产品名称：**N-Desmethyl Clozapine**
产品别名：**N-去甲基氯氮平**

生物活性：	
Description	N-Desmethylclozapine is a major active metabolite of the atypical antipsychotic drug Clozapine. N-Desmethylclozapine is a potent, allosteric and partial M1 receptors agonist (EC50=115 nM) and is able to potentiate hippocampal N-methyl-d-aspartate (NMDA) receptor currents through M1 receptor activation. N-Desmethylclozapine is also a δ-opioid agonist[1][2].
IC_{50} & Target	EC50: 115 nM (M1 receptors)[1] δ -opioid[2]
In Vitro	The brain penetrant metabolite N-desmethylclozapine preferentially bound to M1 muscarinic receptors with an IC50 of 55 nM and was a more potent partial agonist (EC50, 115 nM and 50% of acetylcholine response) at this receptor than clozapine[1]. N-desmethylclozapine exhibits slight agonistic effects on the M1 mAChR, and agonistic properties at the 5-HT1A receptor in the cerebral cortex and hippocampus. This compound also behaves as an agonist at the δ-opioid receptor in the cerebral cortex and striatum[2]. N-desmethylclozapine (3 μM) greatly decreases the outward current in excitatory neurons, but not in inhibitory neurons. In excitatory neurons, N-desmethylclozapine alone is more effective than either clozapine alone or the combination of clozapine and N-desmethylclozapine. The effect of N-desmethylclozapine in excitatory neurons is significantly suppressed by 0.1 μM pirenzepine and 1 μM atropine. N-desmethylclozapine, but not clozapine, suppressed K+ channels via M1 receptors in excitatory cells[3]. N-desmethylclozapine leads to a decrease in TxB2 levels under unstimulated conditions as well as under TSST-1 stimulation. Clozapine, N-desmethylclozapine and CPZ possibly act on neurotransmitter systems via modulation of TxA2 or TxB2 production[5]. The IC50s of N-desmethylclozapine, fluoxetine hydrochloride, and salmeterol xinafoate in Huh-7 cells infected with DENV-2 are 1 μM, 0.38 μM, and 0.67 μM, respectively. The levels of NS3 are reduced in cells treated with all three inhibitors compared to DMSO treatment, suggesting that the inhibitors act at a stage prior to viral protein translation. N-Desmethylclozapine-treated cells show a >75% reduction in negative-strand RNA levels[6].
In Vivo	N-desmethylclozapine in rat and human at M2 and M4 mAChRs underlying presynaptic modulation of GABA and glutamate release, respectively. In particular, N-desmethylclozapine maybe a M2 mAChR antagonist in the rat but has no activity at this receptor in human neocortex. However, N-desmethylclozapine has an agonistic effect at M4 mAChR in the human but no such effect in the rat neocortex[4].

In Vitro:

DMSO : ≥ 50 mg/mL (159.85 mM)

* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions	Solvent / Mass / Concentration	**1 mg**	**5 mg**	**10 mg**
	1 mM	3.1969 mL	15.9847 mL	31.9693 mL
	5 mM	0.6394 mL	3.1969 mL	6.3939 mL
	10 mM	0.3197 mL	1.5985 mL	3.1969 mL

*请根据产品在不同溶剂中的溶解度选择合适的溶剂配制储备液；一旦配成溶液，请分装保存，避免反

Solvent&Solubility	复冻融造成的产品失效。 储备液的保存方式和期限：-80°C, 6 months; -20°C, 1 month。 -80°C 储存时，请在 6 个月内使用，-20°C 储存时，请在 1 个月内使用。 ***In Vivo:*** 请根据您的实验动物和给药方式选择适当的溶解方案。以下溶解方案都请先按照 **In Vitro** 方式配制澄清的储备液，再依次添加助溶剂： ——为保证实验结果的可靠性，澄清的储备液可以根据储存条件，适当保存；体内实验的工作液，建议您现用现配，当天使用； 以下溶剂前显示的百分比是指该溶剂在您配制终溶液中的体积占比；如在配制过程中出现沉淀、析出现象，可以通过加热和/或超声的方式助溶 1.请依序添加每种溶剂： 10% DMSO→40% PEG300 →5% Tween-80 → 45% saline Solubility: ≥ 2.5 mg/mL (7.99 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (7.99 mM，饱和度未知) 的澄清溶液。 以 1 mL 工作液为例，取 100 μL 25.0 mg/mL 的澄清 DMSO 储备液加到 400 μL PEG300 中，混合均匀；向上述体系中加入 50 μL Tween-80，混合均匀；然后继续加入 450 μL 生理盐水定容至 1 mL。 2.请依序添加每种溶剂： 10% DMSO→ 90% (20% SBE-β-CD in saline) Solubility: ≥ 2.5 mg/mL (7.99 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (7.99 mM，饱和度未知) 的澄清溶液。 以 1 mL 工作液为例，取 100 μL 25.0 mg/mL 的澄清 DMSO 储备液加到 900 μL 20% 的 SBE-β-CD 生理盐水水溶液中，混合均匀。
References	[1]. Li Z, et al. N-desmethylclozapine, a major metabolite of clozapine, increases cortical acetylcholine and dopamine release in vivo via stimulation of M1 muscarinic receptors. Neuropsychopharmacology. 2005 Nov;30(11):1986-95. [2]. Odagaki Y, et al. Comparative analysis of pharmacological properties of xanomeline and N-desmethylclozapine in rat brain membranes. J Psychopharmacol. 2016 Sep;30(9):896-912 [3]. Sugawara Y, et al. Electrophysiological evidence showing muscarinic agonist-antagonist activities of N-desmethylclozapine using hippocampal excitatory and inhibitory neurons. Brain Res. 2016 Jul 1;1642:255-62 [4]. Gigout S, et al. Different pharmacology of N-desmethylclozapine at human and rat M2 and M 4 mAChRs in neocortex. Naunyn Schmiedebergs Arch Pharmacol. 2015 May;388(5):487-96 [5]. Himmerich H, et al. Impact of clozapine, N-desmethylclozapine and chlorpromazine on thromboxane production in vitro. Med Chem. 2012 Nov;8(6):1032-8. [6]. Medigeshi GR, et al. N-Desmethylclozapine, Fluoxetine and Salmeterol inhibit post-entry stages of dengue virus life-cycle. Antimicrob Agents Chemother. 2016 Aug 29.