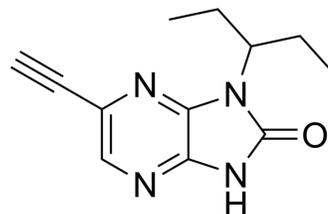


## Tirasemtiv

<b>Cat. No.:</b>	HY-15964		
<b>CAS No.:</b>	1005491-05-3		
<b>Molecular Formula:</b>	C <sub>12</sub> H <sub>14</sub> N <sub>4</sub> O		
<b>Molecular Weight:</b>	230.27		
<b>Target:</b>	Others		
<b>Pathway:</b>	Others		
<b>Storage:</b>	Powder	-20°C	3 years
		4°C	2 years
	In solvent	-80°C	2 years
		-20°C	1 year



### SOLVENT & SOLUBILITY

<b>In Vitro</b>	DMSO : 10.91 mg/mL (47.38 mM; Need ultrasonic)				
		Solvent Concentration	Mass 1 mg	5 mg	10 mg
	<b>Preparing Stock Solutions</b>	1 mM	4.3427 mL	21.7136 mL	43.4273 mL
		5 mM	0.8685 mL	4.3427 mL	8.6855 mL
10 mM		0.4343 mL	2.1714 mL	4.3427 mL	
Please refer to the solubility information to select the appropriate solvent.					
<b>In Vivo</b>	<ol style="list-style-type: none"> <li>Add each solvent one by one: 10% DMSO &gt;&gt; 40% PEG300 &gt;&gt; 5% Tween-80 &gt;&gt; 45% saline Solubility: ≥ 1.09 mg/mL (4.73 mM); Clear solution</li> <li>Add each solvent one by one: 10% DMSO &gt;&gt; 90% (20% SBE-β-CD in saline) Solubility: ≥ 1.09 mg/mL (4.73 mM); Clear solution</li> <li>Add each solvent one by one: 10% DMSO &gt;&gt; 90% corn oil Solubility: ≥ 1.09 mg/mL (4.73 mM); Clear solution</li> </ol>				

### BIOLOGICAL ACTIVITY

<b>Description</b>	Tirasemtiv is an activator of the fast skeletal muscle troponin complex. Tirasemtiv is a click chemistry reagent, it contains an Alkyne group and can undergo copper-catalyzed azide-alkyne cycloaddition (CuAAC) with molecules containing Azide groups.
<b>IC<sub>50</sub> &amp; Target</b>	Troponin <sup>[1]</sup>
<b>In Vitro</b>	Tirasemtiv is a fast skeletal troponin activator that sensitizes the sarcomere to calcium; this mechanism of action amplifies

the response of muscle to neuromuscular input producing greater force when nerve input is reduced. Tirasemtiv selectively sensitizes fast skeletal muscle troponin to calcium ( $\text{Ca}^{2+}$ ), and slows the rate of  $\text{Ca}^{2+}$  release from the regulatory troponin complex of fast skeletal muscle<sup>[1]</sup>.

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

#### In Vivo

A single dose of Tirasemtiv significantly increases submaximal isometric force, forelimb grip strength, grid hang time, and rotarod performance in a female transgenic mouse model (B6SJL-SOD1<sup>G93A</sup>) of ALS with functional deficits. Additionally, diaphragm force and tidal volume are significantly higher in Tirasemtiv-treated female B6SJL-SOD1<sup>G93A</sup> mice. At the 25% deficit milestone, vehicle-treated B6SJL-SOD1<sup>G93A</sup> mice demonstrated forelimb grip strength of 49.6±4.6 g. Tirasemtiv increases grip strength by 38% to 68.6±8.1g ( $p < 0.05$ , single tailed t-test). Tirasemtiv doses of 2, 2, 2, and 4 mg/kg given at approximately 20 min intervals to achieve a cumulative dose of 10 mg/kg. Regression analysis of the log dose vs. response relationship indicated that Tirasemtiv significantly increased muscle force in WT and mid-stage B6SJL-SOD1<sup>G93A</sup> mice (WT  $p < 0.0001$ ; mid-stage  $p = 0.0028$ ). At later stages of disease, the mice exhibited a trend for increased muscle function in response to Tirasemtiv compared to baseline ( $p = 0.064$ )<sup>[1]</sup>.

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## PROTOCOL

#### Animal Administration<sup>[1]</sup>

Mice<sup>[1]</sup>

Wild-type background strain B6SJL/J mice and B6SJL-SOD1<sup>G93A</sup> mice over-expressing the human SOD-1 gene with mutation G93A are group-housed in a 12-hour light cycle and fed standard chow and water ad libitum. Tirasemtiv is administered in solution (50% PEG300/10% EtOH/40% Cavitron cyclodextrin formulation) as a single slow bolus over a 2 minute period via a catheter in the contralateral femoral artery placed above the aortic bifurcation. Tirasemtiv bolus injections (2, 2, 2, and 4 mg/kg) are given at approximately 20 min intervals to achieve a cumulative dose of 10 mg/kg in order to assess the dose response, with a maximal dosage volume of 5 mL/kg. At the end of each experiment, a single terminal blood sample is drawn via cardiac puncture for compound concentration analysis.

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

## REFERENCES

[1]. Hwee DT, et al. Fast skeletal muscle troponin activator tirasemtiv increases muscle function and performance in the B6SJL-SOD1G93A ALS mouse model. PLoS One. 2014 May 7;9(5):e96921.

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

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