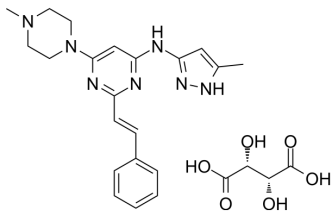
ENMD-2076 Tartrate

Cat. No.:	HY-10987
CAS No.:	1453868-32-0
Molecular Formula:	$C_{25}H_{31}N_7O_6$
Molecular Weight:	525.56
Target:	Aurora Kinase; FLT3; VEGFR; FGFR; Src; PDGFR; Apoptosis
Pathway:	Cell Cycle/DNA Damage; Epigenetics; Protein Tyrosine Kinase/RTK; Apoptosis
Storage:	4°C, sealed storage, away from moisture * In solvent : -80°C, 6 months; -20°C, 1 month (sealed storage, away from moisture)



SOLVENT & SOLUBILITY

In Vitro

DMSO : 25 mg/mL (47.57 mM; Need ultrasonic)

Preparing Stock Solutions	Mass / Solvent / Concentration	1 mg	5 mg	10 mg
	1 mM	1.9027 mL	9.5137 mL	19.0273 mL
	5 mM	0.3805 mL	1.9027 mL	3.8055 mL
	10 mM	0.1903 mL	0.9514 mL	1.9027 mL

Please refer to the solubility information to select the appropriate solvent.

In Vivo

1. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: ≥ 1.43 mg/mL (2.72 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 1.43 mg/mL (2.72 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

ENMD-2076 Tartrate is a multi-targeted kinase inhibitor with IC_{50}s of 1.86, 14, 58.2, 15.9, 92.7, 70.8, 56.4 nM for Aurora A, Flt3, KDR/VEGFR2, Flt4/VEGFR3, FGFR1, FGFR2, Src, PDGFRα, respectively.

IC_{50} & Target

Aurora A 1.86 nM (IC_{50})	KDR 58.2 nM (IC_{50})	Flt-4 15.9 nM (IC_{50})	FGFR1 92.7 nM (IC_{50})
FGFR2 70.8 nM (IC_{50})	PDGFRα 56.4 nM (IC_{50})	Flt3 14 nM (IC_{50})	

In Vitro

ENMD-2076 is selective toward Aurora A versus Aurora B (IC_{50}=350 nM). ENMD-2076 inhibits HUVEC growth with an IC_{50} value of 0.15 mM. Against 10 human leukemia cell lines, the IC_{50} values range from 0.025 to 0.53 mM. Within this panel, MV4:11

	cells are the most sensitive cells by a factor of greater than 4. The lymphoma-derived U937 cell line treated with ENMD-2076 shows that the ENMD-2076 induces a dose-dependent increase in G2-M-phase arrest as well as the induction of apoptosis. ENMD-2076 inhibits cellular Flt3 ligand (FL)-induced Flt3 autophosphorylation in THP-1 cells, which have been shown to express FL-responsive wild-type Flt- 3 (18) with an IC_{50} value of 28 nM. ENMD-2076 inhibits stem cell factor (SCF)-induced Kit autophosphorylation in MO7e cells with an IC_{50} value of 40 nM. ENMD-2076 inhibits VEGFR2/KDR autophosphorylation with an IC_{50} value of 7 nM[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	ENMD-2076 treatment results in statistically significant, dose dependent inhibition of tumor growth or tumor regression. Moreover, there is no correlation between tumor growth rate and antitumor efficacy, which would conceivably be expected for a mitotic kinase inhibitor, as fast growing (e.g., A375 melanoma) and slow-growing (e.g., HT29 colon carcinoma) tumors are similarly inhibited by ENMD-2076. ENMD-2076 is well tolerated at daily doses up to 302 mg/kg (equivalent to 200 mg/kg of the free base), with no weight loss or signs of morbidity noted in any study at this dose with the exception of the A375 model[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Kinase Assay [1]	Recombinant Aurora A and B kinase enzymes assays are carried out in kinase assay buffer (50 mM of HEPES, pH 7.5, 10 mM of $MgCl_2$, 5 mM of EGTA, 0.05% Brij-35) supplemented with 2 mM of DTT. Activities are determined at an ATP concentration equivalent to the apparent Km for each enzyme, and an enzyme concentration that results in approximately 30% phosphorylation of the peptide substrate after 1 hour. Dose–response curves of relative enzyme activity versus ENMD-2076 concentration are plotted with Grafit and used to calculate IC_{50} values[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Cell Assay [1]	The antiproliferative effect of ENMD-2076 on adherent tumor cell lines is measured by plating 500 cells per well in a 96-well plate and incubating with 9 doses of compound, spanning 0.3 nM to 125 mM, for 96 hours. Cellular proliferation is measured using the sulforhodamine B assay[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1]	Mice: Cell lines are injected subcutaneously or into the mammary fat pad (MDA-MB-231 only) of 5- to 6-week-old CB.17 SCID or NCr nude mice. Tumors are allowed to grow for 10 to 50 days before drug treatment. All treatments are with ENMD-2076 in water or ENMD-2076 free base in CMC-Tween vehicle (0.075% carboxymethylcellulose, 0.085% Tween 80 in water), administered orally. Percent tumor growth inhibition is calculated[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Sci Transl Med. 2018 Jul 18;10(450):eaaq1093.
- Am J Pathol. 2019 Oct;189(10):2090-2101.
- Int J Gynecol Cancer. 2017 Oct;27(8):1666-1674.

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REFERENCES

[1]. Fletcher GC, et al. ENMD-2076 is an orally active kinase inhibitor with antiangiogenic and antiproliferative mechanisms of action. Mol Cancer Ther. 2011 Jan;10(1):126-37.

[2]. Wang X, et al. Preclinical activity of a novel multiple tyrosine kinase and aurora kinase inhibitor, ENMD-2076, against multiple myeloma. Br J Haematol. 2010 Aug;150(3):313-25.

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