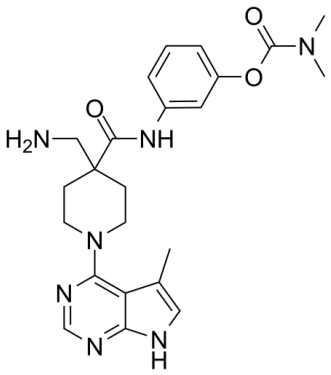
Data Sheet

Product Name:	LX7101
Cat. No.:	CS-5103
CAS No.:	1192189-69-7
Molecular Formula:	$C_{23}H_{29}N_7O_3$
Molecular Weight:	451.52
Target:	ROCK
Pathway:	Cell Cycle/DNA Damage; Cytoskeleton; Stem Cell/Wnt; TGF-beta/Smad
Solubility:	DMSO : 150 mg/mL (332.21 mM; Need ultrasonic)



BIOLOGICAL ACTIVITY:

LX7101 is a potent inhibitor of **LIMK** and **ROCK2** with **IC_{50}** values of 24, 1.6 and 10 nM for LIMK1, LIMK2 and ROCK2, respectively; also inhibits **PKA** with an **IC_{50}** less than 1 nM. IC50 & Target: IC50: 24 nM (LIMK1), 1.6 nM (LIMK2), 10 nM (ROCK2), <1 nM (PKA)[1] **In Vitro:** LX7101 is a dual LIM-kinase and ROCK inhibitor for the treatment of ocular hypertension and associated glaucoma. LX-7101 also displays potent inhibition of Akt1 with an IC_{50} of less than 1 nM[1]. The overall selectivity of LX7101 for LIMK2 increases at the higher physiological ATP concentrations. Under physiological conditions, the activity of LX7101 is primarily due to inhibition of LIMK2[2]. **In Vivo:** LX-7101 is advanced to Phase-I clinical trials as an intraocular pressure (IOP)-lowering agent for treatment of glaucoma. LX-7101 displays a significant IOP reduction at time points ranging from 1 h to 6 h post administration in rabbits[1]. Topical doses of LX-7101 are evaluated for tolerability on the eyes of mice, rats, and rabbits. It is well tolerated at doses up to 0.5% in non-GLP single dose studies. In the mouse IOP assay, LX-7101 (5%) achieved additional reduction of IOP (5.0 mmHg total reduction) compared to the 0.1% formulation and demonstrated a long duration of action, with IOP not returning to baseline until more than 8 h postdose[2].

PROTOCOL (Extracted from published papers and Only for reference)

Kinase assay [1] On-target activity against LIMK1, LIMK2, ROCK2, PKA and Akt is measured externally in a radiometric assay. Enzyme concentration in the assay is 1 nM. Final ATP concentration is 1μM. Further details regarding the assay technology can be obtained in literature. Cell assay [1] In the cellular assay phospho-levels of MLC-Thr18/Ser19 are quantified by direct-ELISA technique. The rat aortic smooth muscle cell line A7r5 are incubated with LX7101 in serum-free medium. Raw data are converted into percent substrate phosphorylation relative to high controls, which are set to 100%. EC50 values are determined with GraphPad Prism 5.01 software, using a nonlinear regression curve fit with variable hill slope. Animal administration [1] IOP lowering efficacy of single topical administration of LX-7101 and 27 was tested in ocular normotensive New Zealand White rabbits (n=5). Eyes are anesthetized by topical instillation of 0.4% oxybuprocaine before initiating the experiment. LX7101 is administered as a single 40 μL drop of a 0.5% w/v solution in 1:1 PEG:Water vehicle. Contralateral eyes are treated with an equivalent volume of vehicle. The study is performed blinded. IOP measurements are performed immediately before and every hour until 8 hours after compound instillation. A calibrated applanation tonometer is used to monitor IOP. Eyes are anesthetized with oxybuproca?ne before each time point.

References:

[1]. Boland S, et al. Design, synthesis and biological characterization of selective LIMK inhibitors. Bioorganic & Medicinal Chemistry Letters (2015), 25(18),

4005-4010.

[2]. Harrison BA, et al. Discovery and Development of LX7101, a Dual LIM-Kinase and ROCK Inhibitor for the Treatment of Glaucoma. ACS Medicinal Chemistry Letters (2015), 6(1), 84-88.

CAIndexNames:

Carbamic acid, N,N-dimethyl-, 3-[[[4-(aminomethyl)-1-(5-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-4-piperidinyl]carbonyl]amino]phenyl ester

SMILES:

NCC1(C(NC2=CC(OC(N(C)C)=O)=CC=C2)=O)CCN(C3=C4C(NC=C4C)=NC=N3)CC1

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