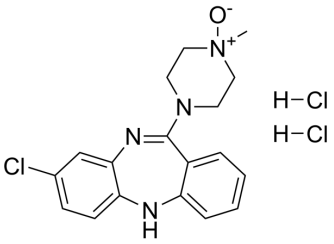
Clozapine N-oxide dihydrochloride

Cat. No.:	HY-17366A
CAS No.:	2250025-93-3
Molecular Formula:	$C_{18}H_{21}Cl_3N_4O$
Molecular Weight:	415.74
Target:	mAChR; Dopamine Receptor; Drug Metabolite
Pathway:	GPCR/G Protein; Neuronal Signaling; Metabolic Enzyme/Protease
Storage:	4°C, stored under nitrogen * In solvent : -80°C, 1 year; -20°C, 6 months (stored under nitrogen)



SOLVENT & SOLUBILITY

In Vitro

DMSO : 240 mg/mL (577.28 mM; Need ultrasonic)
H_2O : 100 mg/mL (240.53 mM; Need ultrasonic)

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	2.4053 mL	12.0267 mL	24.0535 mL
5 mM	0.4811 mL	2.4053 mL	4.8107 mL
10 mM	0.2405 mL	1.2027 mL	2.4053 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: ≥ 6 mg/mL (14.43 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 6 mg/mL (14.43 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Clozapine N-oxide dihydrochloride is a major metabolite of Clozapine and a human muscarinic designer receptors (DREADDs) agonist. Clozapine N-oxide dihydrochloride activates the DREADD receptor hM3Dq and hM4Di. Clozapine N-oxide dihydrochloride can cross the blood-brain barrier[1][2][3][4]. Clozapine is a potent dopamine antagonist and also a potent and selective muscarinic M4 receptor (EC_{50}=11 nM) agonist[5][6].

IC_{50} & Target	mAChR3	mAChR4

In Vitro

Clozapine N-oxide (CNO) can bind to non-DREADD receptors at concentrations required for DREADD activation, and undergoes reverse-metabolism to its parent compound clozapine, an atypical antipsychotic that acts at a variety of pharmacological targets and produces numerous physiological and behavioral effects[2].

	MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	After a single intraperitoneal (i.p.) injection of Clozapine N-oxide (1 mg/kg) into mice, Clozapine N-oxide (CNO) plasma levels peak at 15 min and are very low after 2 h. Despite the short plasma half-life of CNO in mice, the biological effects that have been described after acute treatment of DREADD-expressing experimental animals are usually much longer (6-10 h)[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Cell Metab. 2022 Feb 1;34(2):285-298.e7.
- Nat Neurosci. 2023 Apr;26(4):542-554.
- Nat Commun. 2023 Apr 17;14(1):2182.
- Nat Commun. 2022 Apr 25;13(1):2233.
- Nat Commun. 2020 Nov 27;11(1):6045.

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REFERENCES

[1]. Wess J, et al. Novel designer receptors to probe GPCR signaling and physiology. Trends Pharmacol Sci. 2013 Jul;34(7):385-92.

[2]. Manvich DF, et al. The DREADD agonist clozapine N-oxide (CNO) is reverse-metabolized to clozapine and produces clozapine-like interoceptive stimulus effects in rats and mice. Sci Rep. 2018 Mar 1;8(1):3840.

[3]. van der Peet PL, et al. Gram scale preparation of clozapine N-oxide (CNO), a synthetic small molecule actuator for muscarinic acetylcholine DREADDs. MethodsX. 2018 Mar 23;5:257-267.

[4]. Silva RR, et al. Evaluation of Functional Selectivity of Haloperidol, Clozapine, and LASSBio-579, an Experimental Compound With Antipsychotic-Like Actions in Rodents, at G Protein and Arrestin Signaling Downstream of the Dopamine D2 Receptor. Front Pharmacol. 2019 Jun 4;10:628.

[5]. Zorn SH, et al. Clozapine is a potent and selective muscarinic M4 receptor agonist. Eur J Pharmacol. 1994 Nov 15;269(3):R1-2.

[6]. Joseph Cichon, et al. Branch-specific dendritic Ca(2+) spikes cause persistent synaptic plasticity. Nature. 2015 Apr 9;520(7546):180-5.

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