Cobicistat

Cat. No.: HY-10493

CAS No.: 1004316-88-4

Molecular Formula: $C_{40}H_{53}N_7O_5S_2$

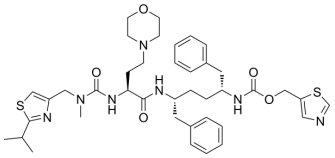
Molecular Weight: 776.02

Target: Cytochrome P450; HIV

Pathway: Metabolic Enzyme/Protease; Anti-infection

Storage:

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



SOLVENT & SOLUBILITY

In Vitro

DMSO : 250 mg/mL (322.16 mM; Need ultrasonic)

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	1.2886 mL	6.4431 mL	12.8863 mL
5 mM	0.2577 mL	1.2886 mL	2.5773 mL
10 mM	0.1289 mL	0.6443 mL	1.2886 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: ≥ 2.08 mg/mL (2.68 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.08 mg/mL (2.68 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.08 mg/mL (2.68 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Cobicistat is a potent and selective inhibitor of cytochrome P450 3A (CYP3A) enzymes with IC_{50}s of 30-285 nM. Cobicistat is a pharmacokinetic enhancer which increases the overall absorption of several HIV medications.

IC_{50} & Target

CYP3 HIV-1

In Vitro

In HIV-1 protease enzymatic assay and antiviral cellular assays. Cobicistat is inactive against HIV-1 protease (IC_{50}>30 μM) . And Cobicistat has no inhibitory effect against HIV replication in a multicycle 5-day MT-2 HIV infection assay (EC_{50}>30 μM). In

assays using MT-2 cells, Cobicistat exhibits minimal cytotoxicity, with a CC_{50} value above 80 μM[1].
The mode of inhibition of human CYP3A by Cobicistat and Ritonavir shares the same mechanism of action for the inhibition of CYP3A. It shows its inhibitory effects on CYP3A may involve directly at the heme group of the CYP3A enzyme[1].
The minimal adverse effects of Cobicistat in these assays suggest a lower potential for toxicity related to altered lipid metabolism.
In the lipid accumulation assay with the human adipocytes, Ritonavir shows a clear effect with an EC_{50} of 16 μM. However, Cobicistat exhibits no effect at a concentration up to 30 μM[1].
In the glucose uptake assay with mouse adipocytes, Ritonavir shows a pronounced effect at the concentration of 10 μM. In contrast, the effects on glucose uptake by Cobicistat (10 μM) is significantly less[1].
MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Kinase Assay [1]

Inhibition of human cytochrome P450 activities is determined in duplicate in pooled human hepatic microsomal fractions following current scientific and regulatory guidelines. Reaction conditions are linear with respect to incubation time and hepatic microsomal protein concentration. Substrates are present at concentrations equal to or less than their respective K_m values determined under the same reaction conditions. Metabolite and/or substrate concentrations are determined using specific, internal standard controlled HPLC MS/MS assays. For reactions monitoring metabolite formation there is less than 20% consumption of substrate during the reaction. Unless otherwise noted microsomal fraction, diluted in potassium phosphate buffer, is preincubated with substrate and inhibitor for 5 min at 37°C and the reaction initiated by the addition of an NADPH generating system followed by further incubation at 37°C with shaking. Enzyme-selective positive control inhibitors are tested in parallel. At appropriate times aliquots of the mixture are removed and the reaction terminated by addition to a mixture of methanol and acetonitrile containing the respective internal standard. After centrifugation aliquots of the supernatant are subjected to HPLC-MS/MS analysis.
MCE has not independently confirmed the accuracy of these methods. They are for reference only.

Cell Assay [1]

Five-fold serial dilutions of the tested compounds are prepared in triplicate in 96-well plates. MT-2 cells are added to plates at a density of 20,000/well in a final assay volume of 200 μL. After a 5-day incubation at 37°C, the cytotoxic effect is determined using a cell viability assay. One hundred μL media is removed from each well and replaced with 100 μL of phosphate-buffered saline containing 1.7 mg/mL XTT and 5 μg/mL PMS. Following 1-hour incubation at 37°C, 20 μL of 2% Triton X- 100 is added to each well and absorbance is read at 450 nm with a background subtraction at 650 nm. The data are plotted as cell viability vs. drug concentration. Cell viability is expressed as a percentage of the signal from untreated samples (0% cytotoxicity) after the subtraction of signal from samples treated with 10 μM of Podophyllotoxin (100% cytotoxicity). The CC_{50} value is calculated from the inhibition plots as the concentration of drug which inhibits cell proliferation by 50%.
MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Acta Pharm Sin B. 2021 Mar 22.
- Acta Pharm Sin B. 2020 Aug.
- Eur J Med Chem. 2020 Oct 15;204:112626.
- Eur J Med Chem. 2020 Aug 15;200:112427.
- Viruses. 2020 Apr 16;12(4):452.

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REFERENCES

[1]. Lianhong Xu, et al. Cobicistat (GS-9350): A Potent and Selective Inhibitor of Human CYP3A as a Novel Pharmacoenhancer. ACS Med. Chem. Lett., 2010, 1 (5), pp 209–213

[2]. Temesgen Z. Cobicistat, a pharmacoenhancer for HIV treatments. Drugs Today (Barc). 2013 Apr;49(4):233-7.

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