Product Data Sheet

Product Name: RGB-286638 free base
Cat. No.: GC37523

Chemical Properties

Cas. No.	784210-88-4		
SMILES	O=C(NN1CCOCC1)NC2=CC=CC(C3=C4C(C5=CC=C(CN6CCN(CCOC)CC6)C=C5)=NN3)=C2C4=O		
Formula	$C_{29}H_{35}N_7O_4$	M.Wt	545.63
Solubility	DMSO: ≥ 36 mg/mL (65.98 mM)	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	RGB-286638 free base		

Protocol

Kinase experiment:

Nuclear proteins are isolated from MM.1S cells treated with 50nM RGB-286638 for 1, 4, and 8 h, using Nuclear Extraction Kit. Nuclear protein aliquots are added to the 96-well plate coated with specific double-stranded DNA sequence containing the p53 response element for overnight incubation. p53 in the nuclear extract is detected by addition of a specific primary antibody directed against p53. A secondary antibody conjugated to HRP is added to provide a sensitive colorimetric readout at 450 nm. All experiments are performed in triplicates[1].

Cell experiment:

Colorimetric assays are performed to assay drug activity at increasing concentrations of RGB-286638 (0-100nM). Expressing wild-type p53 (MM.1S, MM.1R, H929) or mutant-p53 (U266, OPM1, RPMI) cells from 24- or 48-h cultures are pulsed with 10μL of 5mg/mL MTT to each well, followed by incubation at 37°C for 4h, and addition of 100 μL isopropanol containing 0.04 HCl. Absorbance readings at a wavelength of 570nm (with correction using readings at 630nm) are taken on a spectrophotometer. All experiments are performed in triplicates[1].

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Product Data Sheet

Animal experiment:

Mice[1] The in vivo anti-MM activity of RGB-286638 is evaluated in an MM xenograft model. RGB-286638 dosing solutions of 2 and 3 mg/mL in 5% dextrose/water (D5W) pH5.2, as well as D5W pH5.2 for vehicle control dosing group, are prepared and provided by Agennix AG. CB-17 severe combined immunodeficient (SCID) mice are used. Forty male 5-6 week old mice are irradiated (2 Gy [200 rad]) using cesium 137 (137Cs)-irradiator source); 24h after irradiation, 2.5×106 MM.1S cells are inoculated subcutaneously in the upper back. When tumor weight is approximately 100 mg, mice are randomly assigned into 3 cohorts receiving daily IV tail vein injections for 5 consecutive days with either RGB-286638 30 mg/kg (8 mice), 40 mg/kg (9 mice), or control vehicle alone (10 mice). Animals are monitored for body weight and tumor volume by caliper measurements every alternate day. Tumor volume is estimated. Survival is evaluated from the first day of treatment until death. Tumor growth is evaluated using caliper measurements from the first day of treatment until day of first sacrifice. Percentage tumor growth inhibition (TGI) is calculated.

References:

[1]. Cirstea D, et al. Small-molecule multi-targeted kinase inhibitor RGB-286638 triggers P53-dependent and -independent anti-multiple myeloma activity through inhibition of transcriptional CDKs. Leukemia. 2013 Dec;27(12):2366-75.

Background

RGB-286638 is a multi-kinase inhibitor.[1] It inhibits a variety of kinases, including cyclin-dependent kinase 1 (CDK1), CDK2-7 and CDK9, as well as the tyrosine kinases FMS, JAK2, and c-Src and the serine/threonine kinases GSK3β, TAK1, JNK1A1, JNK1A2, AMPK, and MEK1 (IC_{50}s = 1-55 nM). RGB-286638 inhibits proliferation of multiple myeloma cancer cell lines endogenously expressing mutant and wild-type p53 (EC_{50}s = 20-70 nM), as well as patient-derived multiple myeloma cells when used at concentrations of 50

Product Data Sheet

and 100 nM. It induces G_1/S and G_2/M cell cycle arrest and apoptosis of MM.1S human multiple myeloma cells when used at a concentration of 50 nM. RGB-286638 decreases tumor growth in an MM.1S mouse xenograft model when administered at doses of 30 and 40 mg/kg per day for 14 days.

1.Cirstea, D., Hideshima, T., Santo, L., et al.Small-molecule multi-targeted kinase inhibitor RGB-286638 triggers P53-dependent and -independent anti-multiple myeloma activity through inhibition of transcriptional CDKsLeukemia27(12)2366-2375(2013)

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