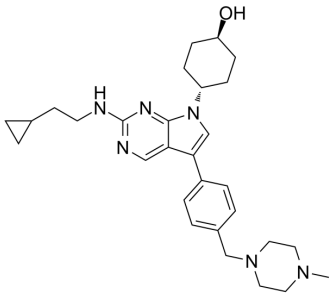
MRX-2843

Cat. No.:	HY-101549
CAS No.:	1429882-07-4
Molecular Formula:	$C_{29}H_{40}N_6O$
Molecular Weight:	488.67
Target:	FLT3
Pathway:	Protein Tyrosine Kinase/RTK
Storage:	Powder -20°C 3 years 4°C 2 years In solvent -80°C 2 years -20°C 1 year



SOLVENT & SOLUBILITY

In Vitro

DMSO : 20 mg/mL (40.93 mM; ultrasonic and warming and heat to 60°C)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	2.0464 mL	10.2319 mL	20.4637 mL
	5 mM	0.4093 mL	2.0464 mL	4.0927 mL
	10 mM	0.2046 mL	1.0232 mL	2.0464 mL

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

In Vivo

1. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.08 mg/mL (4.26 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: 2 mg/mL (4.09 mM); Clear solution; Need ultrasonic
3. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: 2 mg/mL (4.09 mM); Suspended solution; Need ultrasonic

BIOLOGICAL ACTIVITY

Description

MRX-2843 (UNC2371) is an orally active, ATP-competitive dual MERTK and FLT3 tyrosine kinases inhibitor (TKI) with enzymatic IC_{50}s of 1.3 nM for MERTK and 0.64 nM for FLT3, respectively[1].

IC_{50} & Target

MERTK, FLT3[1]

In Vitro

In the Kasumi-1 cell line, treatment with MRX-2843 results in dose-dependent inhibition of MERTK phosphorylation. Decreased phosphorylation is evident at concentrations as low as 10 nM, with near-complete abrogation of MERTK

activation at 100 to 300 nM. Similarly, treatment of Kasumi-1 cells with MRX-2843 mediates inhibition of downstream signaling through pathways important for tumor cell survival and proliferation. MRX-2843 treatment results in a decrease in relative cell numbers, with an IC_{50} of 143.5±14.1 nM, indicating that MRX-2843 significantly inhibits tumor cell proliferation and/or survival. Similarly, there are 34.1%±5.6% and 67.1%±2.7% apoptotic and dead cells in NOMO-1 cultures treated with 150 nM or 300 nM MRX-2843, respectively, compare with 6.8%±0.7% in vehicle-treated cultures (P<0.001). Treatment with 50 nM and 100 nM MRX-2843 results in 62.3%±6.4% and 84.1%±7.8% inhibition of colony formation, respectively, in Kasumi-1 cultures (P<0.01). Similarly, in NOMO-1 cultures, colony formation is inhibited by 54.8%±18.1% in response to treatment with 100 nM MRX-2843 (P<0.001). In MOLM-14 cells, treatment with MRX-2843 inhibits phosphorylation of FLT3 and downstream signaling through STAT5, ERK1/2, and AKT. Activation of FLT3 and its signaling pathways is almost completely abrogated by treatment with 50 nM MRX-2843, indicating somewhat higher cellular potency against FLT3 relative to MERTK [1].

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

In Vivo

MRX-2843 is 78% orally bioavailable at a dose of 3 mg/kg with a C_{max} of 1.3 μM and a $t_{1/2}$ of 4.4 hours. In MOLM-14 parental xenografts, both quizartinib and MRX-2843 increase median survival compare with that of vehicle-treated mice (172.5 days versus 40 days and 121 days versus 36 days, respectively, P<0.001). In this model, quizartinib is more effective than MRX-2843 (P<0.005), although higher doses of MRX-2843 are not evaluated. In MOLM-14:D835Y xenografts, quizartinib prolongs survival compare with that of vehicle-treated mice, but the effect is minimal (median survival 45 days vs. 36 days, P<0.001). In MOLM-14:F691L xenografts, treatment with MRX-2843 prolongs survival by almost 2-fold in NSG and NSGS mice (median survival 87 vs. 44.5 days and 87 vs. 48 days, respectively, P<0.005). Increased survival is observed in response to treatment with MRX-2843 versus quizartinib, but the difference is only significant in NSG mice[1].

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PROTOCOL

Cell Assay [1]

Cell lines are cultured (10,000 cells/sample) in 0.35% Noble agar on a 0.5% Noble agar base layer and overlaid with cRPMI containing kinase inhibitor (including MRX-2843) or vehicle. The overlying medium is replaced 2 to 3 times per week, and vehicle treatment is assessed in duplicate. After 14 days or 21 days (Kasumi-1 cells only), colonies are stained with 1 mg/mL nitrotetrazolium blue for 4 hours and counted using a colony counter. Mononuclear cells are isolated from human cord blood and samples from acute myeloid leukemia (AML) patients. Patient samples are cultured in triplicate at a density of 1×10^6 cells/mL in MethoCult H4434 Classic Methylcellulose-Based Medium with Recombinant Cytokines for Human Cells containing MRX-2843 or vehicle. Colonies are counted after 10 days using the colony counter. Cord blood cells are incubated for 1 hour in serum-free Iscove's modified Dulbecco's medium (IMDM) supplemented with BIT 9500 Serum Substitute, low-density lipoproteins, and 2-ME, and then cultured in triplicate at a density of 2×10^6 cells/mL in Methocult H4434 methylcellulose containing MRX-2843 or vehicle. Colonies are manually counted in a blinded manner after 14 days[1].

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Animal Administration [1]

Mice are used in this study. Established leukemia cell lines or mononuclear cells isolated from samples from patients with acute myeloid leukemia (AML) (1×10^6 to 2.5×10^6 per mouse) are suspended in PBS and injected into the tail veins of mice to establish xenografts. All mice are 4 to 6 months of age at the time of injection and are male, with the exception of the NOMO-1, MOLM-14:D835Y, and MOLM-14:F691L NSG xenografts, which are established in female mice. Myeloblasts are detected in peripheral blood (patient-derived xenografts) or bone marrow (MOLM-14 xenografts) samples after staining with a FITC-conjugated anti-human CD45 Ab. Samples are analyzed by flow cytometry using a Gallios flow cytometer and Kaluza software. After engraftment, the mice are weighed and treated once daily with MRX-2843, quizartinib, or vehicle administered by oral gavage in a volume of 10 mL/kg. When mice appear ill or lost more than 20% of their body weight, they are euthanized[1].

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CUSTOMER VALIDATION

- Vaccines. 2021, 9(11), 1294.
- Cells. 2022 Sep 3;11(17):2752.
- Head Neck. 2023 Mar 20.

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REFERENCES

[1]. Minson KA, et al. The MERTK/FLT3 inhibitor MRX-2843 overcomes resistance-conferring FLT3 mutations in acute myeloid leukemia. JCI Insight. 2016 Mar;1(3):e85630.

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