## N-Desmethylclozapine

**Cat. No.:** HY-G0021  
**CAS No.:** 6104-71-8  
**Molecular Formula:** C₁₇H₁₇ClN₄  
**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 for 3 years, 4°C for 2 years, -80°C for 6 months, -20°C for 1 month  
- 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.

<table>
<thead>
<tr>
<th>Solvent Concentration</th>
<th>Mass 1 mg</th>
<th>Mass 5 mg</th>
<th>Mass 10 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 mM</td>
<td>3.1969 mL</td>
<td>15.9847 mL</td>
<td>31.9693 mL</td>
</tr>
<tr>
<td>5 mM</td>
<td>0.6394 mL</td>
<td>3.1969 mL</td>
<td>6.3939 mL</td>
</tr>
<tr>
<td>10 mM</td>
<td>0.3197 mL</td>
<td>1.5985 mL</td>
<td>3.1969 mL</td>
</tr>
</tbody>
</table>

Preparing Stock Solutions

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 (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]

**IC₅₀ & 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.
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\[6\].

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

<table>
<thead>
<tr>
<th>In Vivo</th>
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| 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\[4\].

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REFERENCES


