal at 120 mg/kg and all clearance mechanisms can be saturated at 240 mg/kg. However, when administered orally at 10 mg/kg in C57BL/6 male mice, it shows very poor PK (3.6% oral bioavailability) consistent with very high in vivo clearance[1].

PROTOCOL (Extracted from published papers and Only for reference)

Cell Assay: [1]MDA-MB-468 and MCF7 cells are seeded in growth medium into 96-well plates at 1000 and 4000 cells/well, respectively. Sixteen hours after plating, MELK-8a are added and incubated for 7 days. For each well, ATPLite reagent is added and incubated. Luminescence is measured on an multilabel plate reader[1]. **Animal Administration:** [1]Mice: For pharmacokinetic studies, the intravenous and oral dose is prepared in a solution containing 5% ethanol, 100% PG, 5% CremophorEL, and 80% PBS. The subcutaneous dose is formulated in 10% PG and 25% (20%, v/v) Solutol. Plasma samples are collected at specified time points and stored frozen (−20 °C) until MELK-8a analysis. An LC−MS/MS method is used to quantitate MELK-8a drug levels in plasma[1].

References:

[1]. Touré BB, et al. Toward the Validation of Maternal Embryonic Leucine Zipper Kinase: Discovery, Optimization of Highly Potent and Selective Inhibitors, and Preliminary Biology Insight. J Med Chem. 2016 May 26;59(10):4711-23.

CAIndexNames:

Piperazine, 1-methyl-4-[4-[4-[3-(4-piperidinylmethoxy)-4-pyridinyl]-1H-pyrazol-1-yl]phenyl]-,hydrochloride

SMILES:

CN(CC1)CCN1C2=CC=C(N3C=C(C4=CC=NC=C4OCC5CCNCC5)C=N3)C=C2.Cl

Caution: Product has not been fully validated for medical applications. For research use only.

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