

产品名称: **GDC-0623**
 产品别名: **RG 7421; MEK inhibitor 1**

生物活性:																									
Description	GDC-0623 (RG 7421) is a potent, ATP-uncompetitive inhibitor of MEK1 ($K_i=0.13$ nM, +ATP), and displays 6-fold weaker potency against HCT116 (KRAS (G13D), $EC_{50}=42$ nM) versus A375 (BRAF ^{V600E} , $EC_{50}=7$ nM).																								
IC₅₀ & Target	MEK1																								
	0.13 nM (K_i , +ATP)																								
In Vitro	GDC-0623 (RG 7421) and G-573 are able to prevent MEK phosphorylation by CRAF in vitro, and able to block MEK phosphorylation by BRAF(V600E)[1]. GDC-0623 (RG 7421) is potent, ATP-uncompetitive inhibitors of MEK1 but shows distinct shifts in cellular activity compared with the other two inhibitors, only 6-fold half-maximum effective concentration (EC_{50}) decreases[2].																								
In Vivo	GDC-0623 (RG 7421) (40 mg/kg, p.o.) shows percent tumour growth inhibition (%TGI) in MiaPaCa-2 xenograft model. GDC-0623 (RG 7421) and G-573 show superior antitumour activity compared to GDC-0623 (RG 7421) in all three KRAS models[1].																								
Solvent&Solubility	<p>In Vitro:</p> <p>DMSO : ≥ 30 mg/mL (65.76 mM)</p> <p>* "\geq" means soluble, but saturation unknown.</p>																								
	<table border="1"> <thead> <tr> <th rowspan="2">Preparing</th> <th>Solvent</th> <th>Mass</th> <th rowspan="2">1 mg</th> <th rowspan="2">5 mg</th> <th rowspan="2">10 mg</th> </tr> <tr> <th colspan="2">Concentration</th> </tr> </thead> <tbody> <tr> <td rowspan="3">Stock Solutions</td> <td>1 mM</td> <td></td> <td>2.1920 mL</td> <td>10.9599 mL</td> <td>21.9197 mL</td> </tr> <tr> <td>5 mM</td> <td></td> <td>0.4384 mL</td> <td>2.1920 mL</td> <td>4.3839 mL</td> </tr> <tr> <td>10 mM</td> <td></td> <td>0.2192 mL</td> <td>1.0960 mL</td> <td>2.1920 mL</td> </tr> </tbody> </table>	Preparing	Solvent	Mass	1 mg	5 mg	10 mg	Concentration		Stock Solutions	1 mM		2.1920 mL	10.9599 mL	21.9197 mL	5 mM		0.4384 mL	2.1920 mL	4.3839 mL	10 mM		0.2192 mL	1.0960 mL	2.1920 mL
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<p>*请根据产品在不同溶剂中的溶解度选择合适的溶剂配制储备液。一旦配成溶液，请分装保存，避免反复冻融造成的产品失效。</p> <p>储备液的保存方式和期限: -80°C, 6 months; -20°C, 1 month。-80°C 储存时，请在 6 个月内使用，-20°C 储存时，请在 1 个月内使用。</p>																									
References	<p>[1]. Hatzivassiliou G, et al. Mechanism of MEK inhibition determines efficacy in mutant KRAS- versus BRAF-driven cancers. Nature. 2013 Sep 12;501(7466):232-6.</p> <p>[2]. Takahashi RH, et al. Elucidating the Mechanisms of Formation for Two Unusual Cytochrome P450-Mediated Fused Ring Metabolites of GDC-0623, a MAPK/ERK Kinase Inhibitor. Drug Metab Dispos. 2015 Dec;43(12):1929-1933.</p>																								
实验参考:																									
Cell Assay	<p>Flag-MEK1 mutants, S212P and S212A, are generated using the QuickChange site directed mutagenesis kit. Mammalian expression vectors for N-terminal Flag tagged MEK-1 are expressed in HCT116 cells. 1.8×10^6 HCT116 cells are plated in 10 cm plate and transfected on the following day with 17 μg of expression constructs using lipofectamine 2000. After 48 hours cells are treated with inhibitors for the indicated times, harvested and lysed in 100 μL cell extraction buffer. Cell lysates from each sample are analyzed by SDS-PAGE. Membranes are incubated with phospho-MEK S221, phospho-ERK1/2 and MEK1 primary antibodies and immunoreactive proteins are analyzed by SuperSignal West Pico Chemiluminescent Substrate. [1]</p>																								

<p>Animal Administration</p>	<p>Colo205 xenografts are established by inoculating 5×10^6 cells resuspended in Hank's Balanced Salt Solution (HBSS) subcutaneously (s.c.) in the rear right flank of 6-8 week old female nude (nu/nu) mice. NCI-H2122 xenografts are established by inoculating 1×10^7 cells resuspended in Hank's Balanced Salt Solution (HBSS) plus matrigel (growth factor reduced) s.c. in the rear right flank of 6-8 week old female nu/nu mice. Both A375 and MiaPaca-2 xenografts are initiated by transplanting 1 mm³ tumor fragments from their respective passaged tumors s.c. into the flank of athymic nu/nu mice. When tumors reached appr 200 mm³, mice are randomized and treated with daily (QD) oral gavage (PO) with either vehicle [methylcellulose 0.1% tween 80 0.1% (MCT)], GDC-0973 (at 10 mg/kg), GDC-0623 (RG 7421) (40 mg/kg), or G-573 (100 mg/kg). All doses of MEK inhibitors represented maximal tolerated doses (MTDs), resulting in no more than 15-20% body weight loss. Tumor volumes are determined using digital calipers using the formula $(L \times W \times W)/2$. Tumor growth inhibition (%TGI) is calculated as the percentage of the area under the fitted curve (AUC) for the respective dose group per day in relation to the vehicle. Animal weights are recorded twice per week and mice are removed from study if body weights dropped $\geq 20\%$. Partial responses (PRs) are defined as any tumor demonstrating a $\geq 50\%$ decrease in tumor volume, whereas complete responses (CRs) are defined as any tumor demonstrating 100% reduction in tumor volume at any point during the study. [1]</p>
<p>References</p>	<p>[1]. Hatzivassiliou G, et al. Mechanism of MEK inhibition determines efficacy in mutant KRAS-versus BRAF-driven cancers. Nature. 2013 Sep 12;501(7466):232-6.</p> <p>[2]. Takahashi RH, et al. Elucidating the Mechanisms of Formation for Two Unusual Cytochrome P450-Mediated Fused Ring Metabolites of GDC-0623, a MAPK/ERK Kinase Inhibitor. Drug Metab Dispos. 2015 Dec;43(12):1929-1933.</p>

源叶生物