

## Product Data Sheet

Product Name: Cevimeline

Cat. No.: GC14215

### Chemical Properties

Cas. No. 107233-08-9

Chemical Name (2R,5R)-2-methylspiro[1,3-oxathiolane-5,3'-1-azabicyclo[2.2.2]octane]

SMILES CC1OC2(CN3CCCC2CC3)CS1

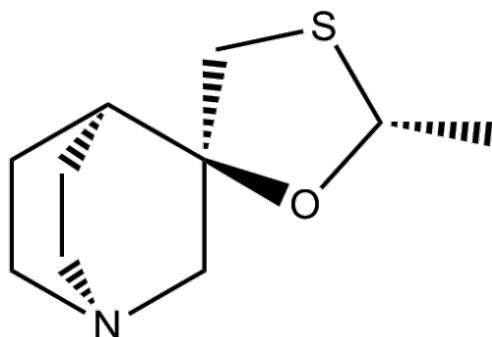
Formula  $C_{10}H_{17}NOS$  M.Wt 199.32

Solubility Soluble in DMSO Storage Store at -20°C

General tips For obtaining a higher solubility, please warm the tube at 37 °C and shake it in the ultrasonic bath for a while. Stock solution can be stored below -20°C for several months.

Shipping Condition Evaluation sample solution: ship with blue ice. All other available size: ship with RT, or blue ice upon request.

Structure



### Protocol

#### Cell experiment [1]:

Cell lines Rat parotid gland cells

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

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**Preparation Method** Rat parotid gland cells were immediately removed from deep anaesthesia of rats and placed in cold balanced salt solution (BSS) containing: 120mM NaCl, 5mM KCl, 1mM Na<sub>2</sub>HPO<sub>4</sub>, 2mM CaCl<sub>2</sub>, 1mM MgCl<sub>2</sub>, 10mM glucose, 20mM HEPES (adjusted to pH 7.4 by NaOH), and 0.5% bovine serum albumin. After mincing, the material was then digested for 30min at 37 °C with 50U/ml collagenase in BSS, and the suspension was gently passed through a pipette 10 times every 10min. After filtering through a 150µm nylon mesh, the cell preparations were loaded with 2µM fura-2AM, which was suspended in 10ml of BSS, and incubated for 30min at room temperature. After dispersing the cell preparation on poly-d-lysine-coated glass-bottom dishes, the dishes were mounted on the stage of an inverted fluorescence microscope and perfused with BSS at a rate of 1ml/min at 36 °C. The excitation of fura-2 was induced every second by an alternate illumination of 340 and 380nm light, and the resultant fluorescence (510-550nm) was collected using an objective lens and a silicon-intensified target camera. Different concentrations of Cevimeline (0, 1, 10, and 100µM) were applied to cells by superfusion. Record the calcium ion concentration data every two minutes.

**Reaction Conditions** 0, 1, 10, and 100µM; 2min

**Applications** Cevimeline treatment dose-dependently increased the calcium ion concentration within the rat parotid gland cells.

### Animal experiment [2]:

**Animal models** Male Sprague-Dawley rats

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|--------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Preparation Method | Male Sprague-Dawley rats (7 weeks old), weighing 170-190g, were kept in temperature-controlled (21°C-25°C) and humidity-maintained (40%-70%) rooms with a 12-h light/dark cycle. Water and food were provided freely. Cervical sympathetic trunk denervation (CSTD) or chorda tympani denervation (CTD) were performed under anesthesia with pentobarbital sodium (50mg/kg). Cevimeline (10mg/kg; p.o.), pilocarpine (0.3mg/kg; p.o.), or chloroquine diphosphate (50mg/kg; p.o.) was administered every day for 7 days starting from the 15th day after the operation. On the 21st day after the operation, the rats were killed and the submandibular glands were immediately dissected to determine AQP protein and mRNA levels. |
| Dosage form        | 10mg/kg/day for 7 days; p.o.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| Applications       | Cevimeline treatment enhanced the levels of AQP5 protein and mRNA in the submandibular glands of rats after parasympathectomy.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |

### References:

- [1] Ono K, Inagaki T, Iida T, et al. Distinct effects of cevimeline and pilocarpine on salivary mechanisms, cardiovascular response and thirst sensation in rats[J]. Archives of oral biology, 2012, 57(4): 421-428.
- [2] Li X, Azlina A, Karabasil M R, et al. Degradation of submandibular gland AQP5 by parasympathetic denervation of chorda tympani and its recovery by cevimeline, an M3 muscarinic receptor agonist[J]. American Journal of Physiology-Gastrointestinal and Liver Physiology, 2008, 295(1): G112-G123.

### Background

Cevimeline is a potent direct-acting muscarinic receptor agonist with oral bioavailability [1]. Cevimeline can bind and activate M1 and M3 muscarinic receptors, and can cross the blood-brain barrier (BBB) to positively influence tau pathology and reduce the levels of amyloid- $\beta$  (A $\beta$ ) peptide [2]. Cevimeline has been widely used to enhance the function of salivary glands and to increase the excitability of neurons in animal models[3].

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In vitro, Cevimeline (10 $\mu$ M) treatment for 2 minutes significantly increased the calcium ion concentration within the rat parotid gland cells<sup>[4]</sup>.

In vivo, Cevimeline treatment via oral administration at a dose of 10mg/kg/day for 7 days restored the level of AQP5 protein in the submandibular gland of rats, which had been decreased by parasympathectomy <sup>[5]</sup>. Oral administration of Cevimeline three times a day at a dose of 9mg/kg for 2 weeks reversed olanzapine-induced body weight gain and decreased feeding efficiency in female rats<sup>[6]</sup>. A single intraperitoneal injection of 10mg/kg dose of Cevimeline for 20 minutes significantly induced salivary secretion in diabetic mice and increased amylase activity<sup>[7]</sup>.

### References:

- [1] Ono M, Takamura E, Shinozaki K, et al. Therapeutic effect of cevimeline on dry eye in patients with Sjögren's syndrome: a randomized, double-blind clinical study[J]. American journal of ophthalmology, 2004, 138(1): 6-17.
- [2] Oleksak P, Novotny M, Patocka J, et al. Neuropharmacology of cevimeline and muscarinic drugs —focus on cognition and neurodegeneration[J]. International Journal of Molecular Sciences, 2021, 22(16): 8908.
- [3] Ueda H, Mitoh Y, Ichikawa H, et al. Cevimeline enhances the excitability of rat superior salivatory neurons[J]. The Journal of Medical Investigation, 2009, 56(Supplement): 267-269.
- [4] Ono K, Inagaki T, Iida T, et al. Distinct effects of cevimeline and pilocarpine on salivary mechanisms, cardiovascular response and thirst sensation in rats[J]. Archives of oral biology, 2012, 57(4): 421-428.
- [5] Li X, Azlina A, Karabasil M R, et al. Degradation of submandibular gland AQP5 by parasympathetic denervation of chorda tympani and its recovery by cevimeline, an M3 muscarinic receptor agonist[J]. American Journal of Physiology-Gastrointestinal and Liver Physiology, 2008, 295(1): G112-G123.
- [6] Lian J, Deng C. The dosage-dependent effects of cevimeline in preventing olanzapine-induced metabolic side-effects in female rats[J]. Pharmacology Biochemistry and Behavior, 2020, 191: 172878.
- [7] ISHII H, NAKAGAWA Y, SHIGA T, et al. Effects of Cevimeline hydrochloride on salivary secretion in streptozotocin-induced diabetic Balb/cA mice[J]. ORAL THERAPEUTICS AND PHARMACOLOGY, 2001, 20(2): 86-91.

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