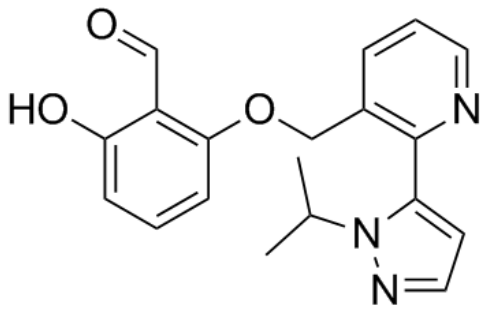
Product Data Sheet

Product Name: Voxelotor (GBT 440)
Cat. No.: GC32434

Chemical Properties

Cas. No.	1446321-46-5		
SMILES	OC1=CC=CC(OCC2=C(C3=CC=NN3C(C)C)N=CC=C2)=C1C=O		
Formula	$C_{19}H_{19}N_3O_3$	M.Wt	337.37
Solubility	DMSO : ≥ 125 mg/mL (370.51 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

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Cell experiment [1]:

Cell lines	Sickle red blood cells
Preparation Method	500μl of PBS (pH 7.4; isotonic) was added to sickle red blood cells (500μl) and centrifuged at 250g for 5min. After centrifugation, the supernatant was discarded. 20μl of packed sickle red blood cells was added to 30μl of PBS in a 96-well gas permeable plate and incubated for 0.5 hours at 37°C in a humidified hypoxic chamber (4% O_2; 96% N_2). Voxelotor (in 100% DMSO) was added to 50μl of deoxygenated-PBS at varying concentrations. DMSO alone was used as acontrol. Next, sickle red blood cells (50μl) were added to 50μl of Voxelotor solution and mixed. The final Voxelotor concentrations were 0, 1mM, 2mM, and 5mM and the final DMSO concentration was 2.5% per reaction. The reaction mixture was incubated under continued hypoxia for an additional 2 hours. Next, cells were imaged using a bright-field microscope fitted with a camera in the hypoxic chamber. Images (40×magnification) were quantified by manually counting round cells versus ill-shaped cells (sickled cells).
Reaction Conditions	0, 1mM, 2mM, and 5mM; 2h
Applications	Voxelotor treatment reversed sickling of already sickled red blood cells under hypoxic conditions in a dose-dependent manner.

Animal experiment [2]:

Animal models	HbSS Townes knock-in sickle mice

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Preparation Method	The HbSS Townes knock-in sickle mice were kept in temperature-controlled (21°C-25°C) and humidity-maintained (40%-70%) room with a 12h light/dark cycle. Water and food were provided freely. Voxelotor [150mg/kg in 0.5% methylcellulose/0.5% Sodium Dodecyl Sulfate (SDS)] was administered twice daily by oral gavage for 12 days. Blood samples (50μl) for sickling measurements were collected 4h following the last dose of the chronic regimen.
Dosage form	150mg/kg; twice a day for 12 days; p.o.
Applications	Voxelotor treatment reduced sickling in whole blood of HbSS Townes knock-in sickle mice.

References:
[1] Dufu K, Oksenberg D. GBT440 reverses sickling of sickled red blood cells under hypoxic conditions in vitro[J]. Hematology reports, 2018, 10(2): 7419.
[2] Oksenberg D, Dufu K, Patel M P, et al. GBT 440 increases haemoglobin oxygen affinity, reduces sickling and prolongs RBC half-life in a murine model of sickle cell disease[J]. British journal of haematology, 2016, 175(1): 141-153.

Background

Voxelotor (GBT 440) is a haemoglobin S (HbS) polymerization inhibitor that improves the chronic hemolytic anemia of sickle cell disease (SCD)[1]. Voxelotor prevents HbS polymerization by bridging the two α-globin subunits together, stabilizing the hemoglobin in the 'relaxed' oxygenated configuration, thereby, increasing oxygen affinity and increasing the ratio of "oxy" HbS to deoxygenated HbS [2]. Voxelotor has been widely used to regulate the affinity of hemoglobin for oxygen, preventing the sickling of isolated red blood cells[3].

In vitro, Voxelotor treatment at 5mM for 2 hours can reverse the sickling of already sickled red blood cells under hypoxic conditions, and reduce the content of intracellular HbS polymers[4]. 1mM of Voxelotor treatment for 0.5h inhibited sickling of sickle cell trait blood under conditions mimicking a combination of hypoxia, dehydration and acidosis[5].

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In vivo, Voxelotor was administered by gavage (200mg/kg) five times a week for three consecutive weeks, which significantly increased the hemoglobin (Hb) levels in the mice[6]. When oral administration of Voxelotor at a dose of 200mg/kg/day for two consecutive weeks, the Hb concentration in mice with SCD reached a steady state level of 802±81μM, and the p50 value (partial pressure of O_2 at which Hb is 50% saturated) in the blood of SCD mice decreased from 39±0.8mmHg to 21±1.6mmHg[7]. Voxelotor treatment via oral administration at a dose of 150mg/kg (twice a day) for 12 days reduced the sickling in in whole blood of HbSS Townes knock-in sickle mice and increased Hb-O_2 affinity[8].

References:

[1] Glaros A K, Razvi R, Shah N, et al. Voxelotor: alteration of sickle cell disease pathophysiology by a first-in-class polymerization inhibitor[J]. Therapeutic advances in hematology, 2021, 12: 20406207211001136.
[2] Jamalapur S L, Glaros A K, Ravindranath Y. Voxelotor (GBT440) in pediatric sickle cell disease: A review[J]. Pediatric Hematology Oncology Journal, 2024, 9(4): 244-249.
[3] Hutchaleelaha A, Patel M, Silva A, et al. GBT440 demonstrates high specificity for red blood cells in nonclinical species[J]. Blood, 2015, 126(23): 2172.
[4] Dufu K, Oksenberg D. GBT440 reverses sickling of sickled red blood cells under hypoxic conditions in vitro[J]. Hematology reports, 2018, 10(2): 7419.
[5] Dufu K, Lehrer-Graiwer J, Ramos E, et al. GBT440 inhibits sickling of sickle cell trait blood under in vitro conditions mimicking strenuous exercise[J]. Hematology reports, 2016, 8(3): 6637.
[6] Wang H, Miranda M, Marutani E, et al. Therapeutic hypoxia for mitochondrial disease via enhancement of hemoglobin affinity and inhibition of HIF-2α[J]. The Journal of Clinical Investigation, 2024, 134(23).
[7] Dufu K, Lucas A, Muller C R, et al. Pharmacological increase of Hb-O2 affinity with a voxelotor analog does not decrease brain tissue pO2 or limit O2 extraction in brain tissues of sickle cell mice[J]. Blood, 2019, 134: 3564.
[8] Oksenberg D, Dufu K, Patel M P, et al. GBT 440 increases haemoglobin oxygen affinity, reduces sickling and prolongs RBC half-life in a murine model of sickle cell disease[J]. British journal of haematology, 2016, 175(1): 141-153.

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