

Product Data Sheet

Product Name: CMPD101

Cat. No.: GC43286

Chemical Properties

Cas. No. 865608-11-3

SMILES O=C(C1=CC=CC(NCC2=NN=C(C3=CC=NC=C3)N2C)=C1)NCC4=CC=CC=C4C(F)(F)F

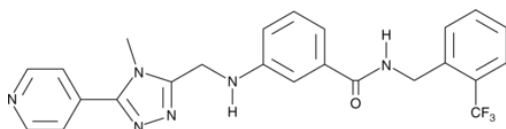
Formula C24H21F3N6O M.Wt 466.5

Solubility 10mg/mL in ethanol, 20mg/mL in DMSO, or in DMF 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 Human embryonic kidney 293 cells

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

Tel: (909) 407-4943 Fax: (626) 353-8530 E-mail: tech@glpbio.com

Address: 10292 Central Ave. #205, Montclair, CA, USA

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Preparation Method Human embryonic kidney 293 cells (HEK 293) cells stably overexpressing hemagglutinin (HA)-tagged rat MOPr (HAMOPr) were cultured at 37°C in 5% CO₂ in Dulbecco's modified Eagle's medium supplemented with 10% fetal bovine serum, 10U/ml penicillin, 10mg/ml streptomycin, and 250mg/ml G418. Cells were seeded onto 60mm dishes and grown to 90% confluence, then subjected to serum starvation for 24 hours. HEK 293 cells were prelabeled with primary antibody for 1 hour at 4°C before incubation with CMPD101 (3 or 30μM) for 30 minutes at 37°C. Cells were then stimulated with [D-Ala², N-MePhe⁴, Gly-ol⁵]-enkephalin(DAMGO) (10mM) at 37°C to induce internalization. DAMGO-induced internalization of HAMOPr was assessed by enzyme-linked immunosorbent assay (ELISA) and by confocal microscopy imaging.

Reaction Conditions 3 or 30μM; 30min

Applications CMPD101 almost completely inhibits DAMGO-induced m-opioid receptor (MOPr) internalization.

Animal experiment [2]:

Animal models C57BL/6J (B6) mice

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Male adult C57BL/6J mice (8 weeks of age) were placed on a 12-hour reverse lightdark cycle (lights off at 7:00 am) and housed individually in ventilated cages with steel lids and filter tops and given *ad libitum* access to food and water. In this two-bottle free choice paradigm, mice had access to alcohol for 24 hours every other day for 3 weeks. Both the 15% alcohol solution and water tubes were provided starting at 3 hours after lights off. After 4, 8 and 24 hours of alcohol access, both the water and alcohol intakes were recorded. Following the 3-week chronic intermittent access (CIA) procedure, the mice had high alcohol intake and preference. The CIA mice were pretreated with CMPD101 (0 or 0.3mg/kg, i.p.) 15 min before the drinking session, followed by nalfurafine (0, 1, 3 or 10µg/kg; i.p.) 5min before a drinking session (n=7–8), and then alcohol and water intake values were recorded.

Dosage form

0 or 0.3 mg/kg, i.p.; 15min

Applications

Pretreatment with CMPD101 enhanced the effect of nalfurafine on reducing alcohol intake in mice.

References:

- [1] Lowe JD, Sanderson HS, Cooke AE, et al. Role of G Protein-Coupled Receptor Kinases 2 and 3 in μ -Opioid Receptor Desensitization and Internalization. *Mol Pharmacol*. 2015;88(2):347-356.
- [2] Zhou Y, Liang Y. Involvement of GRK2 in modulating nalfurafine-induced reduction of excessive alcohol drinking in mice. *Neurosci Lett*. 2021;760:136092.

Background

CMPD101 is a potent, highly selective and membrane-permeable small-molecule inhibitor of G protein-coupled receptor kinase 2 (GRK2) and GRK3 (IC₅₀s=18 and 5.4nM, respectively)^[1]. GRKs phosphorylate GPCRs, regulate their desensitization, internalization, and signaling, are crucial for cellular and physiological regulation^[2]. CMPD101 can be used for the research of GPCR

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desensitization and internalization, opioid tolerance, heart failure, signal transduction mechanisms, and drug development^{[3][4]}.

In vitro, treatment of HEK293 cells with CMPD101 (30 μ M; 30min) completely blocked histamine H₁ receptor-mediated ERK1/2 phosphorylation (IC₅₀=6 μ M)^[5]. CMPD101 (3-30 μ M; 30min) inhibits the desensitization of μ -opioid receptors (MOPr) induced by agonists such as Met-Enk and DAMGO in locus coeruleus (LC) neurons of rats and mice, with an IC₅₀ of approximately 6 μ M. In HEK293 cells, CMPD101 (30 μ M; 30min) almost completely inhibits [D-Ala², N-MePhe⁴, Gly-ol⁵]-enkephalin(DAMGO)-induced m-opioid receptor (MOPr) phosphorylation at Ser375, arrestin translocation, and MOPr internalization^[6].

In vivo, pretreatment with CMPD101(0.3mg/kg, i.p.) 15min before the drinking session enhanced the effect of nalfurafine on reducing alcohol intake in mice by inhibiting GRK2/3 activity^[7].

References:

- [1] Okawa T, Aramaki Y, Yamamoto M, et al. Design, Synthesis, and Evaluation of the Highly Selective and Potent G-Protein-Coupled Receptor Kinase 2 (GRK2) Inhibitor for the Potential Treatment of Heart Failure. *J Med Chem*. 2017;60(16):6942-6990.
- [2] Mayor F Jr, Murga C. G Protein-Coupled Receptor Kinases Take Central Stage. *Cells*. 2022;12(1):23.
- [3] Mann A, Keen AC, Mark H, et al. New phosphosite-specific antibodies to unravel the role of GRK phosphorylation in dopamine D₂ receptor regulation and signaling. *Sci Rep*. 2021;11(1):8288.
- [4] Thal DM, Yeow RY, Schoenau C, Huber J, Tesmer JJ. Molecular mechanism of selectivity among G protein-coupled receptor kinase 2 inhibitors. *Mol Pharmacol*. 2011;80(2):294-303.
- [5] Michinaga S, Nagata A, Ogami R, Ogawa Y, Hishinuma S. Differential regulation of histamine H₁ receptor-mediated ERK phosphorylation by G_q proteins and arrestins. *Biochem Pharmacol*. 2023;213:115595.
- [6] Lowe JD, Sanderson HS, Cooke AE, et al. Role of G Protein-Coupled Receptor Kinases 2 and 3 in μ -Opioid Receptor Desensitization and Internalization. *Mol Pharmacol*. 2015;88(2):347-356.
- [7] Zhou Y, Liang Y. Involvement of GRK2 in modulating nalfurafine-induced reduction of excessive alcohol drinking in mice. *Neurosci Lett*. 2021;760:136092.

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