

Product Data Sheet

Product Name: 666-15
Cat. No.: GC32689

Chemical Properties

Cas. No. 1433286-70-4

SMILES O=C(NC1=CC=C(Cl)C=C1O)C2=CC3=CC=CC=C3C=C2OCCNC(C4=C(OCCCN)C=C(C=CC=C5)C5=C4)=O.Cl

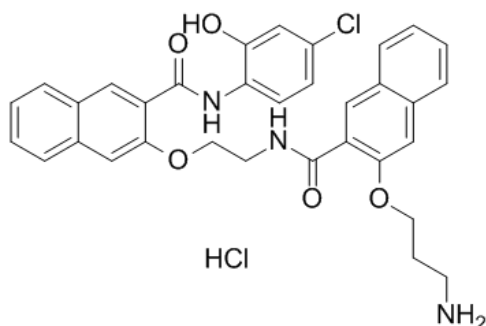
Formula $C_{33}H_{31}Cl_2N_3O_5$ M.Wt 620.52

Solubility DMSO : ≥ 30 mg/mL (48.35 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

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

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Cell experiment [1]:

Cell lines	Neonatal rat cardiac myocytes (NRCM _S)
Preparation Method	NRCMs were incubated with phenylephrine (PE) (50μM) for 24h to induce cardiomyocyte hypertrophy. Before PE treatment, NRCMs were pretreated with 1μM SB 203580 or 1μM 666-15 for 2h to inhibit the phosphorylation of p38 or CREB57.
Reaction Conditions	1μM; 2h
Applications	666-15 effectively inhibited CREB phosphorylation. However, 666-15 had no significant effect on PE-induced p38 activation.

Animal experiment [2]:

Animal models	Nude mice
Preparation Method	One hundred thousand triple-negative breast cancer (TNBC) cells were implanted into the fourth mammary fat pad on both sides of nude mice. After tumors were formed, the mice were divided into four groups and intraperitoneally injected with Vehicle, docetaxel (DOC) (10mg/kg), 666-15 (10mg/kg), or both once a week. The tumor size was monitored once a week, and the tumor images were taken after the mice were killed.
Dosage form	10mg/kg; i.p.

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Applications 666-15 alone can effectively inhibit the growth of breast cancer, and combined with DOC shows better effects, and has no significant effect on the body weight of mice.

References:

- [1]Zhang B, Zhang P, Tan Y, et al. C1q-TNF-related protein-3 attenuates pressure overload-induced cardiac hypertrophy by suppressing the p38/CREB pathway and p38-induced ER stress[J]. Cell death & disease, 2019, 10(7): 520.
- [2]Qin Y, Chen W, Jiang G, et al. Interfering MSN-NONO complex-activated CREB signaling serves as a therapeutic strategy for triple-negative breast cancer. Sci Adv 6: eaaw9960[J]. 2020.

Background

666-15 is a selective cyclic AMP response element binding protein (CREB) inhibitor with an IC₅₀ value of $0.081 \pm 0.04 \mu\text{M}$ ^[1]. 666-15 also inhibits the expression of endogenous CREB target genes, namely the transcription level of nuclear receptor-related protein 1 (Nurr1/NR4A2)^[1]. CREB is a nuclear transcription factor that can be activated by a variety of extracellular signals (including growth factors and hormones)^[2]. 666-15 blocks the neuroprotective effect of necrotizing inhibitor necrotizing inhibitor necrotizing inhibitor 1 (nec-1), which is a specific and effective inhibitor of necroptosis^[3].

In vitro, treatment of newborn rat cardiomyocytes (NRCMs) with 666-15 (1 μM) for 2h effectively inhibited phenylephrine-induced CREB phosphorylation, but had no significant effect on p38 phosphorylation^[4]. Treatment of aged guinea pig chondrocytes with 666-15 (0-500nM) significantly reduced the protein level of p-CREB1 and increased cell viability^[5]. 666-15 (0-10 μM) treatment of HEK293T cells transfected with different transcription factors for 5-7h showed little or no inhibition of Gal4-MLL, Gal4-c-Myb, Gal4-TEAD4/YAP1, and serum response factor (SRF)-mediated gene transcription^[6].

In vivo, 666-15 (10mg/kg) was intraperitoneally injected into mice transplanted with triple-negative breast cancer (TNBC) cells and inhibited breast cancer growth. Combination with docetaxel (DOC) showed better effects and had no significant effect on mouse body weight^[7].

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References:

- [1] Xie F, Li B X, Kassenbrock A, et al. Identification of a potent inhibitor of CREB-mediated gene transcription with efficacious in vivo anticancer activity[J]. Journal of medicinal chemistry, 2015, 58(12): 5075-5087.
- [2] Shaywitz A J, Greenberg M E. CREB: a stimulus-induced transcription factor activated by a diverse array of extracellular signals[J]. Annual review of biochemistry, 1999, 68(1): 821-861.
- [3] Yang C, Li T, Xue H, et al. Inhibition of necroptosis rescues SAH-induced synaptic impairments in hippocampus via CREB-BDNF pathway[J]. Frontiers in neuroscience, 2019, 12: 990.
- [4] Zhang B, Zhang P, Tan Y, et al. C1q-TNF-related protein-3 attenuates pressure overload-induced cardiac hypertrophy by suppressing the p38/CREB pathway and p38-induced ER stress[J]. Cell death & disease, 2019, 10(7): 520.
- [5] Wang Y, Wu Z, Yan G, et al. The CREB1 inhibitor 666-15 maintains cartilage homeostasis and mitigates osteoarthritis progression[J]. Bone & Joint Research, 2024, 13(1): 4-18.
- [6] Li B X, Gardner R, Xue C, et al. Systemic inhibition of CREB is well-tolerated in vivo[J]. Scientific Reports, 2016, 6(1): 34513.
- [7] Qin Y, Chen W, Jiang G, et al. Interfering MSN-NONO complex-activated CREB signaling serves as a therapeutic strategy for triple-negative breast cancer. Sci Adv 6: eaaw9960[J]. 2020.

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