# Data Sheet

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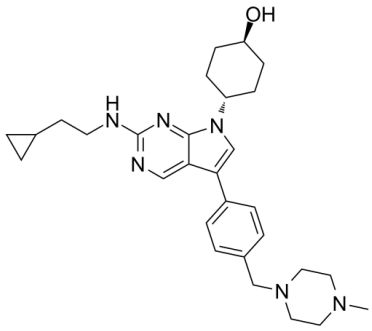
| **Product Name:** | MRX-2843 |
| **Cat. No.:** | CS-8117 |
| **CAS No.:** | 1429882-07-4 |
| **Molecular Formula:** | C29H40N6O |
| **Molecular Weight:** | 488.67 |
| **Target:** | FLT3 |
| **Pathway:** | Protein Tyrosine Kinase/RTK |
| **Solubility:** | DMSO : 31.25 mg/mL (63.95 mM; Need ultrasonic) |



## BIOLOGICAL ACTIVITY:

MRX-2843 is an orally available, dual **MERTK** and **FLT3** tyrosine kinase inhibitor (TKI) with enzymatic $IC_{50}$s of 1.3 nM for MERTK and 0.64 nM for FLT3, respectively. 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%±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]. **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].

## PROTOCOL (Extracted from published papers and Only for reference)

**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 $1\times10^6$ 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 $2\times10^6$ cells/mL in Methocult H4434 methylcellulose containing MRX-2843 or vehicle. Colonies are

manually counted in a blinded manner after 14 days[1]. **Animal 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) ($1\times10^6$ to $2.5\times10^6$ 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].

## 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.

## CAIndexNames:

Cyclohexanol, 4-[2-[(2-cyclopropylethyl)amino]-5-[4-[(4-methyl-1-piperazinyl)methyl]phenyl]-7H-pyrrolo[2,3-d]pyrimidin-7-yl]-, trans-

## SMILES:

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



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