

## Product Data Sheet

Product Name: JTV 519 fumarate

Cat. No.: GC50064

### Chemical Properties

Cas. No. 1883549-36-7

Chemical Name 1-(2,3-Dihydro-7-methoxy-1,4-benzothiazepin-4(5H)-yl)-3-[4-(phenylmethyl)-1-piperidiny  
l]-1-propanone fumarate

SMILES O=C(CCN3CCC(CC4=CC=CC=C4)CC3)N2CCSC1=CC=C(OC)C=C1C2.O=C(/C=C/C(O)=O)O

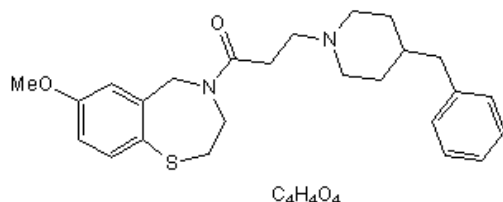
Formula  $C_{25}H_{32}N_2O_2 \cdot C_4H_4O_4$  M.Wt 540.67

Solubility 54.07mg/ml in DMSO Storage Store at 4°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 HL-1 cells

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

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HL-1 cells were grown in DMEM medium with 10% (v/v) fetal bovine serum (FBS), 100µg/ml streptomycin, 100U/ml penicillin, 0.1mM norepinephrine, and 2mM L-glutamine at 37°C in 5% CO<sub>2</sub>/atmosphere. For hypoxic exposures, cells

Preparation Method were placed in the modular chamber incubators and flushed with calibration quality gas mixtures of 1% O<sub>2</sub> + 5% CO<sub>2</sub> to achieve hypoxic exposures. The cells were treated with 1µM JTV 519 for 7 days. Cell viability was evaluated. The expression of the RyR2 gene was analyzed.

Reaction  
Conditions 1µM; 7 days

Applications JTV 519 treatment significantly promoted RyR2 gene expression in HL-1 cells in hypoxic conditions.

### Animal experiment [2]:

Animal models C57BL/6 mice

C57BL/6 mice (18-22g) were housed singly in a standard environment with food and water ad libitum. The mice were endotracheally intubated under deep anesthesia with a mixture of pentobarbital sodium (50mg/kg; i.p.). The abdominal cavity was opened, and the distal 1cm of the cecum was ligated with a suture and punctured twice with a needle of 16 gauge. After surgery, all mice received a 1-ml subcutaneous injection of physiological saline. As controls, sham-operated mice received the same procedures except for ligation and puncture. JTV 519 (0.5mg/kg/h) was applied intraperitoneally 2h before the surgery. The hearts of the mice were collected for analysis.

Dosage form 0.5mg/kg/h; 2h; i.v.

Applications JTV 519 treatment significantly improved cardiac function in mice with cecal ligation and puncture.

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### References:

- [1] Trinh M D, Fiserova I, Vacek L, et al. Hypoxia-Induced Sarcoplasmic Reticulum  $\text{Ca}^{2+}$  Leak Is Reversed by Ryanodine Receptor Stabilizer JTV-519 in HL-1 Cardiomyocytes[J]. Anatolian Journal of Cardiology, 2022, 26(6): 476.
- [2] Yang J, Zhang R, Jiang X, et al. Toll-like receptor 4-induced ryanodine receptor 2 oxidation and sarcoplasmic reticulum  $\text{Ca}^{2+}$  leakage promote cardiac contractile dysfunction in sepsis[J]. Journal of Biological Chemistry, 2018, 293(3): 794-807.

### Background

JTV 519 is a  $\text{Ca}^{2+}$ -dependent blocker of SERCA that inhibits the ATPase activity [1]. JTV 519 can inhibit  $\text{Na}^{+}$ ,  $\text{Ca}^{2+}$  and  $\text{K}^{+}$  currents in guinea-pig ventricular cells, and exhibit cardioprotection against ischaemia/reperfusion injury in isolated rat hearts through the activation of protein kinase C [2]. JTV 519 has been widely used to alter the spatiotemporal properties of diastolic  $\text{Ca}^{2+}$  release and the associated diastolic contraction in rat ventricular cardiomyocytes [3].

In vitro, JTV 519 pretreatment (1  $\mu\text{M}$ ) for 12 hours stabilized the RyR1 channel in flexor digitorum brevis muscle fibers of mice and reduced the delay in calcium reuptake induced by FK506 [4]. Treatment with 1  $\mu\text{M}$  JTV 519 for 7 days on HL-1 cells significantly reduced the calcium leak from the sarcoplasmic reticulum caused by hypoxia and increased the expression of the RyR2 gene [5]. The treatment of PC14 cells with 10  $\mu\text{M}$  JTV 519 for 72 hours significantly increased the platinum level in the cells and enhanced the cytotoxic effect of platinum on the cells [6].

In vivo, JTV 519 treatment via intravenous infusion (0.5mg/kg/h) for 2 hours inhibited the leak of cytosolic calcium from the sarcoplasmic reticulum in septic mice and improved cardiac function [7]. Intravenous infusion of JTV 519 (0.5mg/kg/h) for 4 weeks significantly improved the cardiac function of the myocardial infarction mouse model and reversed cardiac remodeling [8].

### References:

- [1] Darcy Y L, Diaz-Sylvester P L, Copello J A. K201 (JTV519) is a  $\text{Ca}^{2+}$ -dependent blocker of SERCA and a partial agonist of ryanodine receptors in striated muscle[J]. Molecular Pharmacology, 2016, 90(2): 106-115.

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- [2] Nakaya H, Furusawa Y, Ogura T, et al. Inhibitory effects of JTV-519, a novel cardioprotective drug, on potassium currents and experimental atrial fibrillation in guinea-pig hearts[J]. British journal of pharmacology, 2000, 131(7): 1363-1372.
- [3] Elliott E B, Hasumi H, Otani N, et al. K201 (JTV-519) alters the spatiotemporal properties of diastolic Ca<sup>2+</sup> release and the associated diastolic contraction during  $\beta$ -adrenergic stimulation in rat ventricular cardiomyocytes[J]. Basic research in cardiology, 2011, 106(6): 1009-1022.
- [4] Breckner A, Ganz M, Marcellin D, et al. Effect of Calstabin1 depletion on calcium transients and energy utilization in muscle fibers and treatment opportunities with RyR1 stabilizers[J]. PloS one, 2013, 8(11): e81277.
- [5] Trinh M D, Fiserova I, Vacek L, et al. Hypoxia-Induced Sarcoplasmic Reticulum Ca<sup>2+</sup> Leak Is Reversed by Ryanodine Receptor Stabilizer JTV-519 in HL-1 Cardiomyocytes[J]. Anatolian Journal of Cardiology, 2022, 26(6): 476.
- [6] Nakamura T, Koizumi F, Kaneko N, et al. Reversal of Cisplatin Resistance by the 1, 4-Benzothiazepine Derivative, JTV-519[J]. Japanese journal of cancer research, 2001, 92(6): 597-602.
- [7] Yang J, Zhang R, Jiang X, et al. Toll-like receptor 4-induced ryanodine receptor 2 oxidation and sarcoplasmic reticulum Ca<sup>2+</sup> leakage promote cardiac contractile dysfunction in sepsis[J]. Journal of Biological Chemistry, 2018, 293(3): 794-807.
- [8] Wehrens X H T, Lehnart S E, Reiken S, et al. Enhancing calstabin binding to ryanodine receptors improves cardiac and skeletal muscle function in heart failure[J]. Proceedings of the National Academy of Sciences, 2005, 102(27): 9607-9612.

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