Product Data Sheet

Product Name: GATA4-NKX2-5-IN-1
Cat. No.: GC25450

Chemical Properties

Cas. No.	544681-96-1		
Formula	C21H23N3O2	M.Wt	349.43
Solubility	DMSO: 70 mg/mL (200.33 mM);Water: Insoluble;Ethanol: 9 mg/mL (25.76 mM)	Storage	Store at -20°C
General tips	For obtaining a higher solubility , please warm the tube at 37 ℃ and shake it in the ultrasonic bath for a while.Stock solution can be stored below -20℃ 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	GATA4-NKX2-5-IN-1		

Protocol

Cell experiment [1]:

Cell lines	human induced pluripotent stem cell-derived cardiomyocyte (hiPSC-CM) cells
Preparation Method	The cells were exposed to doxorubicin and/or GATA4-NKX2-5-IN-1 for 2-21 days and cell viability was quantified with MTT assay. MTT was added to the cells at a final concentration of 0.5 mg/ml followed by 2 h incubation in cell culture conditions.
Reaction Conditions	0-10 μM, 2-21 days

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Applications	In the MTT assay, GATA4-NKX2-5-IN-1 alone at 10 μM concentration reduced hiPSC-CM viability 34%, 50% and 65% after 7, 14 and 21 days of exposure, respectively. At the concentration of 3 μM, the decrease was only 16% even after 21-day exposure.

Animal experiment [2]:

Animal models	male Sprague Dawley rats
Preparation Method	Doxorubicin was administered i.p. to 7 weeks old male Sprague Dawley rats with average weight 216 g (range 189-245 g) at the dose of 1 mg/kg/day for 10 days. Control animals received an equivalent volume of saline. The compound GATA4-NKX2-5-IN-1 was administered i.p. at the dose of 15 mg/kg two times a day for 2 weeks from week 7 to week 9. It was diluted to DMSO and administered to animals as 1:1 dilution in corn oil, control animals receiving DMSO with corn oil in equivalent volume.
Dosage form	15 mg/kg two times a day for 2 weeks, i.p.
Applications	treatment with compound GATA4-NKX2-5-IN-1 significantly inhibited doxorubicin-induced cardiotoxicity by restoring the left ventricular ejection fraction (EF) and fractional shortening (FS).

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References:

[1]: Karhu S T, Kinnunen S M, TÖlli M, et al. GATA4-targeted compound exhibits cardioprotective actions against doxorubicin-induced toxicity in vitro and in vivo: establishment of a chronic cardiotoxicity model using human iPSC-derived cardiomyocytes[J]. Archives of Toxicology, 2020, 94(6): 2113-2130.

Background

GATA4-NKX2-5-IN-1 (3i-1000) is a small-molecule compound inhibiting GATA4 and NKX2-5 transcriptional synergy with IC50 of 3μM [1].

GATA4-NKX2-5-IN-1 inhibits hypertrophic growth. GATA4-NKX2-5-IN-1 (10μM, 48h) significantly inhibited the increase in the area of the myocytes in response to the mechanical stretching (48h) [1]. GATA4-NKX2-5-IN-1 (30μM), inhibited epidermal growth factor receptor kinase (EGFR) by 54% and vascular endothelial growth factor receptor 2 kinase/kinase insert domain receptor (VEGFR2/KDR) by 64% [1]. GATA4-NKX2-5-IN-1 inhibited cannabinoid receptor type 2 (CB2), parathyroid hormone 2 receptor (PTH2), and niacin receptor 1/G-protein-coupled receptor 109A (GPR109A) with mean percentage inhibition values of 91.8, 59.5, and 58.5, respectively [1]. GATA4-NKX2-5-IN-1 inhibits BNP transcription, and stretch-, endothelin-1- and phenylephrine-stimulated gene expression of ANP and BNP, as well as hypertrophic cell growth in cardiomyocytes while having no effect on GATA4 or NKX2-5 DNA binding or on the activity of protein kinases involved in the regulation of GATA4 phosphorylation [1,2]. GATA4-NKX2-5-IN-1 showed cardioprotective effects in vitro. It attenuated doxorubicin-induced increase in proBNP expression in hiPSC-CMs after a 4-day exposure. GATA4-NKX2-5-IN-1 (3 μM, 10 μM) attenuated doxorubicin-induced increase in caspase activation up to 14 days.

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however the long-term exposures (up to 21 days), revealed toxic effects of GATA4-NKX2-5-IN-1 in cardiomyocytes [3].

GATA4-NKX2-5-IN-1(30mg/kg/day i.p.) significantly improved left ventricular ejection fraction and fractional shortening, and attenuated myocardial structural changes in mice after myocardial infarction. GATA4-NKX2-5-IN-1 improved cardiac function in an experimental model of angiotensin II -mediated hypertension in rats. The concentration of GATA4-NKX2-5-IN-1 was highest at 0.5h and decreased to about half within 6h in vivo in rats (single dose i.p. 10mg/kg) [2].

References:
[1]. Va?lima?ki M J, To?lli M A, Kinnunen S M, et al. Discovery of small molecules targeting the synergy of cardiac transcription factors GATA4 and NKX2-5[J]. Journal of Medicinal Chemistry, 2017, 60(18): 7781-7798.
[2]. Kinnunen S M, TÖlli M, VÄlimÄki M J, et al. Cardiac actions of a small molecule inhibitor targeting GATA4-NKX2-5 interaction[J]. Scientific reports, 2018, 8(1): 1-14.
[3]. Karhu S T, Kinnunen S M, TÖlli M, et al. GATA4-targeted compound exhibits cardioprotective actions against doxorubicin-induced toxicity in vitro and in vivo: establishment of a chronic cardiotoxicity model using human iPSC-derived cardiomyocytes[J]. Archives of Toxicology, 2020, 94(6): 2113-2130.

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