

Product Data Sheet

Product Name: AMG-3969

Cat. No.: GC19029

Chemical Properties

Cas. No. 1361224-53-4

SMILES CC#C[C@@H]1N(C2=CC=C(C(C(F)(F)F)(O)C(F)(F)F)C=C2)CCN(S(=O)(C3=CN=C(N)C=C3)=O)C1

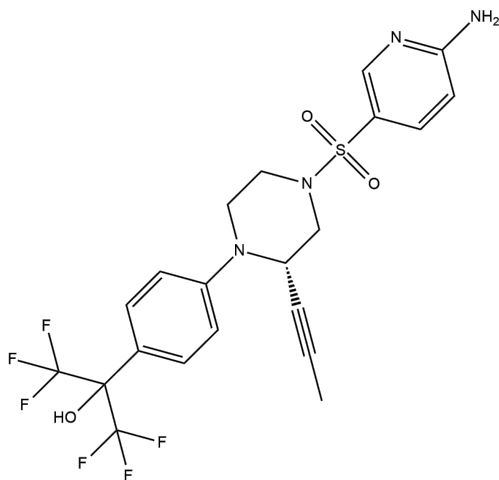
Formula $C_{21}H_{20}F_6N_4O_3S$ M.Wt 522.46

Solubility DMSO : ≥ 100 mg/mL (191.40 mM) Storage Store at $-20^{\circ}C$

General tips For obtaining a higher solubility , please warm the tube at $37^{\circ}C$ and shake it in the ultrasonic bath for a while. Stock solution can be stored below $-20^{\circ}C$ 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

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

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Animal experiment: 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 μ L 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.

Background

AMG-3969 is a potent glucokinase-glucokinase regulatory protein interaction (GK-GKRP) disruptor with an IC₅₀ of 4 nM.

AMG-3969 exhibits potent cellular activity with an EC₅₀ of 0.202 μ M and IC₅₀ 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].

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:

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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].

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'-aryl piperazine 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.

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