Product Data Sheet

Product Name: RK-33
Cat. No.: GC17781

Chemical Properties

Cas. No.	1070773-09-9		
Chemical Name	3,7-bis(4-methoxybenzyl)-3,7-dihydro-2H-diimidazo[4,5-d:4',5'-f][1,3]diazepin-2-one		
SMILES	COC1=CC=C(CN2C=NC3=C2N=CN=C(N4CC5=CC=C(OC)C=C5)C3=NC4=O)C=C1		
Formula	$C_{23}H_{20}N_6O_3$	M.Wt	428.44
Solubility	≥ 21.4mg/mL in DMSO	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	RK-33		

Protocol

Cell experiment: Briefly, 8×102 MCF-7 cells are seeded in a 96-well plate, and treated with different concentrations of RK-33 loaded nanoparticles and unloaded nanoparticles next day. After 72-h incubation, MTS reagent is added to the cells, and the absorbance is measured at 490 nm after 2-h incubation with MTS reagent. The experiment is repeated three independent times.

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Animal experiment:

Mice are randomLy redistributed into four groups of eight according to their tumor growth, which results in an approximately equal distribution of tumor size at the beginning of radiation and RK-33 drug treatment. The four groups of mice are blindly chosen for four different experimental procedures, including control (injection of DMSO only), RK-33 treatment (injection of RK-33 only 50 mg/kg), radiation (one-time radiation of 5 Gy), or radiation and RK-33 treatment (combination of radiation of 5 Gy and RK-33 injection). RK-33 and DMSO are injected intraperitoneally thrice weekly for two weeks. Radiation is performed at the beginning of drug injection using the Small Animal Radiation Research Platform (SARRP) with a circular beam of 1 cm diameter, focusing on the tumor site. Mice of each group are euthanized 0 h and 24 h after radiation and tumors are extracted for γH2AX, cleaved Caspase 3, and Ki67 staining. The remaining mice of each group are imaged with a Xenogen IVIS Spectrum, with injection of D-luciferin 5 minutes before imaging. Mice are euthanized after six weeks of imaging and tumors are extracted for H&E staining, cleaved Caspase 3, and i67 staining. Morphology of the tumors after RK-33 and radiation treatment is assessed by a veterinary pathologist on hematoxylin and eosin stained sections.

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References:

[1]. Xie M,et al. RK-33 radiosensitizes prostate cancer cells by blocking the RNA helicase DDX3. Cancer Res. 2016 Sep 12.
[2]. Bol GM, e tal. PLGA nanoparticle formulation of RK-33: an RNA helicase inhibitor against DDX3. Cancer Chemother Pharmacol. 2015 Oct;76(4):821-7.

Background

IC50: 4.4-8.4 μM for cancer cell lines with high levels of DDX3 expression (A549, H1299, H23, and H460)

RK-33 is a DDX3 inhibitor.

DDX3 has been identified as a RNA helicase that is overexpressed in various cancer types such as lung cancer and is correlated with lower survival in lung cancer patients.

In vitro: RK-33 was reported to bind to DDX3 and abrogated its activity. Inhibition of DDX3 by

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RK-33 resulted in G1 cell cycle arrest, induced apoptosis, and promoted radiation sensitization in DDX3-overexpressing cells. Moreover, the loss of DDX3 function caused by RK-33 impaired Wnt signaling via disruption of the DDX3-β-catenin axis [1].

In vivo: The effect of RK-33 with a fractional dosing regimen was studied in the Twist1/KrasG12D lung cancer model. Results showed that during the 3 weeks treatment, a modest decrease in tumor growth with radiation and even more so with the combination of RK-33 and radiation. Therefore, these data indicated that RK-33 in combination with hypofractionated radiation was able to decrease lung tumor load effectively in preclinical lung cancer models and performed much better than the commonly used radiosensitizer carboplatin [1].

Clinical trial: Up to now, RK-33 is still in the preclinical development stage.

Reference:
[1] Bol GM et al. Targeting DDX3 with a small molecule inhibitor for lung cancer therapy. EMBO Mol Med. 2015 Mar 27;7(5):648-69.

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