Efavirenz

Cat. No.: HY-10572
CAS No.: 154598-52-4
Molecular Formula: C₁₄H₉ClF₃NO₂
Molecular Weight: 315.68
Target: Reverse Transcriptase; HIV; Autophagy
Pathway: Anti-infection; Autophagy
Storage: Powder
-20°C 3 years
-4°C 2 years
In solvent
−80°C 6 months
−20°C 1 month

SOLVENT & SOLUBILITY

<table>
<thead>
<tr>
<th>Preparing Stock Solutions</th>
<th>Solvent Mass</th>
<th>1 mg</th>
<th>5 mg</th>
<th>10 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<tr>
<td>DMSO</td>
<td>≥ 38 mg/mL (120.38 mM)</td>
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</tbody>
</table>

* "≥" means soluble, but saturation unknown.

In Vivo
1. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: ≥ 2.5 mg/mL (7.92 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (7.92 mM); Clear solution

BIOLOGICAL ACTIVITY

Description
Efavirenz is a potent inhibitor of the wild-type HIV-1 reverse transcriptase with a Ki of 2.93 nM and exhibits an IC₉₅ of 1.5 nM for the inhibition of HIV-1 replicative spread in cell culture.

IC₉₅ & Target
Ki: 2.93 nM (HIV-1 RT)[¹]

In Vitro
Efavirenz (L-743726) is found to be capable of inhibiting, with 95% inhibitory concentrations of ≤ 1.5 μM, a panel of nonnucleoside reverse transcriptase (RT) inhibitors (NNRTIs)-resistant mutant viruses, each of which expresses a single RT amino acid substitution. Efavirenz is also tested for its activity against a variety of polymerase enzymes and
is found to be inactive (IC₅₀ > 300 μM). Efavirenz effectively inhibits several wild-type T-lymphoid cell line-adapted variants. Identical activity (IC₉₅, 1.5 to 3.0 nM) is seen with wild-type primary isolates of the virus in both primary lymphoid and monocytoid cell cultures. Efavirenz also effectively inhibits HIV-1 variants that expressed RT amino acid substitutions which confer the loss of susceptibility to other NNRTIs. For purposes of comparison[1]. Efavirenz is a non-nucleoside analog reverse transcriptase inhibitor (NNRTI) with IC₅₀ of 60 nM[2]. Efavirenz inhibits synthesis using an RNA PPT-primed substrate with an IC₅₀ of 17 nM[3].

| In Vivo | After i.v. administration, Efavirenz (L-743726) is cleared rapidly from rats, but it is cleared considerably more slowly from monkeys. The large volume of distribution (two to four times the amount of body water) in both species indicates extensive tissue binding. The oral bioavailability in rats is 16%. In monkeys, the half-life of Efavirenz after administration of a 1 mg/kg i.v. dose exceeded 2.5 h. Efavirenz is well absorbed orally. Administration to monkeys of oral doses as fine suspensions in 0.5% aqueous methylcellulose yields consistently high levels in plasma. A 2.0 mg/kg dose produces peak levels of 0.5 μM at approximately 3.0 h. The absolute bioavailability is estimated to be 42%. A 10 mg/kg dose yields a peak level in plasma of 3.22 μM. A 10 mg/kg oral dose given to a single chimpanzee gave concentrations in plasma of 4.12, 2.95, and 2.69 μM at 2, 8, and 24 h after dosing, respectively[1]. |
| PROTOCOL | Recombinant RT enzymes are expressed, purified, and assessed for inhibition by Efavirenz (L-743726). Kᵢ and Kᵢᵢ values are determined for each enzyme tested. The wild-type RT exhibited exclusively noncompetitive inhibition kinetics (data not shown), and, therefore, the Kᵢ and Kᵢᵢ values are identical. Pure noncompetitive inhibition is not assumed for the mutant enzymes, and, hence, the values of both Kᵢ and Kᵢᵢ are obtained from the linear mixed-type inhibition equation. The two- to threefold differences between the Kᵢ and Kᵢᵢ values probably reflect a small contribution of competitive inhibition with the mutant RTs[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only. |
| Animal Administration [1] | Mice[1] Studies are performed in rats, rhesus monkeys, and a single chimpanzee. For analyses of the drug given to rats intravenously (i.v.), a group (n=4 or 5) of fasted male Sprague-Dawley rats (weight, 250 to 450 g) receive a bolus (at a volume of 1 mL/kg of body weight) of Efavirenz in DMSO via a cannula implanted in the right jugular vein. For oral studies, rats are dosed by gavage by using a suspension of Efavirenz prepared in 0.5% aqueous methylcellulose. Similarly, four monkeys receive either an i.v. bolus of the compound in DMSO via the saphenous vein at a volume of 0.1 mL/kg or are administered the compound orally in suspension by using a nasogastric tube. Monkeys are fasted for 18 h prior to dosing. One nonanesthetized, nonfasted male chimpanzee (weight, approximately 60 kg) is dosed orally by voluntary ingestion by using an aqueous suspension of the compound. In all studies, heparinized blood is obtained at appropriate times. Plasma is separated immediately by centrifugation and is stored at -20°C until analysis. Plasma samples are extracted with methylene chloride; this is followed by analysis by high-performance liquid chromatography. MCE has not independently confirmed the accuracy of these methods. They are for reference only. |

CUSTOMER VALIDATION

- Faculty of Pharmacy in Hradec Králové Department of Pharmacological and Toxicology. University of Oxford. 2019 Jul.

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Tel: 609-228-6898 Fax: 609-228-5909 E-mail: tech@MedChemExpress.com
Address: 1 Deer Park Dr, Suite Q, Monmouth Junction, NJ 08852, USA