

Product Data Sheet

Product Name: GKT137831

Cat. No.: GC11882

Chemical Properties

Cas. No. 1218942-37-0

Chemical Name 2-(2-chlorophenyl)-4-(3-(dimethylamino)phenyl)-5-methyl-1H-pyrazolo[4,3-c]pyridine-3,6(2H,5H)-dione

SMILES CN(C1=CC=CC(C2=C(C3=O)C(NN3C4=CC=CC=C4Cl)=CC(N2C)=O)=C1)C

Formula C₂₁H₁₉ClN₄O₂

M.Wt 394.85

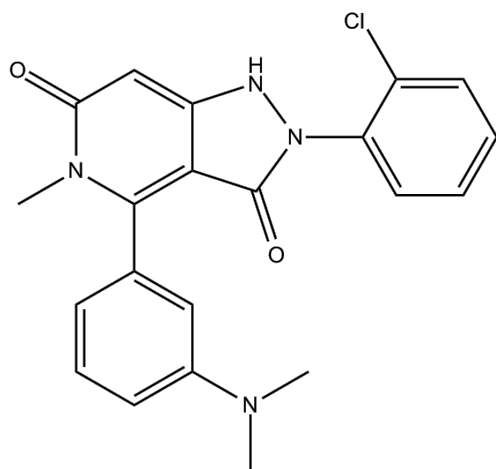
Solubility ≥ 39.5mg/mL in DMSO

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



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

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Protocol

Cell experiment [1]:

Cell lines Human pulmonary artery smooth muscle cells (HPASMCs)

Preparation Method Monolayers of HPASMCs were propagated in culture and placed in hypoxic (1% O₂, 5% CO₂) conditions for 72 hours. GKT137831 (0.1-20μM), provided through a material transfer agreement from GenKyoTex, or vehicle (1% DMSO) was added to the culture medium at the onset (prevention regimen) or during the last 24 hours (intervention regimen) of a 72 hours hypoxia exposure regimen.

Reaction Conditions 0, 0.1, 5, 20μM; 24h (intervention paradigm) and 72h (prevention paradigm)

Applications Exposure to hypoxia increased the proliferation of HPASMCs. Treatment with graded concentrations of GKT137831 during the last 24 hours of hypoxia exposure attenuated cell proliferation in HPASMCs in a dose-dependent manner. Administration of GKT137831 throughout the 72 hours period of hypoxia exposure attenuated HPASMC proliferation under at the 20μM concentration.

Animal experiment [2]:

Animal models WT C57BL/6J mice, Superoxide dismutase 1 (SOD1) G37R mutant mice in a C57BL/6 background

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For the CCl₄ model of liver fibrosis, 6-week-old male mice were injected intraperitoneally with CCl₄, which was diluted 1:3 in corn oil, or with vehicle (corn oil) at a dose of 0.5μL/g of body weight twice weekly for a total of 12 Preparation Method injections. During the last half of CCl₄ treatment, mice were treated with 60mg/kg of GKT137831, or vehicle by intragastric (IG) injection daily. Mice were sacrificed 48 hours after the last CCl₄ injection. Mice were sacrificed 21 days after the operation.

Dosage form 60mg/kg; intragastric (IG) injection

Applications Liver fibrosis was increased in SOD1^{mu} mice, and ROS production and Ras-related botulinum toxin substrate 1 (Rac1) activity were increased in SOD1^{mu} hepatic stellate cells (HSCs). GKT137831, attenuated liver fibrosis and ROS production in both SOD1^{mu} and WT mice, as well as messenger RNA expression of fibrotic and NOX genes. Treatment with GKT137831 suppressed ROS production and NOX and fibrotic gene expression, but not Rac1 activity, in SOD1^{mut} and WT HSCs.

References:

- [1] Green DE, Murphy TC, Kang BY, et al. The Nox4 inhibitor GKT137831 attenuates hypoxia-induced pulmonary vascular cell proliferation. *Am J Respir Cell Mol Biol*. 2012;47(5):718-726.
- [2] Aoyama T, Paik YH, Watanabe S, et al. Nicotinamide adenine dinucleotide phosphate oxidase in experimental liver fibrosis: GKT137831 as a novel potential therapeutic agent. *Hepatology*. 2012;56(6):2316-2327.

Background

GKT137831, an orally dual NADPH oxidase 1/4 (NOX1/NOX4) inhibitor with potency in the submicromolar range, could prevent oxidative stress in human aortic endothelial cells induced by hyperglycemia and attenuate the development of atherosclerosis in diabetic mice^[1-2]. GKT137831 does not affect NOX2-mediated phagocyte function^[3].

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In vitro, monolayers of Human pulmonary artery smooth muscle cells (HPASMCs) were propagated in culture and placed in hypoxic conditions for 72 hours. Treatment with graded concentrations of GKT137831 (0, 0.1, 5, 20 μ M) during the last 24 hours of hypoxia exposure attenuated cell proliferation in HPASMCs in a dose-dependent manner, while administration of GKT137831 throughout the 72 hours of hypoxia attenuated HPASMC proliferation at the 20 μ M concentration^[4]. In primary neonatal rat cardiomyocytes (NRCMs), pretreatment with GKT137831 (5 μ mol/L, 1h) before Doxorubicin (DOX) treatment attenuated DOX-induced apoptosis^[5].

In vivo, in C57BL/6J-background CCl₄-induced liver fibrosis WT and superoxide dismutase 1 (SOD1) G37R mutant (SOD1^{mu}) mice, after once-daily intragastric administration of 60mg/kg GKT137831 during the latter half of CCl₄ treatment, GKT137831 attenuated liver fibrosis and ROS production in both SOD1^{mu} and WT mice, as well as messenger RNA expression of fibrotic and NOX genes^[6]. In Sprague Dawley rats subjected to the AAC-induced hypertensive model, oral gavage administration of GKT137831 (30mg/kg) markedly reduced the ratio of heart weight to body weight (HW/BW), the ratio of left ventricular weight to body weight (LVW /BW), and myocyte cross-sectional area in AAC-induced hypertensive rats^[7].

References:

- [1] Dong Y, Zhang Y, Li F, et al. GKT137831 in combination with adipose-derived stem cells alleviates high glucose-induced inflammaging and improves diabetic wound healing. *J Leukoc Biol.* 2024;115(5):882-892.
- [2] Demircan MB, Mgbecheta PC, Kresinsky A, et al. Combined Activity of the Redox-Modulating Compound Setanaxib (GKT137831) with Cytotoxic Agents in the Killing of Acute Myeloid Leukemia Cells. *Antioxidants (Basel).* 2022;11(3):513.
- [3] Gray SP, Jha JC, Kennedy K, et al. Combined NOX1/4 inhibition with GKT137831 in mice provides dose-dependent reno- and atheroprotection even in established micro- and macrovascular disease. *Diabetologia.* 2017;60(5):927-937.
- [4] Green DE, Murphy TC, Kang BY, et al. The Nox4 inhibitor GKT137831 attenuates hypoxia-induced pulmonary vascular cell proliferation. *Am J Respir Cell Mol Biol.* 2012;47(5):718-726.
- [5] Zheng H, Xu N, Zhang Z, et al. Setanaxib (GKT137831) Ameliorates Doxorubicin-Induced Cardiotoxicity by Inhibiting the NOX1/NOX4/Reactive Oxygen Species/MAPK Pathway. *Front Pharmacol.* 2022;13:823975.

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[6] Aoyama T, Paik YH, Watanabe S, et al. Nicotinamide adenine dinucleotide phosphate oxidase in experimental liver fibrosis: GKT137831 as a novel potential therapeutic agent. *Hepatology*.

2012;56(6):2316-2327.

[7] Zeng SY, Yang L, Yan QJ, et al. Nox1/4 dual inhibitor GKT137831 attenuates hypertensive cardiac remodelling associating with the inhibition of ADAM17-dependent proinflammatory cytokines-induced signalling pathways in the rats with abdominal artery constriction. *Biomed Pharmacother*.

2019;109:1907-1914.

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