Acoziborole

Cat. No.: HY-19910

CAS No.: 1266084-51-8

Molecular Formula: $C_{17}H_{14}BF_4NO_3$

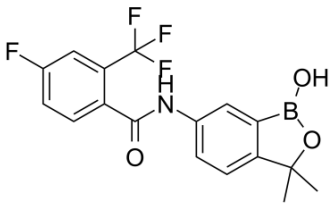
Molecular Weight: 367.1

Target: Parasite

Pathway: Anti-infection

Storage:

Powder	-20°C	3 years
	4°C	2 years
In solvent	-80°C	6 months
	-20°C	1 month



SOLVENT & SOLUBILITY

In Vitro

DMSO : ≥ 125 mg/mL (340.51 mM)

* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions

Concentration \ Solvent, Mass	1 mg	5 mg	10 mg
1 mM	2.7241 mL	13.6203 mL	27.2405 mL
5 mM	0.5448 mL	2.7241 mL	5.4481 mL
10 mM	0.2724 mL	1.3620 mL	2.7241 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: ≥ 8 mg/mL (21.79 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 8 mg/mL (21.79 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Acoziborole (SCYX-7158) is an effective, safe and orally active antiprotozoal agent for the research of human african trypanosomiasis (HAT). In the ***T. b. brucei*** S427 strain, the MIC value for SCYX-7158 is 0.6 μg/mL[1].

In Vitro

Acoziborole is active in vitro against relevant strains of Trypanosoma brucei, including T. b. rhodesiense and T. b. gambiense .In whole cell assays, Acoziborole exhibits potent activity against representative T. b. brucei, T. b. rhodesiense and T. b. gambiense strains. IC_{50} values for Acoziborole are approximately 0.07 μg/mL to 0.37 μg/mL following incubation of the parasite strains with Acoziborole for 72 h. In the T. b. brucei S427 strain, the MIC value for Acoziborole is 0.6 μg/mL, approximately two times the IC_{50} measured for this strain. In contrast to the potent activity of Acoziborole against trypanosomes, no significant inhibition of cell proliferation is observed in an in vitro mammalian cell (L929 mouse cell line)

	assay at drug concentrations up to 50 μg/mL. The potential for Acoziborole to inhibit cytochrome P450 (CYP) enzymes is evaluated using P450-Glo assays for the human isoforms CYP3A4, CYP1A2, CYP2C19, CYP2C9 and CYP2D6. The IC_{50} values for Acoziborole in these assays are all above 10 μM[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	In uninfected mice, 4.3 mg/kg intravenous dose of Acoziborole show an apparent elimination half-life ($t_{1/2}$) of 26.6 h; systemic clearance (CL) of 0.089 L/h/kg; a volume of distribution (Vd_{ss}) of 1.69 L/kg and area under the concentration-time curve ($AUC_{0\text{-}24\ h}$) of 48 h•μg/mL. Following an oral dose of 13.4 mg/kg, which corresponds to the lowest efficacious dose in the murine stage 2 HAT model, Acoziborole is rapidly absorbed, as a C_{max} of 6.96 μg/mL is achieved in plasma at 6 h after dose, with an oral clearance (Cl/F) value of 0.163 L/h/kg, an $AUC_{0\text{-}24\ h}$ of 82 h•μg/mL and absolute oral bioavailability of 55%. After a 26 mg/kg oral dose, which corresponds to the dose giving a 100% cure rate in the murine stage 2 HAT model, C_{max} increases to 9.8 μg/mL and the $AUC_{0\text{-}24\ h}$ is 113 h•μg/mL. In uninfected rats, following oral administration of Acoziborole at a nominal dose of 25 mg/kg (dose affording a 100% cure rate in mice), C_{max} increases approximately 2 fold more than that in mice (C_{max}=18.2 μg/mL) and $AUC_{0\text{-}24\ h}$, and hence oral clearance, improves approximately 4 fold ($AUC_{0\text{-}24\ h}$ 291 h•μg/mL and CL/F=0.092 L/kg/h). The time to maximum concentration is similar to that in mice (t_{max}=8 h). Uninfected male and female cynomolgus monkeys are treated with Acoziborole at 2 mg/kg (IV) on study day 1 and 10 mg/kg (NG) on study day 8. Acoziborole exhibits excellent plasma pharmacokinetics, with CL of 0.022 L/h/kg; Vd_{ss} of 0.656 L/kg and area under the concentration-time curve 78.8 h•μg/mL, and 94.4 for $AUC_{0\text{-}24\ h}$ and $AUC_{0\text{-}inf}$, respectively, following intravenous administration[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Cell Assay [1]	Compounds (e.g., Acoziborole) to be tested are serially diluted in DMSO and added to 96-well plates to give final concentrations ranging from 5 to 0.01 μg/mL. T. b. brucei parasites in the log phase of growth are diluted in HMI-9 media and added to each well for a final concentration of 1×10^4 parasites per well. For the sensitivity assays using T. b. rhodesiense and T. b. gambiense, pararasites are cultured in MEM supplemented with Baltz components, diluted in the aforementioned culture media, and added to each well at a density of 1×10^3 cells/well. The final concentration of DMSO is 0.5% and the total volume is 100 μL/well. After 72 h incubation, Resazurin is added to each well (20 μL of 25 mg/100 mL stock in PBS) and incubated for an additional 4-6 h. To assess cell viability, fluorescence is quantified using an EnVision Multilabel Plate Reader at an excitation wavelength of 530 nm and emission of 590 nm. Triplicate data points are averaged to generate sigmoidal dose-response curves and determine IC_{50} values using XLfit curve fitting software. The IC_{50} is defined as the amount of compound required to decrease parasite or cell viability by 50% compared to those grown in the absence of the test compound. The MIC, defined as the lowest concentration of compound that completely inhibits visible parasite growth, is determined by visual inspection of 96-well plates after 48-72 h of incubation with the test compounds. To evaluate the effects of serum on trypanocidal activity, assays are performed in the presence of increasing concentration (2.5% to 50%) of fetal calf serum. The results are expressed as a fold-change in IC_{50} values relative to standard conditions (10% FCS) [1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1]	Mice, Rats and Monkeys[1] Male CD-1 mice (~25 g), male Sprague-Dawley rats (~225 g), or male cynomolgus monkeys (~3-5 kg) are administered test article by either bolus intravenous injection (IV) or oral gavage. Male CD-1 mice, Sprague-Dawley rats, cynomolgus monkeys or male beagle dogs are administered a single oral dose of Acoziborole at a dose of 25 mg/kg (mouse, rat) or 10 mg/kg (monkey, dog). Blood samples are collected and analyzed. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

REFERENCES

[1]. Jacobs RT, et al. SCYX-7158, an orally-active benzoxaborole for the treatment of stage 2 human African trypanosomiasis. PLoS Negl Trop Dis. 2011 Jun;5(6):e1151.

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

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