N-Desmethylclozapine

Cat. No.: HY-G0021

CAS No.: 6104-71-8

Molecular Formula: $C_{17}H_{17}ClN_4$

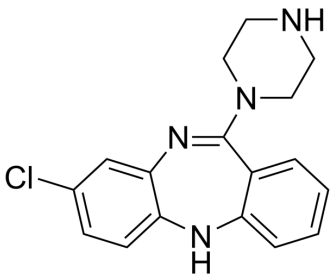
Molecular Weight: 312.8

Target: mAChR; Opioid Receptor; Drug Metabolite; Virus Protease

Pathway: GPCR/G Protein; Neuronal Signaling; Metabolic Enzyme/Protease; Anti-infection

Storage:

Powder	-20°C	3 years
	4°C	2 years
In solvent	-80°C	6 months
	-20°C	1 month



SOLVENT & SOLUBILITY

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

Please refer to the solubility information to select the appropriate solvent.

In Vivo

1. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: ≥ 2.5 mg/mL (7.99 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.5 mg/mL (7.99 mM); Clear solution

BIOLOGICAL ACTIVITY

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 (EC_{50}=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		
	mAChR1	δ Opioid Receptor/DOR

In Vitro

The brain penetrant metabolite N-desmethylclozapine preferentially bound to M1 muscarinic receptors with an IC_{50} of 55 nM and was a more potent partial agonist (EC_{50}, 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 IC_{50}s 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]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
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]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

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.

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

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