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产品名称：Genz-644282
产品别名：Genz-644282

生物活性：

Description	Genz-644282 is a non-camptothecin topoisomerase I inhibitor, used for cancer research.
IC_{50} & Target	Topoisomerase I
In Vitro	Genz-644282 is a topoisomerase I inhibitor. Genz-644282 shows potent activities against 29 human tumor cell lines with IC50s ranging from 1.8 nM to 1.8 μM[1]. Genz-644282 suppresses the PPTP cell lines, with IC50s of 0.2-21.9 nM, and the mean IC50 value is 1.2 nM[2]. Genz-644282 is potent at trapping Top1-DNA covalent cleavage complexes. Genz-644282 (0.1 μM) induces γH2AX foci in human colon cancer HCT116 cells and breast cancer MCF7 cells. Genz-644282 is cytotoxic on the CPT-resistant human cancer cell lines[3].
In Vivo	Genz-644282 (1-4 mg/kg) is active when administered intravenously to the mice. Genz-644282 (2.7 mg/kg, i.v.) causes tumor growth delay (TGD) of 34 days in the human HCT-116 colon cancer xenograft, 27 days in the human HT-29 colon carcinoma xenograft and mice bearing the NCI-H460 human non-small cell lung carcinoma. Genz-644282 (2 mg/kg, i.v.) results in a TGD of 33 days in the human HCT-15 colon carcinoma xenograft, and 28 days in mice bearing LOX-IMVI melanoma. Moreover, Genz-644282 (1 mg/kg, i.v.) leads to 14 days of TGD in mice bearing the DLD-1 human colon carcinoma xenograft. Genz-644282 (1.7 mg/kg, i.v.) also produces a TGD of 23 days in mice bearing 786-O tumors and 33 days in NCI-H1299 human non-small cell lung carcinoma xenograft[1]. Genz644282 at maximum tolerated dose (MTD, 4 mg/kg) results in maintained complete responses (MCR) in 6/6 evaluable solid tumor models. Genz644282 (2 mg/kg) induces CR or MCR in 3/3 tumor models and causes objective regressions in 7 of 17 (41%) models, but there are no objective responses at 1 mg/kg[2].
Solvent&Solubility	***In Vitro:*** **DMSO : 5 mg/mL** (**12.27 mM;** Need ultrasonic and warming)

Preparing Stock Solutions (Solvent / Mass / Concentration)	1 mg	5 mg	10 mg
1 mM	2.4545 mL	12.2723 mL	24.5447 mL
5 mM	0.4909 mL	2.4545 mL	4.9089 mL
10 mM	0.2454 mL	1.2272 mL	2.4545 mL

*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。

储备液的保存方式和期限：-80°C, 6 months; -20°C, 1 month (protect from light)。-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。

References

[1]. Kurtzberg LS, et al. Genz-644282, a novel non-camptothecin topoisomerase I inhibitor for cancer treatment. Clin Cancer Res. 2011 May 1;17(9):2777-87.

[2]. Houghton PJ, et al. Testing of the topoisomerase 1 inhibitor Genz-644282 by the pediatric preclinical testing program. Pediatr Blood Cancer. 2012 Feb;58(2):200-9.

[3]. Sooryakumar D, et al. Molecular and cellular pharmacology of the novel noncamptothecin

	topoisomerase I inhibitor Genz-644282. Mol Cancer Ther. 2011 Aug;10(8):1490-9.

实验参考：

Cell Assay	Twenty-nine established human tumor cell lines are exposed to a concentration range of Genz-644282 in two-four independent experiments. Human tumor cell lines representing a range of histology and potential resistance mechanisms includ MIA PaCa-2, AsPC-1, BxPC-3, CFPAC-1, Hs766T and Capan-1 pancreatic cancers, MEL624, C32, Hs695T and SK-MEL-3 melanomas, NCI-H1299, NCI-H292, NCI-H1915 and SW900 non-small cell lung cancers, HCC1395, HCC1937, HCC202, Hs578T, T-47D and ZR-75-1 breast cancer, ACHN, 769-P, A-498, A-704, SW156, Caki-2 and TK-10 renal cancers and OVCAR-4 and OVCAR-5 ovarian cancers. Cells are plated at 4 × 10^3/well in 96-well tissue culture plates in 100 µL RPMI medium supplemented with 5% FBS and 12 concentrations of Genz-644282 from 0.1 nM to 10 µM, with each concentration tested in triplicate. Plates are incubated overnight at 37ºC in humidified air with 5% CO_2. Plates are incubated with Genz-644282 at 37ºC with humidified air/5% CO_2 for 72 hrs. After the incubation period, the test plates are read utilizing Cell Titer-Glo Luminescent Cell Viability Assay. Luminescence is measured with a Synergy HT plate reader utilizing the associated ineticalc software, Version #3.4. Luminescence data are converted to growth fraction by comparison to the luminescence for the untreated control for each cell line and IC_{50} and IC_{90} values determined from the graphical data. Each cell line is tested in t least two independent experiments[1].
Animal Administration	Nu/nu mice are implanted subcutaneously with a 4 mm^3 tumor fragment, and treatments are initiated when tumors reach 200 mm^3. Compounds are prepared freshly prior to injection, with Genz-644282 is formulated in M/6 lactate, irinotecan in D5W (5% Dextrose, aqueous), gemcitabine in saline, and docetaxel in ethanol, Cremophor EL and saline. Genz-644282 is compared with irinotecan in experiments with the human HCT-116, HT-29, HCT-15 and DLD-1 colon carcinoma and 786-O renal cell carcinoma xenografts. Irinotecan is administered at 60 mg/kg/day by IV injection every fourth day for three injections. Genz-644282 is compared with docetaxel in the human CIH460 non-small cell lung carcinoma xenograft. Docetaxel is administered at 12, 16 or 20 mg/kg/day by IV injection on alternate days for three injections. Genz-644282 is compared with dacarbazine in the human LOX-IMVI melanoma xenograft. Dacarbazine is administered at 90 mg/kg/day by IP injection once daily for 5 days. Genz-644282 is administered at 1, 1.36, 1.7, 2.7 or 4.1 mg/kg/day by IV on alternate days 3-times per week for 2 weeks in all in vivo experiments[1].
References	[1]. Kurtzberg LS, et al. Genz-644282, a novel non-camptothecin topoisomerase I inhibitor for cancer treatment. Clin Cancer Res. 2011 May 1;17(9):2777-87. [2]. Houghton PJ, et al. Testing of the topoisomerase 1 inhibitor Genz-644282 by the pediatric preclinical testing program. Pediatr Blood Cancer. 2012 Feb;58(2):200-9. [3]. Sooryakumar D, et al. Molecular and cellular pharmacology of the novel noncamptothecin topoisomerase I inhibitor Genz-644282. Mol Cancer Ther. 2011 Aug;10(8):1490-9.