

Product Data Sheet

Product Name: Phenformin HCl

Cat. No.: GC10461

Chemical Properties

Cas. No. 834-28-6

Chemical Name 1-(diaminomethylidene)-2-(2-phenylethyl)guanidine;hydrochloride

SMILES C1=CC=C(C=C1)CCN=C(N)N=C(N)N.Cl

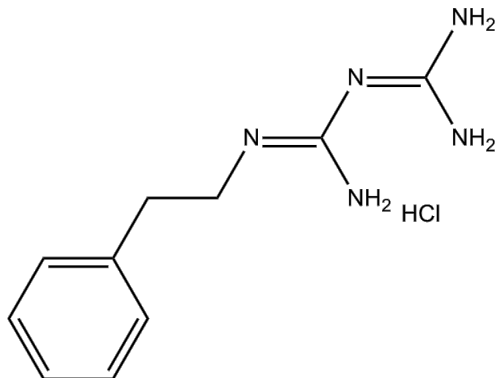
Formula $C_{10}H_{16}ClN_5$ M.Wt 241.72

Solubility $\geq 12.1\text{mg/mL}$ 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



Protocol

Cell experiment [1]:

Cell lines BRAFV600E Me-1 melanoma cells and HEK-293 cells

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

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Preparation method The solubility of this compound in DMSO is > 12.1 mg/mL. General tips for obtaining a higher concentration: Please warm the tube at 37 °C for 10 minutes and/or shake it in the ultrasonic bath for a while. Stock solution can be stored below - 20 °C for several months.

Reacting condition 1 or 5 mM; 2 hrs

Applications In BRAFV600E Me-1 melanoma cell line (with impaired AMPK activation), 1 and 5 mM Phenformin significantly increased AMPK kinase activity, in a dose-dependent manner. A similar increase was also observed in HEK-293 cells (as control cells). These results implied that the presence of BRAFV600E in melanoma cells did not prevent the pharmacological activation of AMPK, and that AMPK was activated by the increase in phosphorylation of a key AMPK downstream target (ACC).

Animal experiment [2]:

Animal models Tyr::CreER; BRAFCA/+; PTENlox/lox mice bearing single tumor induced by 4-HT

Dosage form 100 mg/kg; p.o.; b.i.d.

Applications In Tyr::CreER; BRAFCA/+; PTENlox/lox mice bearing single tumor induced by 4-HT, the combination of Phenformin and PLX4720 significantly inhibited tumor growth. PLX4720 alone substantially reduced the rate of tumor progression, but Phenformin alone only showed a modest inhibition on tumor growth in these mice. According to immunohistochemical analyses of these tumors, the Phenformin/PLX4720 combination dramatically promoted apoptotic cell death and inhibited tumor cell proliferation.

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Other notes Please test the solubility of all compounds indoor, and the actual solubility may slightly differ with the theoretical value. This is caused by an experimental system error and it is normal.

References:

- [1]. Petti C, Vegetti C, Molla A, Bersani I, Cleris L, Mustard KJ, Formelli F, Hardie GD, Sensi M, Anichini A. AMPK activators inhibit the proliferation of human melanomas bearing the activated MAPK pathway. *Melanoma Res.* 2012 Oct;22(5):341-50.
- [2]. Yuan P, Ito K, Perez-Lorenzo R, Del Guzzo C, Lee JH, Shen CH, Bosenberg MW, McMahon M, Cantley LC, Zheng B. Phenformin enhances the therapeutic benefit of BRAF(V600E) inhibition in melanoma. *Proc Natl Acad Sci U S A.* 2013 Nov 5;110(45):18226-31.

Background

Phenformin hydrochloride is an anti-diabetic drug from the biguanide class, can activate AMPK activity.

Phenformin stimulates the phosphorylation and activation of AMPK α 1 and AMPK α 2 without altering LKB1 activity[1]. Phenformin increases AMPK activity and phosphorylation in the isolated heart, the increase in AMPK activity is always preceded by and correlated with increased cytosolic [AMP][2]. Phenformin is a 50-fold more potent inhibitor of mitochondrial complex I than metformin. Phenformin robustly induces apoptosis in LKB1 deficient NSCLC cell lines. Phenformin at 2 mM similarly induces AMPK signaling as shown by increased P-AMPK and P-Raptor levels. Phenformin induces higher levels of cellular stress, triggering induction of P-Ser51 eIF2 α and its downstream target CHOP, and markers of apoptosis at later times. Phenformin induces a significant increase in survival and therapeutic response in KLLuc mice following long-term treatment[3]. Phenformin and AICAR increases AMPK activity in H441 cells in a dose-dependent fashion, stimulating the kinase maximally at 5-10 mM and 2 mM, respectively. Phenformin significantly decreases basal ion transport (measured as short circuit current) across H441 monolayers by approximately 50% compared with that of controls. Phenformin and AICAR significantly reduce amiloride-sensitive transepithelial Na⁺ transport compared with controls. Phenformin and AICAR suppress amiloride-sensitive Na⁺ transport across H441 cells via a pathway that includes activation of AMPK and inhibition of both apical Na⁺

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entry through ENaC and basolateral Na⁺ extrusion via the Na⁺,K⁺-ATPase[4]. Phenformin-treated rats reveals a tendency towards a decrease in blood insulin level (radioimmunoassay)[5].

Phenformin increases levels of P-eIF2 α and its target BiP/Grp78 in normal lung as well as in lung tumors of mice[3].

References:

- [1]. Sakamoto K, et al. Activity of LKB1 and AMPK-related kinases in skeletal muscle: effects of contraction, phenformin, and AICAR. Am J Physiol Endocrinol Metab. 2004 Aug;287(2):E310-7.
- [2]. Zhang L, et al. Metformin and phenformin activate AMP-activated protein kinase in the heart by increasing cytosolic AMP concentration. Am J Physiol Heart Circ Physiol. 2007 Jul;293(1):H457-66.
- [3]. Moreira AL, et al. Thalidomide exerts its inhibitory action on tumor necrosis factor alpha by enhancing mRNA degradation. J Exp Med. 1993 Jun 1;177(6):1675-80.
- [4]. Woollhead AM, et al. Phenformin and 5-aminoimidazole-4-carboxamide-1-beta-D-ribofuranoside (AICAR) activation of AMP-activated protein kinase inhibits transepithelial Na⁺ transport across H441 lung cells. J Physiol. 2005 Aug 1;566(Pt 3):781-92. Epub 2005
- [5]. Dilman VM, et al. Inhibition of DMBA-induced carcinogenesis by phenformin in the mammary gland of rats. Arch Geschwulstforsch. 1978;48(1):1-8.

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