Product Data Sheet

Product Name: CC-223
Cat. No.: GC13648

Chemical Properties

Cas. No.	1228013-30-6		
Chemical Name	7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-1-((1r,4r)-4-methoxycyclohexyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one		
SMILES	O=C1N([C@H]2CC[C@H](OC)CC2)C3=NC(C4=CN=C(C(O)(C)C)C=C4)=CN=C3NC1		
Formula	$C_{21}H_{27}N_5O_3$	M.Wt	397.47
Solubility	DMF: 30 mg/mL,DMF:PBS(pH 7.2)(1:1): 0.5 mg/mL,DMSO: 25 mg/mL,Ethanol: 20 mg/mL	Storage	Store at -20°C
General tips	For obtaining a higher solubility , please warm the tube at 37 ℃ and shake it in the ultrasonic bath for a while.Stock solution can be stored below -20℃ 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	CC-223		

Protocol

Kinase experiment:	Counter screen against 246 protein kinases is outsourced and completed at a fixed CC-223 concentration (10 μM). Follow-up IC50 value determinations for ephrin type-B receptor 3 kinase (EPHB3), colony stimulating factor 1 receptor tyrosine kinase (CSF1R or cFMS), and FMS-related tyrosine kinase 4 (FLT4) are outsourced to Invitrogen[1].

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Cell experiment:

For other cell panel proliferation assays, CC-223 (1 nM, 100 nM and 1 μM) is spotted via an acoustic dispenser (EDC ATS-100) into an empty 384-well plate. Cells are diluted to desired densities and added directly to the compound-spotted plates. Cells are allowed to grow for 72 hours. Viability is assessed via Cell Titer-Glo. All data are normalized and represented as a percentage of the DMSO-treated cells. Results are then expressed as GI50 and/or IC50 values[1].

Animal experiment:

Mice[1]Female 6- to 8-weeks-old CB17 SCID mice are inoculated s.c. with 2×106 PC-3 cells. When tumors reach approximately 125 mm3, mice are randomized and treated once daily, twice daily, or every 2 days orally with vehicle or various doses of CC-223, at a dose volume of 5 mL/kg. The twice-daily doses are administered with a 10 hours separation between the morning and evening doses. Tumor volumes are determined before the initiation of treatment and are considered as the starting volumes. Tumors are measured twice a week for the duration of the study. The long and short axes of each tumor are measured using a digital caliper in millimeters. The tumor volumes are calculated. The tumor volumes are expressed in cubic millimeters (mm3).

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References:

[1]. Mortensen DS, et al. CC-223, a Potent and Selective Inhibitor of mTOR Kinase: In Vitro and In Vivo Characterization. Mol Cancer Ther. 2015 Jun;14(6):1295-305.

Background

IC50: 16 nM

CC-223 is an orally bioavailable mTOR inhibitor.

The mammalian target of rapamycin (mTOR) pathway is critical for tumor development, and mTOR inhibitors have revealed modest results.

In vitro: CC-223 was identified as an ATP–competitive inhibitor of the mTOR kinase targeting mTORC1 of both 4EBP1 and p70 S6 kinase 1 and mTORC2, which prevented the upregulation of AKT phosphorylation. Moreover, CC-223 was selectively potent to mTOR kinase while showed more than 150-fold sensitivity against the related lipid kinase, PI3Ka. In addition, CC-223 was active over many non-Hodgkin lymphoma cell lines and solid tumor lines such as including glioma, breast, hepatocellular carcinoma, as well as non–small cell lung cancer [1].

In vivo: In animal study, CC-223 was selected for evaluation in PC-3 tumor bearing efficacy mouse models. Mice were orally treated with vehicle or various doses of CC-223 once daily or twice daily at a dose of 5 mL/kg for 21 days, and the final reductions of tumor volume were measured following the final day of dosing. Results showed that All

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CC-223 had dose- and schedule-dependent inhibition of tumor growth in the PC-3 model. Moreover, the maximum observed efficacy for CC-223 was determined to be 87%, at its tolerated dose of 25 mg/kg q.d. [1].

Clinical trial: In previous clinical study, CC-223 was found to be tolerable with manageable toxicities. In addition, the preliminary antitumor activity, such as tumor regression and evidence of mTORC1/mTORC2 pathway inhibition were also observed [2].

References:
[1] Mortensen DS, et al. Discovery of Mammalian Target of Rapamycin (mTOR) Kinase Inhibitor CC-223. J Med Chem. 2015 Jul 9;58(13):5323-5333.
[2] Bendell JC, et al. A phase I dose-escalation study to assess safety, tolerability, pharmacokinetics, and preliminary efficacy of the dual mTORC1/mTORC2 kinase inhibitor CC-223 in patients with advanced solid tumors or multiple myeloma. Cancer. 2015 Oct 1;121(19):3481-90.