(+)-SJ733

Cat. No.: HY-19556

CAS No.: 1424799-20-1

Molecular Formula: $C_{24}H_{16}F_4N_4O_2$

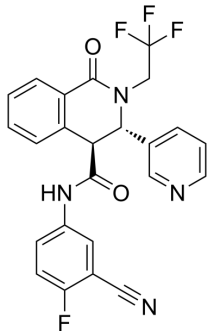
Molecular Weight: 468.4

Target: Na+/K+ ATPase; Parasite

Pathway: Membrane Transporter/Ion Channel; Anti-infection

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 (106.75 mM; Need ultrasonic)

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	2.1349 mL	10.6746 mL	21.3493 mL
5 mM	0.4270 mL	2.1349 mL	4.2699 mL
10 mM	0.2135 mL	1.0675 mL	2.1349 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 (5.34 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.5 mg/mL (5.34 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (5.34 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

(+)-SJ733 is an anti-malaria agent which can also inhibit Na^+-ATPase PfATP4.

IC_{50} & Target

Plasmodium

In Vitro

(+)-SJ733 binds to a single receptor site in P. falciparum-infected erythrocytes with equivalent affinity to its growth-inhibitory potency (k_d=50 nM). (+)-SJ733 has not exhibited either significant safety liabilities at any dose in extensive profiling in vitro or significant safety or tolerability liabilities in either single- or repeat-dose studies at any dose tested in any

	preclinical species (no observed adverse effect level and maximum tolerated dose >240 mg/kg from 7-d repeat dosing study in rat). Therefore, (+)-SJ733 is expected to have a safety margin of at least 43-fold[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	Treatment of P. falciparum-infected NOD-scid IL2Rγ^{null} mice with (+)-SJ733 causes rapid clearance of parasites, which are 80% depleted within the first 24 h and undetectable by 48 h. (+)-SJ733 is highly potent and efficacious against P. falciparum 3D7$^{0087/N9}$ in vivo when administered as four sequential daily oral doses in the NOD-scid IL2Rγ^{null} mouse model, with a 90% effective dose, (ED_{90} 1.9 mg/kg) and exposure [area under the curve at ED_{90} (AUC_{ED90}), 1.5 μM□h] superior to artesunate (11.1 mg/kg; AUC_{ED90} not determined), chloroquine (4.3 mg/kg; AUC_{ED90} 3.1 μM□h), and pyrimethamine (0.9 mg/kg; AUC_{ED90} 5. μM□h) in the same model. When treated with the ED_{90} dose, (+)-SJ733 concentrations in blood remain above the average in vitro EC_{90} for 6 to 10 h after each dose[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Cell Assay [1]	10 mL of asynchronous culture suspensions (2% hematocrit), at different parasite densities (104, 105, 106, 107, and 108 parasites), are added to each well of a 6-well plate. (+)-SJ733 is added to each well to make a final compound concentration of 1.8 μM, corresponding to 30×EC_{50} of the compound. Three wells are used for each parasite density. Plates are incubated at 37° C under an atmosphere of 90% N_2, 5% O_2, 5% CO_2 for 90 days under constant drug pressure. The media of each well is replaced 3 times a week with freshly made media containing a compound concentration of 30×EC_{50}. In addition, each well is split (1:2) once a week. Parasite outgrowth is monitored 3 times a week by transferring quadruplicate 40 μL aliquots from each well into a 384-well assay plate and determining parasitemia by a previously described method[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1]	The pharmacokinetics of (+)-SJ733 are studied in overnight-fasted male Sprague Dawley rats weighing 267 to 291 g predose. Rats have access to water ad libitum throughout the pre- and post-dose sampling period, and access to food is reinstated 4 h post-dose. (+)-SJ733 is administered intravenously as a 10 min constant rate infusion (1.0 mL per rat, n=3 rats) and orally by gavage (10 mL/kg, n=3 rats). The IV formulation consists of pH 7.4 isotonic phosphate buffered saline containing 1% (w/v) hydroxypropyl-β-cyclodextrin, 10% (v/v) ethanol, 10% (v/v) propylene glycol and 40% (v/v) PEG400 whereas the oral formulation is an aqueous suspension in 0.5% (w/v) hydroxypropyl methylcellulose, 0.5% (v/v) benzyl alcohol and 0.4% (v/v) Tween80. Aliquots of the formulations are retained for analysis of the actual dose administered. Samples of arterial blood and total urine are collected at various time points up to 24 h post-dose[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

REFERENCES

[1]. Jimenez-Diaz MB, et al. (+)-SJ733, a clinical candidate for malaria that acts through ATP4 to induce rapid host-mediated clearance of Plasmodium. Proc Natl Acad Sci U S A. 2014 Dec 16;111(50):E5455-62.

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