

Product Data Sheet

Product Name: EX229
Cat. No.: GC31411

Chemical Properties

Cas. No. 1219739-36-2

SMILES O=C(O)C1=CC(OC2=NC3=CC(Cl)=C(C4=CC5=C(N(C)C=C5)C=C4)C=C3N2)=CC=C1C

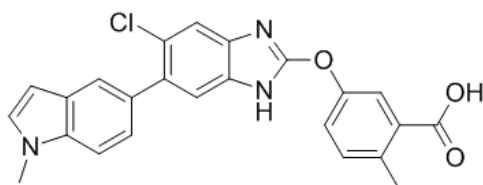
Formula $C_{24}H_{18}ClN_3O_3$ M.Wt 431.87

Solubility DMSO : 5.4 mg/mL (12.50 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

Cell experiment [1]:

Cell lines C2C12 myotubes (mouse skeletal muscle cell line)

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C2C12 myoblasts were differentiated into myotubes in high-glucose DMEM Preparation Method supplemented with 2% horse serum for 4 days. Myotubes were treated with EX229 at concentrations ranging from 2 to 25 μ M for 12 hours.

Reaction
Conditions 2-25 μ M; 12 hours

Applications EX229 dose-dependently activated AMPK signaling, as evidenced by increased phosphorylation of AMPK α (p-AMPK α). This activation subsequently induced the unfolded protein response (UPR), marked by upregulated protein expression of UPR markers ATF4 and CHOP. EX229 also enhanced the mRNA levels of UPR-related genes, including BIP, ATF4, GADD34, and XBP1s, demonstrating EX229 role in promoting ER stress adaptation.

Animal experiment [2]:

Animal models Male Wistar rats with heart failure induced by ligation of the left anterior descending coronary artery

Preparation Method Rats were treated with EX229 (2.0mg/kg) via daily intramuscular injection for 8 weeks, starting 4 weeks after heart failure induction. The treatment was combined with Fuyu Decoction (5.0g/kg, oral gavage) in the Fuyu Soup+EX229 group.

Dosage form 2.0mg/kg; i.m.

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Applications

EX229 administration significantly reversed the cardioprotective effects of Fuyu Decoction, exacerbating heart failure progression. EX229 increased left ventricular end-diastolic volume (LVEDV) and end-systolic volume (LVESV), reduced ejection fraction (LVEF) and fractional shortening (LVFS), and worsened ventricular remodeling indicators. EX229 also amplified myocardial infarction area, promoted cardiomyocyte apoptosis, and enhanced autophagy activation via the AMPK/mTOR pathway, as evidenced by upregulated p-AMPK, LC3-II/LC3-I, and Beclin1 expressions, and suppressed p-mTOR and p62 levels.

References:

- [1] Gong J, Wang L, Tao W, et al. AMPK Mediates Early Activation of the Unfolded Protein Response through a Positive Feedback Loop in Palmitate-Treated Muscle Cells. *Front Biosci (Landmark Ed)*. 2023 Aug 7;28(8):159.
- [2] Ma J, Xu Z, Zhu J, et al. Fuyu Decoction improves ventricular remodeling in rats with heart failure by inhibiting AMPK/mTOR pathway-mediated autophagy. *Nan Fang Yi Ke Da Xue Xue Bao*. 2023 Mar 20;43(3):466-473.

Background

EX229 is a benzimidazole derivative that functions as a potent allosteric agonist of AMP-activated protein kinase (AMPK)^[1]. EX229 binds to AMPK with high specificity, exhibiting differential binding affinity for various isoforms: $\alpha 1\beta 1\gamma 1$ ($K_d=0.06\mu\text{M}$), $\alpha 2\beta 1\gamma 1$ ($K_d=0.06\mu\text{M}$), and $\alpha 1\beta 2\gamma 1$ ($K_d=0.51\mu\text{M}$)^[2]. EX229 effectively regulates glucose transport and inhibits lipogenesis^[3].

In vitro, treatment of C2C12 myotube cells with EX229 (2–25 μM) for 12 hours significantly activated the AMPK signaling pathway, as indicated by a dose-dependent increase in AMPK α phosphorylation. This was accompanied by upregulation of key unfolded protein response (UPR) markers, including ATF4 and CHOP, at the protein level^[4].

In vivo, daily intramuscular administration of EX229 (2.0mg/kg) for 8 weeks in a rat model of heart failure induced by coronary artery ligation significantly reversed the cardioprotective effects of Fuyu

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Decoction. This was demonstrated by a marked increase in left ventricular end-diastolic volume (LVEDV) and end-systolic volume (LVESV), along with a significant reduction in left ventricular ejection fraction (LVEF) and fractional shortening (LVFS)^[5].

References:

- [1] Lai YC, Kviklyte S, Vertommen D, et al. A small-molecule benzimidazole derivative that potently activates AMPK to increase glucose transport in skeletal muscle: comparison with effects of contraction and other AMPK activators. *Biochem J.* 2014 Jun 15;460(3):363-75.
- [2] Xiao B, Sanders MJ, Carmena D, et al. Structural basis of AMPK regulation by small molecule activators. *Nat Commun.* 2013;4:3017.
- [3] Bultot L, Jensen TE, Lai YC, et al. Benzimidazole derivative small-molecule 991 enhances AMPK activity and glucose uptake induced by AICAR or contraction in skeletal muscle. *Am J Physiol Endocrinol Metab.* 2016 Oct 1;311(4):E706-E719.
- [4] Gong J, Wang L, Tao W, et al. AMPK Mediates Early Activation of the Unfolded Protein Response through a Positive Feedback Loop in Palmitate-Treated Muscle Cells. *Front Biosci (Landmark Ed).* 2023 Aug 7;28(8):159.
- [5] Ma J, Xu Z, Zhu J, et al. Fuyu Decoction improves ventricular remodeling in rats with heart failure by inhibiting AMPK/mTOR pathway-mediated autophagy. *Nan Fang Yi Ke Da Xue Xue Bao.* 2023 Mar 20;43(3):466-473.

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