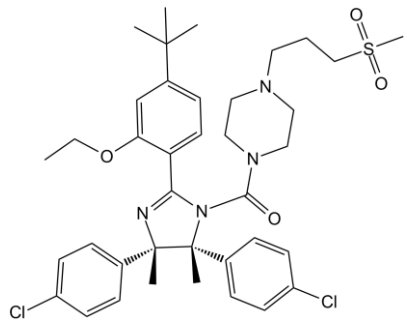
Product Name: RG7112

Revision Date: 6/30/2016

Product Data Sheet

Chemical Properties



Product Name:	RG7112
Cas No.:	939981-39-2
M.Wt:	727.78
Formula:	C38H48Cl2N4O4S
Synonyms:	RG-7112;RG 7112
Chemical Name:	[(4S,5R)-2-(4-tert-butyl-2-ethoxyphenyl)-4,5-bis(4-chlorophenyl)-4,5-dimethylimidazol-1-yl]-[4-(3-methylsulfonylpropyl)piperazin-1-yl]methanone
Canonical SMILES:	CCOC1=C(C=CC(=C1)C(C)(C)C)C2=NC(C(N2C(=O)N3CCN(CC3)CCCS(=O)(=O)C)(C)C4=CC=C(C=C4)Cl)(C)C5=CC=C(C=C5)Cl
Solubility:	>36.4mg/mL in DMSO
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.
Shopping Condition:	Evaluation sample solution : ship with blue ice All other available size: ship with RT , or blue ice upon request

Biological Activity

Targets :	MDM2
Pathways:	Apoptosis >> MDM2

Description:

RG7112 is a selective inhibitor of p53-MDM2 binding that frees p53 from negative control, activating the p53 pathway in cancer cells leading to cell cycle arrest and apoptosis. [1]
P53 is a potent tumor suppressor that activates the transcription of a subset of genes controlling cell-cycle progression and apoptosis. MDM2 is a negative regulator of p53 that binds the transactivation domain of p53 and inhibits its ability to activate transcription. MDM2 is also an E3

ubiquitin ligase that targets p53 for proteosomal degradation. MDM2 overexpression is one of the mechanisms by which the wild type p53 function is impaired. [2]
RG7112 has been profiled extensively in many cell lines. In 15 cancer cell lines expressing wild-type p53, it shows IC50 in the range of 0.18 - 2.2 μM. However, the inhibition is much less in seven cancer cell lines with p53 mutation, IC50 5.7 - 20.3 μM. The overall selectivity is 14-fold. In the animal models, RG7112-induced thrombocytopenia occurred rather late during the treatment period and persisted after drug discontinuation, suggesting that the drug acts on early hematopoietic progenitor cells. This is supported by the RG7112 ability to inhibit CFU-MK colonies formation by the CD34t cells in vitro. Administration of RG7112 in rats and monkeys reduces WBC counts and, to a lesser extent, hemoglobin levels. In patients treated with RG7112, neutropenia is among the serious adverse events while anemia occurred only in 2 of 20 patients. Interestingly, when tested in vitro, the same concentration of RG7112 that reduced CFU-MK colony formation do not significantly affect the formation of BFU-E and CFU-GM derived colonies.

***Reference**:*

[1] Hernan Carol, C. Patrick Reynolds, Min H. Kang et al. Initial Testing of the MDM2 Inhibitor RG7112 by the Pediatric Preclinical Testing Program. Pediatr Blood Cancer 2013;60:633–641
[2] Binh Vu, Peter Wovkulich, Giacomo Pizzolato et al. Discovery of RG7112: A Small-Molecule MDM2 Inhibitor in Clinical Development. ACS Med. Chem. Lett. 2013, 4, 466−469
[3] Camelia Iancu-Rubina, Goar Mosoyana, Kelli Glenn et al. Activation of p53 by the MDM2 inhibitor RG7112 impairs thrombopoiesis. Experimental Hematology 2014;42:137–145

Protocol

Cell experiment:

Cell lines	SJSA1 osteosarcoma cells
Preparation method	The solubility of this compound in DMSO is >10 mM. General tips for obtaining a higher concentration: Please warm the tube at 37 °C for 10 minutes and/or shake it in the ultrasonic bath for a while.Stock solution can be stored below -20°C for several months.
Reacting conditions	24 h; 10 μM
Applications	Treatment of cultured cancer cells with RG7112 led to concentration-dependent accumulation of p53 protein and its transcriptional targets, p21 and MDM2. RG7112 dose dependently inhibited the growth and killed SJSA1 osteosarcoma cells expressing high-levels of MDM2 protein due to MDM2 gene ampli fication

Animal experiment [3]:

Animal models	Female Balb/c nude mice

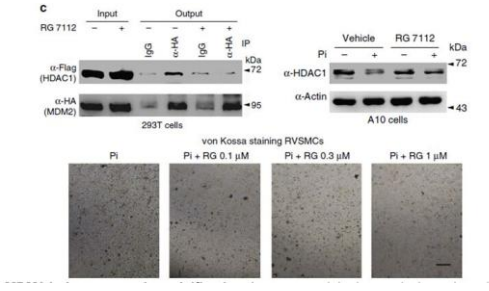
Dosage form	200 mg/kg; oral taken
Applications	Pharmocodynamic effects of RG7112 were assessed in the SJSA1 xenograft model. To assess the ability of RG7112 to activate p53 response in vivo, SJSA1 tumor-bearing mice were treated with a single dose of vehicle or 50 to 200 mg/kg RG7112 for 4 to 24 hours. Western blot analysis showed a dose-dependent increase in p53 protein and its targets, p21 and MDM2. The p53 protein levels were highest at 4 hours after dose and continue to persist at 24 hours at the highest dose level (200 mg/kg), whereas the duration of p53 modulation was shorter at lower dose levels.
Other notes	Please test the solubility of all compounds indoor, and the actual solubility may slightly differ with the theoretical value. This is caused by an experimental system error and it is normal.

***Reference**:*
[1] Tovar C, Graves B, Packman K, et al. MDM2 small-molecule antagonist RG7112 activates p53 signaling and regresses human tumors in preclinical cancer models[J]. Cancer research, 2013, 73(8): 2587-2597.

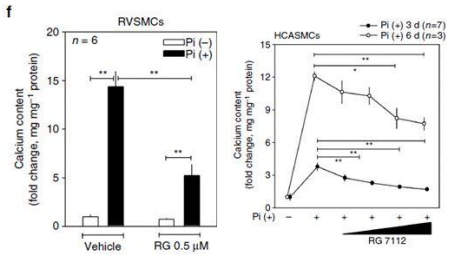
Product Citations

1. Kwon DH, Eom GH, et al. "MDM2 E3 ligase-mediated ubiquitination and degradation of HDAC1 in vascular calcification." Nat Commun.2016 Feb 1;7:10492. PMID:26832969

Product Validation



MDM2 induces vascular calcification. Immunoprecipitation analysis to show that RG 7112 (RG), an MDM2 inhibitor, interfered with the association of HDAC1 with MDM2.RG 7112 (0.1 mM) blocked the Pi-induced reduction of HDAC1 protein amount in A10 cells.RG 7112 attenuated Pi-induced VC in RVSMCs in a dose-dependent manner. Pi-containing media with either RG or vehicle were replaced every 2 days for 6 days and von Kossa staining was performed. Nat Commun. 2016 Feb 1;7:10492.



MDM2 induces vascular calcification. Quantification results to show the inhibitory effect of RG on Pi-induced VC. RG 7112 (0.5 mM) significantly reduced the calcium deposition in RVSMCs (n¼6 from two sets). Dose-dependent attenuation of calcium deposition by RG 7112 compound (0.1–3 mM) in human coronary artery smooth muscle cells (HCASMCs). Nat Commun. 2016 Feb 1;7:10492.

Caution

FOR RESEARCH PURPOSES ONLY.

NOT FOR HUMAN, VETERINARY DIAGNOSTIC OR THERAPEUTIC USE.

Specific storage and handling information for each product is indicated on the product datasheet. Most ApexBio products are stable under the recommended conditions. Products are sometimes shipped at a temperature that differs from the recommended storage temperature. Shortterm storage of many products are stable in the short-term at temperatures that differ from that required for long-term storage. We ensure that the product is shipped under conditions that will maintain the quality of the reagents. Upon receipt of the product, follow the storage recommendations on the product data sheet.

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