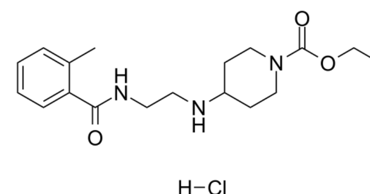
Data Sheet



Product Name:	VU0357017 (hydrochloride)
Cat. No.:	CS-5434
CAS No.:	1135242-13-5
Molecular Formula:	C18H28ClN3O3
Molecular Weight:	369.89
Target:	mAChR
Pathway:	GPCR/G Protein; Neuronal Signaling
Solubility:	DMSO : 25 mg/mL (67.59 mM; Need ultrasonic)

BIOLOGICAL ACTIVITY:

VU0357017 hydrochloride is a highly selective M1 agonists that appear to act at an allosteric site to activate the receptor (EC50 = 477 ± 172 nM; pEC50 = 6.37 ± 0.15). IC50 value: 477 ± 172 nM (EC50) [1] Target: M1 in vitro: VU0357017 is a M1-selective agonists that appear to activate M1 through actions at an allosteric site. Ki values of VU0357017 derived from competition binding experiment is 9.91(rM1), 21.4 (rM2), 55.3 (rM3), 35 (rM4), and 50 (rM5), respectively. [1] VU0357017 is a potent and efficacious M1 agonist, selective versus M2 M5 family members and allosteric agonist. VU0357017 is a highly selective M1 agonist suggests that these compounds are unlikely to act at the highly conserved orthosteric site on M1 and are more likely to act as allosteric agonists. [2] VU0357017 has robust effects on M1-activation of calcium mobilization and ERK1/2 phosphorylation but have little effect on β-arrestin recruitment. VU0357017 induces calcium release and ERK phosphorylation but is without effects on β-arrestin recruitment. VU0357017 significantly enhances threshold Θ-burst LTP and VU0364572 induces LTD at the Schaffer collateral-CA1 synapse of rodent hippocampal slices. [3] in vivo: VU0357017 has robust efficacy in improving hippocampal-dependent learning in rats. VU0357017 enhances performance in Morris water maze and contextual fear conditioning in rats. [3]

PROTOCOL (Extracted from published papers and Only for reference)

Cell Assay [3] For all calcium assays, humanM1-TREx CHO or hM1-CHO cells were seeded at a density of 50,000 cells/well in clear-bottomed, black-walled 96-well plates in media containing a range of TET concentrations. The following day, media was removed from the cells and replaced with 50 μL of calcium indicator dye, fluo-4 (2 μM), dissolved in Hank's balanced salt solution (HBSS-Invitrogen) containing 20 mM HEPES and 2.5 mM probenecid, pH 7.4. Cells were allowed to incubate in the fluo-4/HBSS solution for 45 min; solution was removed and replaced with 50 μL HBSS. Agonists were serial diluted into assay buffer for a 2X stock concentration in 1% DMSO; stock compounds were added to assay for final concentration of 0.5% DMSO. 50 uL of VU0357017 test solution was added to each well and fluorescent signals were measured at λ525 nm fluorescence emission after λ480 nm excitation at 1 second intervals for 60 seconds using either a Flextation II or a Flexstation III. To generate concentration response curves (CRCs), baseline responses were subtracted from agonist-induced response and were normalized to the maximal response elicited by carbachol. Animal administration [2] VU0357017 was dissolved in sterile water at a concentration of 5 mg/mL (base form) and administered intraperiteoneally to male Sprague-Dawley rats weighing 225-250 g at a dose of 10 mg/kg. The rat blood and brain were collected at 0.5, 1, 2, 4, and 8 h. Animals were euthanized and decapitated, and the brains were removed, thoroughly washed with cold phosphate-buffered saline, and immediately frozen on dry ice. Trunk blood was collected in EDTA Vacutainer tubes, and plasma was separated by centrifugation and stored at -80 °C until analysis. Three animals were used for each time point. On the day of analysis, frozen whole rat brains were weighed and homogenized in 1:3 (w/w) volumes of ice-cold phosphate-buffered saline (pH 7.4). The sample extraction of plasma (100 μL) and brain homogenate (250 μL) was performed by a method based on protein precipitation, using 3 volumes of cold acetonitrile containing 0.1% formic acid and an internal standard (VU-178) having final concentration of 50 ng/mL. Extracts were vortex mixed for 5 min followed by centrifugation at 14000 rpm for 10 min. The final PK parameters were

calculated by noncompartmental analysis using WinNonlin software.

References:

[1]. Digby GJ, et al. Chemical modification of the M(1) agonist VU0364572 reveals molecular switches in pharmacology and a bitopic binding mode. ACS Chem Neurosci. 2012 Dec 19;3(12):1025-36.

[2]. Lebois EP, et al. Discovery and characterization of novel subtype-selective allosteric agonists for the investigation of M(1) receptor function in the central nervous system. ACS Chem Neurosci. 2010;1(2):104-121.

[3]. Digby GJ, et al. Novel allosteric agonists of M1 muscarinic acetylcholine receptors induce brain region-specific responses that correspond with behavioral effects in animal models. J Neurosci. 2012 Jun 20;32(25):8532-44.

[4]. Sheffler DJ, et al. Further exploration of M? allosteric agonists: subtle structural changes abolish M? allosteric agonism and result in pan-mAChR orthosteric antagonism. Bioorg Med Chem Lett. 2013 Jan 1;23(1):223-7.

CAIndexNames:

1-Piperidinecarboxylic acid, 4-[[2-[(2-methylbenzoyl)amino]ethyl]amino]-, ethyl ester, hydrochloride (1:1)

SMILES:

O=C(N1CCC(NCCNC(C2=CC=CC=C2C)=O)CC1)OCC.[H]Cl

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

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