Ravoxertinib hydrochloride

Cat. No.: HY-15947A

CAS No.: 2070009-58-2

Molecular Formula: $C_{21}H_{19}Cl_2FN_6O_2$

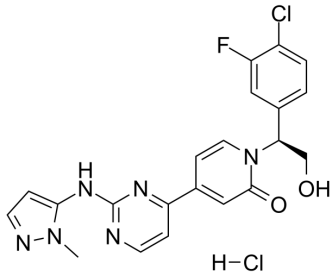
Molecular Weight: 477.32

Target: ERK

Pathway: MAPK/ERK Pathway; Stem Cell/Wnt

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 : 100 mg/mL (209.50 mM; Need ultrasonic)

H_2O : < 0.1 mg/mL (ultrasonic;warming;heat to 80°C) (insoluble)

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	2.0950 mL	10.4752 mL	20.9503 mL
5 mM	0.4190 mL	2.0950 mL	4.1901 mL
10 mM	0.2095 mL	1.0475 mL	2.0950 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: ≥ 2.5 mg/mL (5.24 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.5 mg/mL (5.24 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Ravoxertinib hydrochloride (GDC-0994 hydrochloride) is an orally bioavailable inhibitor selective for ERK kinase activity with IC_{50} of 6.1 nM and 3.1 nM for ERK1 and ERK2, respectively.

IC_{50} & Target

ERK2	ERK1	p-RSK
3.1 nM (IC_{50})	6.1 nM (IC_{50})	12 nM (IC_{50})

In Vitro

Ravoxertinib also inhibits p90RSK with IC_{50} of 12 nM[1].

Ravoxertinib is highly selective for ERK1 and ERK2, with biochemical potency of 1.1 nM and 0.3 nM, respectively[2].

Ravoxertinib (GDC0994; 50 nM, 0.5 μM, and 5 μM; 48 hours) decreases the viability of lung adenocarcinoma cell lines (A549, HCC827, HCC4006)[4].

	MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	In CD-1 mice, a 10 mg/kg oral dose of Ravoxertinib is sufficient to achieve the desired target coverage for at least 8 h[1]. Daily, oral dosing of Ravoxertinib results in significant single-agent activity in multiple in vivo cancer models, including KRAS-mutant and BRAF-mutant human xenograft tumors in mice[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Animal Administration [1]	Mice[1] PK/PD data for Ravoxertinib in the HCT116 mouse xenograft model. HCT116 tumors are established in nude mice to a tumor volume of 400−600 mm^3. Mice are treated with a single oral dose of 22 at 15, 30, or 100 mg/kg versus vehicle control alone (40% PEG400/60% (10% HPβCD)) follow by tumor and plasma collection at 2, 8, 16, and 24 h postdose. Tumor levels of phosphorylated p90RSK (pRSK) relative total p90RSK (tRSK) are measured by quantitative Western blot and are normalized to vehicle control at 2 h postdose (set to 100%). Plasma and tumor concentrations are measured by LC−MS. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Cell. 2018 Sep 20;175(1):186-199.e19.
- Cancer Cell. 2023 Jul 10;41(7):1345-1362.e9.
- Cell Mol Immunol. 2023 Jan 5.
- Nat Metab. 2022 Mar;4(3):374-388.
- Sci Transl Med. 2021 Jan 27;13(578):eaba7308.

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REFERENCES

[1]. Blake JF, et al. Discovery of (S)-1-(1-(4-Chloro-3-fluorophenyl)-2-hydroxyethyl)-4-(2-((1-methyl-1H-pyrazol-5-yl)amino)pyrimidin-4-yl)pyridin-2(1H)-one (GDC-0994), an Extracellular Signal-Regulated Kinase 1/2 (ERK1/2) Inhibitor in Early Clinical Developme

[2]. Kirk Robarge, et al. Abstract DDT02-03: Discovery of GDC-0994, a potent and selective ERK1/2 inhibitor in early clinical development. Proceedings: AACR Annual Meeting 2014; April 5-9, 2014.

[3]. MICHAEL LAI. Opportunity for Pharmaceutical Intervention in Lung Cancer: Selective Inhibition of JAK1/2 to Eliminate EMT-Derived Mesenchymal Cells.

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