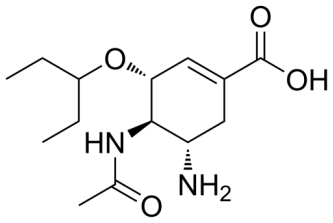
Data Sheet

Product Name:	Oseltamivir (acid)
Cat. No.:	CS-0553
CAS No.:	187227-45-8
Molecular Formula:	$C_{14}H_{24}N_2O_4$
Molecular Weight:	284.35
Target:	Influenza Virus
Pathway:	Anti-infection
Solubility:	H_2O: ≥ 56 mg/mL



BIOLOGICAL ACTIVITY:

Oseltamivir acid is an active metabolite of Oseltamivir, which is a potent and selective inhibitor of **influenza A** and **B** virus neuraminidases.

IC50 & Target: Influenza A and B[1]

In Vitro: Oseltamivir acid inhibits virus replication in vitro and in vivo. Influenza B and A/H1N1 viruses appeare to be sensitive to Oseltamivir (mean B IC_{50} value: 13 nM; mean H1N1 IC_{50} value: 1.34 nM), while A/H1N2 and A/H3N2 viruses are more sensitive to Oseltamivir (mean H3N2 IC_{50} value: 0.67 nM; mean H1N2 IC_{50} value: 0.9 nM)[1]. In neuraminidases inhibition assays with influenza A viruses, the median 50% inhibitory concentration (IC_{50}) of RWJ-270201 (approximately 0.34 nM) is comparable to that of Oseltamivir carboxylate (0.45 nM) For influenza B virus isolates, the IC_{50} of RWJ-270201 (1.36 nM) is comparable to that of Zanamivir (2.7 nM) and less than that of Oseltamivir carboxylate (8.5 nM)[2].

In Vivo: Oseltamivir (0.1, 1, or 10 mg/kg/day, twice daily by oral gavage) produces a dose-dependent antiviral effect against Vietnam/1203/04 (VN1203/04) virus. The 5-day regimen at 10 mg/kg/day protects 50% of mice; deaths in this treatment group are delayed and indicated the replication of residual virus after the completion of treatment. Eight-day regimens improved Oseltamivir efficacy, and dosages of 1 and 10 mg/kg/day significantly reduced virus titers in organs and provided 60% and 80% survival rates, respectively[3]. In the pharmacokinetic study, after the oral administration of 1,000 mg/kg Oseltamivir, peak plasma concentrations are reached at 2 h postdose for Oseltamivir and 8 h for Oseltamivir carboxylate (OC). Rats are exposed to Oseltamivir over the whole sampling interval and had a ~2.7-fold-higher rate of exposure to OC than Oseltamivir. In CSF, peak concentrations are reached at 2 h postdose for Oseltamivir and 6 h for OC. CSF/plasma exposure ratios ($AUC_{0\text{-}8\ h}$) are ~0.07 for Oseltamivir and 0.007 for OC. In perfused brain samples, peak concentrations are reached at 8 h postdose for Oseltamivir and 6 h for OC. Brain/plasma exposure ratios ($AUC_{0\text{-}8\ h}$) of ~0.12 for Oseltamivir and 0.01 for OC are recorded. Corresponding CSF/brain exposure ratios ranged between ~0.55 and 0.64 for both analytes. A further group of animals that received a single oral administration of Oseltamivir at a lower dose produced similar results[4].

PROTOCOL (Extracted from published papers and Only for reference)

Animal Administration: Oseltamivir is dissolved in sterile PBS (Mice)[3].[3][4]Mice[3]

Female 6-week-old BALB/c mice are anesthetized with isofluorane and intranasally inoculated with 50 µL of 10-fold serial dilutions of VN1203/04 virus in PBS. The mouse lethal dose (MLD_{50}) is calculated after a 16-day observation period. Oseltamivir is administered by oral gavage twice daily for 5 or 8 days to groups of 10 mice at dosages of 0.1, 1, and 10 mg/kg/day. Control (infected but untreated) mice received sterile PBS (placebo) on the same schedule. Four hours after the first dose of Oseltamivir, the mice are inoculated intranasally with 5 MLD_{50} of VN1203/04 virus in 50 µL of PBS. Survival and weight change are observed for 24 days. Virus titers in the

mouse organs are determined on days 3, 6, and 9 after inoculation. Three mice from each experimental and placebo group are killed, and the lungs and brains are removed. The organs are homogenized and suspended in 1 mL of PBS. The cellular debris is cleared by centrifugation at 2000 g for 5 min. The limit of virus detection is 0.75 $\log_{10}$ EID_{50}. For calculation of the mean, samples with a virus titer <0.75 $\log_{10}$ EID_{50}/mL are assigned a value of 0. Virus titers in each organ are calculated by use of the method of Reed and Muench and are expressed as mean $\log_{10}$ EID_{50}/mL±SE.

Rats[4]

Several studies are performed to characterize the pharmacokinetics of Oseltamivir and OC in the plasma, cerebrospinal fluid (CSF), and brain of Sprague-Dawley rats following single-dose bolus administration of Oseltamivir (intravenous [i.v.] and oral) and OC (i.v.). In the i.v. studies, nonfasted adult rats (two groups of 35 animals for each test substance) received a dose of 30 mg/kg body weight of either Oseltamivir or Oseltamivir carboxylate (OC) in aqueous solution with sodium chloride (0.9%; pH 4.0) via slow injection into the tail vein over 20 to 30 s. In both i.v. studies, pharmacokinetic sampling took place at 5 min and at 0.25, 0.5, 1, 2, 4, and 8 h postdose (four or five rats/time point).

References:

[1]. Ferraris O, et al. Sensitivity of influenza viruses to zanamivir and oseltamivir: a study performed on viruses circulating in France prior to the introduction of neuraminidase inhibitors in clinical practice. Antiviral Res. 2005 Oct;68(1):43-8.

[2]. Gubareva LV, et al. Comparison of the activities of zanamivir, oseltamivir, and RWJ-270201 against clinical isolates of influenza virus and neuraminidase inhibitor-resistant variants.Antimicrob Agents Chemother. 2001 Dec;45(12):3403-8.

[3]. Yen HL, et al. Virulence may determine the necessary duration and dosage of oseltamivir treatment for highly pathogenic A/Vietnam/1203/04 influenza virus in mice. J Infect Dis. 2005 Aug 15;192(4):665-72.

[4]. Hoffmann G, et al. Nonclinical pharmacokinetics of oseltamivir and oseltamivir carboxylate in the central nervous system. Antimicrob Agents Chemother. 2009 Nov;53(11):4753-61.

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