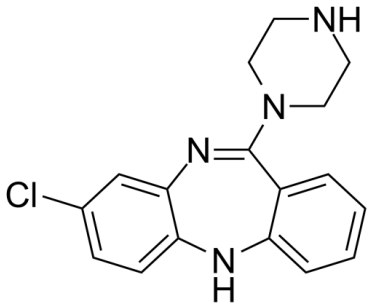
Data Sheet

Product Name:	N-Desmethylclozapine
Cat. No.:	CS-6103
CAS No.:	6104-71-8
Molecular Formula:	$C_{17}H_{17}ClN_4$
Molecular Weight:	312.80
Target:	Drug Metabolite; mAChR; Opioid Receptor; Virus Protease
Pathway:	Anti-infection; GPCR/G Protein; Metabolic Enzyme/Protease; Neuronal Signaling
Solubility:	DMSO : ≥ 50 mg/mL (159.85 mM)



BIOLOGICAL ACTIVITY:

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]. 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 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]. **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].

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.

CAIndexNames:

5H-Dibenzo[b,e][1,4]diazepine, 8-chloro-11-(1-piperazinyl)-

SMILES:

ClC1=CC=C2C(N=C(N3CCNCC3)C4=CC=CC=C4N2)=C1

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