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产品名称：AMG-3969
产品别名：AMG-3969

生物活性：

Description	AMG-3969 is a potent glucokinase-glucokinase regulatory protein interaction (GK-GKRP) disruptor with an IC_{50} of 4 nM.
IC_{50} & Target	IC50: 4 nM (GK-GKRP)[1]
In Vitro	AMG-3969 exhibits potent cellular activity with an EC_{50} of 0.202 μM and IC_{50} of 4 nM[1], [2]. It potently reverses the inhibitory effect of GKRP on GK activity and promotes GK translocation in vitro (isolated hepatocytes)[3].
In Vivo	AMG-3969 has good in vivo pharmacokinetic (PK) properties in rats (75%) and significantly lowers blood glucose levels in a dose-dependent manner db/db mice[1]. AMG-3969 (100 mg/kg) demonstrates significant reductions in blood glucose with robust efficacy (56% reduction) observed at the 8 h time point[2]. AMG-3969 demonstrates dose-dependent efficacy in three models of diabetes: diet induced obese (DIO), ob/ob and db/db mice; however,AMG-3969 is ineffective in lowering blood glucose in normoglycaemic C57BL/6 (B6) mice. AMG-3969 is highly effective in promoting carbohydrate substrate. AMG-3969 exhibits extended changes to carbohydrate oxidation as observed by increased respiratory exchange ratio into the next night and day after a single dose[3].
Solvent&Solubility	***In Vitro:*** **DMSO : ≥ 100 mg/mL (191.40 mM)** * "≥" means soluble, but saturation unknown.

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	1.9140 mL	9.5701 mL	19.1402 mL
5 mM	0.3828 mL	1.9140 mL	3.8280 mL
10 mM	0.1914 mL	0.9570 mL	1.9140 mL

*请根据产品在不同溶剂中的溶解度选择合适的溶剂配制储备液；一旦配成溶液，请分装保存，避免反复冻融造成的产品失效。

储备液的保存方式和期限：-80°C, 6 months; -20°C, 1 month。-80°C 储存时，请在 6 个月内使用，-20°C 储存时，请在 1 个月内使用。

In Vivo:

请根据您的实验动物和给药方式选择适当的溶解方案。以下溶解方案都请先按照 In Vitro 方式配制澄清的储备液，再依次添加助溶剂：

——为保证实验结果的可靠性，澄清的储备液可以根据储存条件，适当保存；体内实验的工作液，建议您现用现配，当天使用； 以下溶剂前显示的百分比是指该溶剂在您配制终溶液中的体积占比；如在配制过程中出现沉淀、析出现象，可以通过加热和/或超声的方式助溶

1.请依序添加每种溶剂： 10% DMSO→40% PEG300 →5% Tween-80 → 45% saline

Solubility: ≥ 2.5 mg/mL (4.79 mM); Clear solution

此方案可获得 ≥ 2.5 mg/mL (4.79 mM，饱和度未知) 的澄清溶液。

以 1 mL 工作液为例，取 100 μL 25.0 mg/mL 的澄清 DMSO 储备液加到 400 μL PEG300 中，混合均匀；向上述体系中加入 50 μL Tween-80，混合均匀；然后继续加入 450 μL 生理盐水定容至 1 mL

	2.请依序添加每种溶剂： 10% DMSO→ 90% (20% SBE-β-CD in saline) Solubility: ≥ 2.5 mg/mL (4.79 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (4.79 mM，饱和度未知) 的澄清溶液。 以 1 mL 工作液为例，取 100 μL 25.0 mg/mL 的澄清 DMSO 储备液加到 900 μL 20% 的 SBE-β-CD 生理盐水水溶液中，混合均匀。 3.请依序添加每种溶剂： 10% DMSO →90% corn oil Solubility: ≥ 2.5 mg/mL (4.79 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (4.79 mM，饱和度未知) 的澄清溶液，此方案不适用于实验周期在半个月以上的实验。 以 1 mL 工作液为例，取 100 μL 25.0 mg/mL 的澄清 DMSO 储备液加到 900 μL 玉米油中，混合均匀。
References	[1]. Lloyd DJ, et al. Antidiabetic effects of glucokinase regulatory protein small-molecule disruptors. Nature. 2013 Dec 19;504(7480):437-40. [2]. Nishimura N, et al. Small molecule disruptors of the glucokinase-glucokinase regulatory protein interaction: 3. Structure-activity relationships within the aryl carbinol region of the N-arylsulfonamido-N'-arylpiperazine series. J Med Chem. 2014 Apr 10;57(7):3094-116. [3]. St Jean DJ Jr, et al. Small molecule disruptors of the glucokinase-glucokinase regulatory protein interaction: 2. Leveraging structure-based drug design to identify analogues with improved pharmacokinetic profiles. J Med Chem. 2014 Jan 23;57(2):325-38.

实验参考：

Animal Administration	Mice: Diabetic db/db mice are used in the study. At 8:00 AM, mice are bled via retro-orbital sinus puncture and blood glucose values are determined and used to randomize the animals in which their averages are similar, and only mice with blood glucose ranges between 300 and 500 mg/dL are included. Vehicle (2% hydroxypropyl methycellulose, 1% Tween 80, pH 2.2 adjusted with MSA) or AMG-3969 (10, 30, 100 mg/kg) are gavaged at 9:00 AM. Blood glucose is measured at 4, 6, or 8 h posttreatment. At each time point, a 15 μL sample of whole blood is analyzed for drug exposure[2].
References	[1]. Lloyd DJ, et al. Antidiabetic effects of glucokinase regulatory protein small-molecule disruptors. Nature. 2013 Dec 19;504(7480):437-40. [2]. Nishimura N, et al. Small molecule disruptors of the glucokinase-glucokinase regulatory protein interaction: 3. Structure-activity relationships within the aryl carbinol region of the N-arylsulfonamido-N'-arylpiperazine series. J Med Chem. 2014 Apr 10;57(7):3094-116. [3]. St Jean DJ Jr, et al. Small molecule disruptors of the glucokinase-glucokinase regulatory protein interaction: 2. Leveraging structure-based drug design to identify analogues with improved pharmacokinetic profiles. J Med Chem. 2014 Jan 23;57(2):325-38.