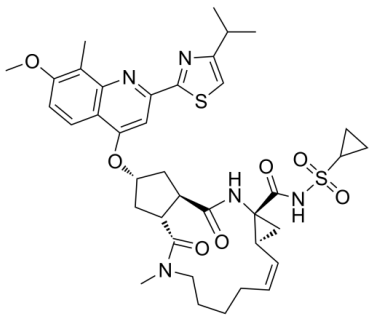
Data Sheet

Product Name:	Simeprevir
Cat. No.:	CS-0338
CAS No.:	923604-59-5
Molecular Formula:	$C_{38}H_{47}N_5O_7S_2$
Molecular Weight:	749.94
Target:	DNA/RNA Synthesis; HCV; HCV Protease; SARS-CoV
Pathway:	Anti-infection; Cell Cycle/DNA Damage; Metabolic Enzyme/Protease
Solubility:	DMSO : 14.29 mg/mL (ultrasonic)



BIOLOGICAL ACTIVITY:

Simeprevir (TMC435; TMC435350) is an oral, potent and highly specific **hepatitis C virus (HCV) NS3/4A protease** inhibitor with a **K_i** of 0.36 nM. Simeprevir inhibits HCV replication with an **EC_{50}** of 7.8 nM. Simeprevir also potently suppresses **SARS-CoV-2** replication and synergizes with Remdesivir. Simeprevir inhibits the main protease (M^{pro}) and the RNA-dependent RNA polymerase (RdRp) of SARS-CoV-2, and also modulates host immune responses[1][4]. IC50 & Target: K_i: 0.36 nM (HCV NS3/4A protease)[1]

EC_{50}: 7.8 nM (HCV replication)[1]

IC_{50}: 9.6±2.3 μM (SARS-CoV-2 M^{pro}), 5.5±0.2 μM (SARS-CoV-2 RdRp)[4] ***In Vitro:*** Simeprevir (TMC435) inhibits HCV in a dose-dependent manner in Huh7-Luc cells, with EC_{50} and EC_{90} values of 8 nM and 24 nM, respectively[2].

Simeprevir (TMC435) inhibits NS3/4A proteases from HCV genotypes 1 to 6 with IC_{50}s of 1/0.9/7/30/1.5/2.2/1.6 nM for 1a/1b/2b/3a/4/5/6, respectively[3].

Simeprevir inhibits SARS-CoV-2 in Vero E6 cells with IC_{50}s of 9.6±2.3 μM and 5.5±0.2 μM for M^{pro} and RdRp, respectively[4]. ***In Vivo:*** Simeprevir (TMC435) has moderate terminal elimination half-life ($t_{1/2}$=1.5 h and 4.1 h for rat (3 mg/kg, p.o.), monkey (3 mg/kg, p.o.))[3].

Simeprevir (TMC435350) exhibits a medium-slow rate of absorption, well distribution with the high concentration observed in the liver, and a low clearance[1].

Pharmacokinetic Parameters of Simeprevir (TMC435350) in male Sprague-Dawley rats[1].

	IV (2 mg/kg)	PO (10 mg/kg)
CL (L/h/kg)	0.505	
Vd_{ss} (h)	0.49	
AUC_{0-24} (μM·h)	5.21	2.79
C_{max} (μM)		0.73
T_{max} (h)		3.0

$T_{1/2}$ (h)		2.8
F (%)		11
Liver/plasma ratio at 6 h	63.5	32

PROTOCOL (Extracted from published papers and Only for reference)

Kinase Assay: [1]In vitro inhibition of NS3/4A activity is determined using a fluorescence resonance energy transfer cleavage assay with the RetS1 peptide substrate, derived from the genotype 1a NS4A-4B junction, and bacterially expressed full-length NS3 protease domain, supplemented with an NS4A peptide. Briefly, NS3/4A is preincubated in the presence of TMC435350 for 10 min, and then the RetS1 substrate is added and fluorescence is continuously measured for 20 min (excitation, 355 nm; emission, 500 nm). Cleavage of the substrate is expressed as a percentage of the cleavage seen with the vehicle control. **Cell Assay:** Simeprevir is diluted in in a final DMSO concentration of 0.5% in the absence of G418.[1]Huh7-Luc cells are seeded at a density of 2,500 cells/well in a 384-well plate in Dulbecco's modified Eagle's medium plus 10% fetal calf serum and incubated with a range of concentrations of serially diluted simeprevir (TMC435350), in a final DMSO concentration of 0.5% in the absence of G418. After 72 h of incubation, Steady Lite reagent is added in a 1:1 ratio to the medium, and luciferase signal is measured using a ViewLux reader. **Animal Administration:** [1]Twenty-four male specific-pathogen-free Sprague-Dawley rats, weighing between 200 and 300 g at the time of dosing, are divided into eight groups of three rats each. Seven groups are dosed orally (p.o.) by gastric intubation of a vitamin E acetate-d-α-tocopheryl polyethylene glycol 1000 succinate-polyethylene glycol 400 solution of Simeprevir (TMC435350) at 2 mL/kg body weight to provide a dose of 40 mg/kg. One group is dosed intravenously (i.v.) by slow bolus injection in a tail vein of a 20% 2-hydroxypropyl-β-cyclodextrin formulation of TMC435350 (containing TMC435350, 100 mg/mL 2-hydroxypropyl-β-cyclodextrin, 0.1 N NaOH to pH 8.0±0.1, and mannitol-and pyrogen-free water) at 2 mL/kg body weight to provide a dose of 4 mg/kg. Water and food are available ad libitum during the study.

References:

[1]. Raboisson P, et al. Structure-activity relationship study on a novel series of cyclopentane-containing macrocyclic inhibitors of the hepatitis C virus NS3/4A protease leading to the discovery of TMC435350. Bioorg Med Chem Lett. 2008 Sep 1;18(17):4853-8.

[2]. Lin TI, et al. In vitro activity and preclinical profile of TMC435350, a potent hepatitis C virus protease inhibitor.Antimicrob Agents Chemother. 2009 Apr;53(4):1377-85. Epub 2009 Jan 26.

[3]. Rajagopalan R, et al. Preclinical Characterization and Human Microdose Pharmacokinetics of ITMN-8187, a Nonmacrocyclic Inhibitor of the Hepatitis C Virus NS3 Protease. Antimicrob Agents Chemother. 2016 Dec 27;61(1). pii: e01569-16.

[4]. Lo HS, et al. Simeprevir Potently Suppresses SARS-CoV-2 Replication and Synergizes with Remdesivir. ACS Cent Sci. 2021 May 26;7(5):792-802.

CAIndexNames:

Cyclopenta[c]cyclopropa[g][1,6]diazacyclotetradecine-12a(1H)-carboxamide, N-(cyclopropylsulfonyl)-2,3,3a,4,5,6,7,8,9,11a,12,13,14,14a-tetradecahydro-2-[[7-methoxy-8-methyl-2-[4-(1-methylethyl)-2-thiazolyl]-4-quinolinyl]oxy]-5-methyl-4,14-dioxo-, (2R,3aR,10Z,11aS,12aR,14aR)-

SMILES:

COC1=C(C)C2=C(C(O[C@H]3C[C@@H](C(N(C)CCCC/C=C\[C@H](C4)[C@]4(C(NS(=O)(C5CC5)=O)=O)N6)=O)[C@H](C6=O)C3)=CC(C7=NC(C(C)C)=CS7)=N2)C=C1

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