

Product Data Sheet

Product Name: MRX-2843 (UNC2371)

Cat. No.: GC32769

Chemical Properties

Cas. No. 1429882-07-4

SMILES O[C@H]1CC[C@H](N2C=C(C3=CC=C(CN4CCN(C)CC4)C=C3)C5=CN=C(NCCC6CC6)N=C52)CC1

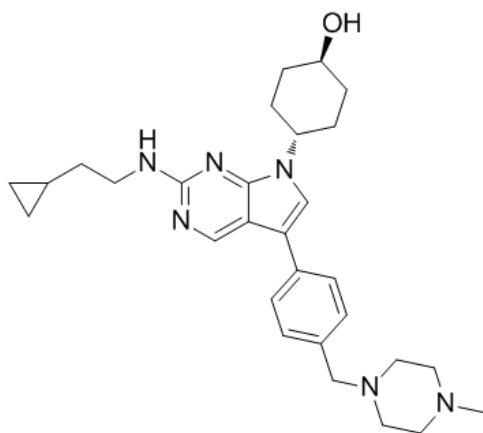
Formula C29H40N6O M.Wt 488.67

Solubility DMSO : 31.25 mg/mL (63.95 mM) Storage Store at -20°C

General tips For obtaining a higher solubility , please warm the tube at 37 °C and shake it in the ultrasonic bath for a while. Stock solution can be stored below -20°C for several months.

Shipping Condition Evaluation sample solution : ship with blue ice All other available size: ship with RT , or blue ice upon request.

Structure



Protocol

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

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Cell experiment: 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 nitroterazolium 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].

Animal experiment: 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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References:

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Background

MRX-2843 is an orally available small-molecule inhibitor of both MERTK and FLT3.

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 IC₅₀ 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].

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

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versus quizartinib, but the difference is only significant in NSG mice[1].

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