GS967

Cat. No.: HY-12593

CAS No.: 1262618-39-2

Molecular Formula: $C_{14}H_7F_6N_3O$

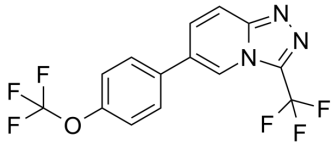
Molecular Weight: 347.22

Target: Sodium Channel

Pathway: Membrane Transporter/Ion Channel

Storage:

Powder	-20°C	3 years
	4°C	2 years
In solvent	-80°C	2 years
	-20°C	1 year



SOLVENT & SOLUBILITY

In Vitro

DMSO : 50 mg/mL (144.00 mM; Need ultrasonic)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	2.8800 mL	14.4001 mL	28.8002 mL
	5 mM	0.5760 mL	2.8800 mL	5.7600 mL
	10 mM	0.2880 mL	1.4400 mL	2.8800 mL

Please refer to the solubility information to select the appropriate solvent.

In Vivo

1. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: 2.5 mg/mL (7.20 mM); Suspended solution; Need ultrasonic
2. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (7.20 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

GS967 (GS-458967) is a potent, and selective inhibitor of cardiac late sodium current (late I_{Na}) with IC_{50} values of 0.13 and 0.21 μM for ventricular myocytes and isolated hearts, respectively.

IC_{50} & Target

IC50: 0.13 μM (late I_{Na}, ventricular myocytes)and 0.21 μM (late I_{Na}, isolated hearts)[1]

In Vitro

GS967 (10, 100, 300 nM) completely attenuates the effect of ATX-II (10 nM) to increase action potential duration (APD) and APD variability in ventricular myocytes, with an apparent IC_{50} value of -10 nM and decreased the beat-to-beat variability of APD[1].

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

In Vivo	GS967 prevents and reverses proarrhythmic effects of the late I_{Na} enhancer ATX-II and the I_{Kr} inhibitor E-4031. GS967 significantly attenuates the proarrhythmic effects of methoxamine 1 clofilium and suppressed ischemia-induced arrhythmias[1]. GS967 causes a reduction of I_{NaP} in a frequency-dependent manner, consistent with use-dependent block (UDB). GS967 evokes more potent UDB of I_{NaP} (IC_{50}=0.07 μM) than ranolazine (16 μM) and lidocaine (17 μM). GS967 is found to exert these same effects on a prototypical long QT syndromemutation (delKPQ)[2]. GS967 prevents ischemia-induced increases in alternans in the left atrium and left ventricle. GS967 reduces ischemia-induced increases in depolarization heterogeneity and repolarizationheterogeneity. GS967 does not alter heart rate, arterial blood pressure, PR and QT intervals, or QRS duration, but it mildly decreased contractility during ischemia, which was consistent with late INa inhibition[3]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Animal Administration [1][2]	Rats: Ventricular tachycardia or fibrillation are induced either by local aconitine injection (50 μg) in the left ventricular muscle of adult male rats or by arterial perfusion of 0.1 mM hydrogen peroxide in aged male rats. The left ventricular epicardial surface of the isolated-perfused hearts is optically mapped using fluorescent voltage-sensitive dye, and microelectrode recordings of action potentials are made adjacent to the aconitine injection site. The suppressive and preventive effects of GS967 (1 μM) against EAD/DAD-mediated ventricular tachycardia or fibrillation are then determined[2]. Rabbits: To determine the effect of GS967 on the inducibility of TdP by clofilium in the presence of methoxamine, rabbits are first treated with either vehicle or GS967 (in randomized manner) given as a 60 μg/kg bolus, followed by a 16 μg/kg/min infusion that is maintained for the duration of an experiment. After 10 minutes, methoxamine is infused intravenously at 15 μg/kg/min, followed 10 minutes later by clofilium at 100 nmol/kg/min. The incidences of premature ventricular contractions (PVCs), ventricular tachycardia (VT; defined as three or more consecutive abnormal beats), and TdP are determined from the ECG recordings[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Cell Stem Cell. 2020 Nov 5;27(5):813-821.e6.
- J Clin Invest. 2021 Sep 21;e142202.
- Circ Arrhythm Electrophysiol. 2017 Mar;10(3). pii: e004331.
- J Headache Pain. 2019 Nov 15;20(1):107.
- Cardiovasc Drugs Ther. 2018 Oct;32(5):413-425.

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REFERENCES

[1]. Belardinelli L, et al. A novel, potent, and selective inhibitor of cardiac late sodium current suppresses experimental arrhythmias. J Pharmacol Exp Ther. 2013 Jan;344(1):23-32.

[2]. Potet F, et al. Use-Dependent Block of Human Cardiac Sodium Channels by GS967. Mol Pharmacol. 2016 Jul;90(1):52-60.

[3]. Bonatti R, et al. Selective late sodium current blockade with GS-458967 markedly reduces ischemia-induced atrial and ventricular repolarization alternans and ECG heterogeneity. Heart Rhythm. 2014 Oct;11(10):1827-35.

[4]. Wei X, et al. Pre- and Delayed Treatments With Ranolazine Ameliorate Ventricular Arrhythmias and Nav1.5 Downregulation in Ischemic/Reperfused Rat Hearts. J Cardiovasc Pharmacol. 2016 Oct;68(4):269-279.

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