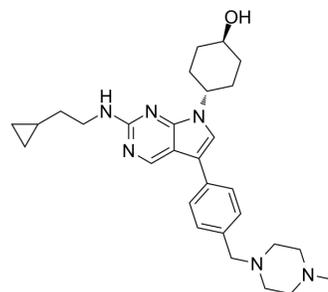


MRX-2843

Cat. No.:	HY-101549		
CAS No.:	1429882-07-4		
Molecular Formula:	C ₂₉ H ₄₀ N ₆ O		
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)

Concentration	Solvent	Mass		
		1 mg	5 mg	10 mg
Preparing Stock Solutions	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

- Add each solvent one by one: 10% DMSO >> 90% corn oil
Solubility: ≥ 2.08 mg/mL (4.26 mM); Clear solution
- 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
- 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 IC₅₀s of 1.3 nM for MERTK and 0.64 nM for FLT3, respectively^[1].

IC₅₀ & 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 $34.1 \pm 5.6\%$ and $67.1 \pm 2.7\%$ apoptotic and dead cells in NOMO-1 cultures treated with 150 nM or 300 nM MRX-2843, respectively, compare with $6.8 \pm 0.7\%$ in vehicle-treated cultures ($P < 0.001$). Treatment with 50 nM and 100 nM MRX-2843 results in $62.3 \pm 6.4\%$ and $84.1 \pm 7.8\%$ inhibition of colony formation, respectively, in Kasumi-1 cultures ($P < 0.01$). Similarly, in NOMO-1 cultures, colony formation is inhibited by $54.8 \pm 18.1\%$ 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 μ M 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].

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

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 nitroretazolium 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].

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

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].

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

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.

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

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