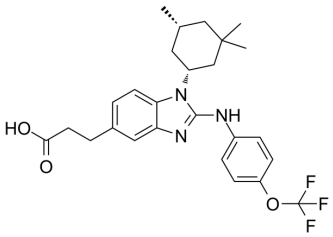
BAY-1436032

Cat. No.:	HY-100020
CAS No.:	1803274-65-8
Molecular Formula:	$C_{26}H_{30}F_3N_3O_3$
Molecular Weight:	489.53
Target:	Isocitrate Dehydrogenase (IDH)
Pathway:	Metabolic Enzyme/Protease
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 : 125 mg/mL (255.35 mM; Need ultrasonic and warming)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	2.0428 mL	10.2139 mL	20.4278 mL
	5 mM	0.4086 mL	2.0428 mL	4.0856 mL
	10 mM	0.2043 mL	1.0214 mL	2.0428 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 (5.11 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: 2.5 mg/mL (5.11 mM); Suspended solution; Need ultrasonic
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (5.11 mM); Clear solution

BIOLOGICAL ACTIVITY

Description	BAY-1436032 is a novel pan-mutant isocitrate dehydrogenase 1 (IDH1) inhibitor.
IC_{50} & Target	IDH1[1]
In Vitro	BAY-1436032 is a novel pan-mutant isocitrate dehydrogenase 1 (IDH1) inhibitor. BAY-1436032 inhibits intracellular (R)-2-hydroxyglutarate (R-2HG) production in mouse hematopoietic cells expressing IDH1R132H or IDH1R132C with IC_{50}s of 60 and 45 nM, respectively. R-2HG levels are not reduced in IDH2R140Q and IDH2R172K expressing mouse hematopoietic cells

	by BAY-1436032 at concentrations up to 10 μM. Colony growth is inhibited by 50% at a concentration of 0.1 μM BAY-1436032, while concentrations up to 100 μM do not suppress colony growth of patient-derived IDH1 wild-type AML cells. On morphologic evaluation myelomonocytic differentiation of myeloid progenitors is strongly induced by BAY-1436032[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	Long-term exposure to once daily oral BAY-1436032 reveals nearly complete suppression of (R)-2-hydroxyglutarate (R-2HG) production with 150 mg/kg BAY1436032. White blood cell counts constantly increase in vehicle-treated mice and, at a lower rate, in animals receiving 45 mg/kg BAY-1436032, while they remain constant in the 150 mg/kg cohort. Hemoglobin levels are slightly lower in the vehicle and 45 mg/kg groups as compare to the 150 mg/kg cohort at day 60, while platelet counts are significantly reduced in vehicle and 45 mg/kg BAY-1436032 treated mice compare to the 150 mg/kg cohort at day 60. All mice receiving 150 mg/kg BAY-1436032 survive with minimal $hCD45^+$ cell load in their peripheral blood until the end of observation at day 150 after treatment start ($P<0.001$), while vehicle-treated animals die from leukemia with a median survival of 91 days. Mice treated with 45 mg/kg BAY-1436032 display intermediate levels of CD14/CD15 expression[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Cell Assay [1]	Colony-forming cell (CFC) units are assayed in methylcellulose supplemented with 10 ng/mL IL-3, 10 ng/mL GM-CSF, 50 ng/mL SCF, 50 ng/mL FLT3-ligand and 3 U/mL EPO. Vehicle or BAY-1436032 is added to methylcellulose containing 10^5 human mononuclear cells, which are plated in duplicate. Colonies are evaluated microscopically 10 to 14 days after plating by standard criteria[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1]	NSG mice are used and transplanted with primary acute myeloid leukemia (AML) cells from a patient with IDH1R132C mutant AML. Per condition 10 mice are treated with vehicle, 45 or 150 mg/kg body weight BAY-1436032 once daily by oral gavage for 150 days starting 17 days after transplantation. Finally, serum R-2HG levels and human $CD45^+$ ($hCD45^+$) cells are measured[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Nature. 2022 Oct;610(7932):555-561.
- J Med Chem. 2023 Mar 23.
- Metabolites. 2021 Feb 13;11(2):109.

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REFERENCES

[1]. Chaturvedi A, et al. Pan-mutant-IDH1 inhibitor BAY1436032 is highly effective against human IDH1 mutant acute myeloid leukemia in vivo. Leukemia. 2017 Oct;31(10):2020-2028.

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