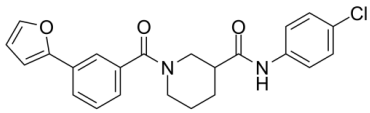
Data Sheet

Product Name:	CCG-203971
Cat. No.:	CS-0028459
CAS No.:	1443437-74-8
Molecular Formula:	C23H21ClN2O3
Molecular Weight:	408.88
Target:	Ras
Pathway:	GPCR/G Protein
Solubility:	DMSO : ≥ 155 mg/mL (379.08 mM); H2O : < 0.1 mg/mL (insoluble)



BIOLOGICAL ACTIVITY:

CCG-203971 is a second-generation **Rho/MRTF/SRF** pathway inhibitor. CCG-203971 potently targets RhoA/C-activated SRE-luciferase (IC_{50} =6.4 μM). CCG-203971 inhibits PC-3 cell migration with an IC_{50} of 4.2 μM. Potential anti-metastasis Agent[1][2]. IC50 & Target: RhoA/MRTF-A[1] **In Vitro:** CCG-203971, a second-generation Ras homolog gene family, member A (RhoA)/myocardin-related transcription factor A (MRTF-A)/serum response factor (SRF) pathway inhibitor, represses both matrix-stiffness and transforming growth factor beta–mediated fibrogenesis as determined by protein and gene expression in a dose-dependent manner. CCG-203971 significantly represses TGF-β- induced MKL1 expression at 25 μM concentration[2]. Human dermal fibroblasts are plated onto 96-well plates and allowed to grow for 3 days in the presence of 30 μM CCG-203971 or DMSO vehicle. Viable cell density is assessed through enzymatic reduction of the water-soluble tetrazolium dye WST-1. Scleroderma dermal fibroblasts proliferate faster than normal cells, and this is inhibited by CCG-203971[3]. **In Vivo:** CCG-203971 is tested in a Bleomycin skin injury model. Bleomycin is administered in 50 μL of DMSO intraperitoneally. Preliminary studies show that Bleomycin administered in this manner is well tolerated at 100 mg/kg twice a day. Intradermal Bleomycin for 2 weeks along with the DMSO control (50 μL i.p.) results in marked dermal thickening ($P<0.0001$) compared with the PBS+DMSO group, which does not receive Bleomycin. CCG-203971 treatment strongly and significantly ($P<0.001$) suppresses the Bleomycin-induced skin thickening in this model. Skin collagen amounts, assessed by measurement of hydroxyproline content, show similar results. Bleomycin injections promote collagen deposition ($P<0.01$) and CCG-203971 is able to block this effect ($P<0.05$)[3].

PROTOCOL (Extracted from published papers and Only for reference)

Cell Assay: [3]**Human dermal fibroblasts** (2.0×10^4) are plated into a 96-well plate and grown overnight in DMEM containing 10% FBS. Media are removed and replaced with DMEM containing 2% FBS and **30 μM CCG-203971** or 0.1% DMSO control. After 72 hours WST-1 dye is added to each well, and after 60 minutes absorbance at 490 nm is read using a Wallac Victor2 plate reader[3].

Animal Administration: [3]Mice[3]

Skin fibrosis is induced in **C57BL/6 mice** (female, 8 weeks old) by local intracutaneous injection of 100 μL of Bleomycin (1 mg/mL) in phosphate-buffered saline (PBS), every day for 2 weeks in a defined area (~1 cm^2) on the upper back. Intracutaneous injection of 100 μL of PBS is used as a control. Three groups of mice with a total of 21 mice are used. One group receives injections of PBS and the other two are challenged with Bleomycin. Twice-a-day intraperitoneal administration of **CCG-203971** (**100 mg/kg** in 50 μL of DMSO) is initiated together with the first challenge of Bleomycin and continues for 2 weeks. DMSO is used as the vehicle control. The three groups of animals are: (1) PBS/DMSO; (2) Bleomycin/DMSO; and (3) Bleomycin/CCG-203971. After treatment, animals are humanely killed by cervical dislocation, and tissue is collected[3].

References:

[1]. Johnson LA, et al. Novel Rho/MRTF/SRF inhibitors block matrix-stiffness and TGF-β-induced fibrogenesis in human colonic myofibroblasts. Inflamm Bowel Dis. 2014 Jan;20(1):154-65.

[2]. Haak AJ, et al. Targeting the myofibroblast genetic switch: inhibitors of myocardin-related transcription factor/serum response factor-regulated gene transcription prevent fibrosis in a murine model of skin injury. J Pharmacol Exp Ther. 2014 Jun;349(3):480-6.

[3]. Bell JL, et al. Optimization of novel nipecotic bis(amide) inhibitors of the Rho/MKL1/SRF transcriptional pathway as potential anti-metastasis agents. Bioorg Med Chem Lett. 2013 Jul 1;23(13):3826-32.

CAIndexNames:

3-Piperidinecarboxamide, N-(4-chlorophenyl)-1-[3-(2-furanyl)benzoyl]-

SMILES:

O=C(C1CN(C(C2=CC=CC(C3=CC=CO3)=C2)=O)CCC1)NC4=CC=C(Cl)C=C4

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