

Product Data Sheet

Product Name: Genz-644282

Cat. No.: GC15853

Chemical Properties

Cas. No. 529488-28-6

Chemical Name 2,3-dimethoxy-12-(2-(methylamino)ethyl)-[1,3]dioxolo[4',5':4,5]benzo[1,2-h]benzo[c][1,6]naphthyridin-13(12H)-one

SMILES O=C1N(C([H])([H])C([H])([H])N([H])C([H])([H])[H])C(C(C(N=C2[H])=C3[H])=C([H])C4=C3OC([H])([H])O4)=C2C(C1=C5[H])=C([H])C(OC([H])([H])[H])=C5OC([H])([H])[H])

Formula C₂₂H₂₁N₃O₅ M.Wt 407.42

Solubility DMF: 0.5 mg/ml, DMSO: 0.5 mg/ml, DMSO: PBS (pH 7.2) (1:20): 0.04 mg/ml, Ethanol: 0.2 mg/ml Storage 4°C, protect from light

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.

Shipping Condition Evaluation sample solution: ship with blue ice All other available size: ship with RT, or blue ice upon request.

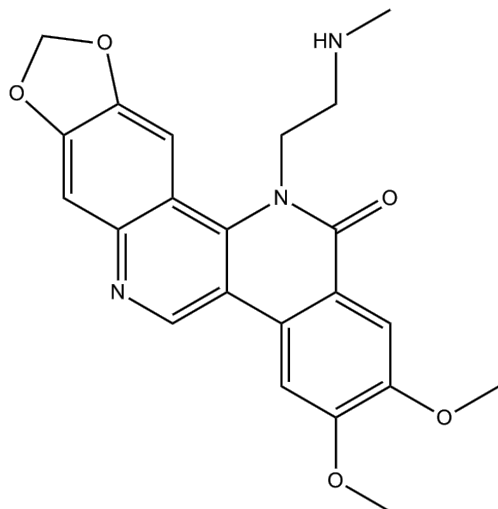
Caution: Product has not been fully validated for medical applications. For research use only.

Tel: (909) 407-4943 Fax: (626) 353-8530 E-mail: tech@glpbio.com

Address: 10292 Central Ave. #205, Montclair, CA, USA

Product Data Sheet

Structure



Protocol

Caution: Product has not been fully validated for medical applications. For research use only.

Tel: (909) 407-4943 Fax: (626) 353-8530 E-mail: tech@glpbio.com

Address: 10292 Central Ave. #205, Montclair, CA, USA

Product Data Sheet

Cell experiment: 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 include 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 μ L RPMI medium supplemented with 5% FBS and 12 concentrations of Genz-644282 from 0.1 nM to 10 μ M, with each concentration tested in triplicate. Plates are incubated overnight at 37°C in humidified air with 5% CO₂. Plates are incubated with Genz-644282 at 37°C with humidified air/5% CO₂ 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 IC₅₀ and IC₉₀ values determined from the graphical data. Each cell line is tested in at least two independent experiments[1].

Caution: Product has not been fully validated for medical applications. For research use only.

Tel: (909) 407-4943 Fax: (626) 353-8530 E-mail: tech@glpbio.com

Address: 10292 Central Ave. #205, Montclair, CA, USA

Product Data Sheet

**Animal
experiment:**

Nu/nu mice are implanted subcutaneously with a 4 mm³ tumor fragment, and treatments are initiated when tumors reach 200 mm³. 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.

Background

Description: IC₅₀ Value: 1.2 nM [1] Genz-644282 [8,9-dimethoxy-5-(2-N-methylaminoethyl)-2,3-methylenedioxy-5H-dibenzo[c,h][1,6]naphthyridin-6-one] has emerged as a promising candidate of non-Camptothecin topoisomerase I inhibitor for antitumor agents. in vitro: Genz-644282 demonstrated potent cytotoxic activity with a median IC₅₀ of 1.2 nM (range 0.2-21.9 nM) [1]. Limited cross-resistance to Genz-644282 was also found in the Top1 knockdown colon cancer (HCT116) and breast cancer (MCF7) cell lines and in human adenocarcinoma cells (KB31/KBV1)

Caution: Product has not been fully validated for medical applications. For research use only.

Tel: (909) 407-4943 Fax: (626) 353-8530 E-mail: tech@glpbio.com

Address: 10292 Central Ave. #205, Montclair, CA, USA

Product Data Sheet

that overexpress (P-glycoprotein, ABCB1), a member of the ATP-binding cassette family of cell surface transport proteins known to confer MDR [3]. in vivo: Genz-644282 at its MTD (4mg/kg) induced maintained complete responses (MCR) in 6/6 evaluable solid tumor models. At 2mg/kg Genz-644282 induced CR or MCR in 3/3 tumor models relatively insensitive to topotecan, but there were no objective responses at 1mg/kg [1]. Genz-644282 was tolerated at doses up to 4 mg/kg when administered intravenously on alternate days, and the compound was active at doses from 1 to 4 mg/kg. The efficacy of Genz-644282 was compared with irinotecan in 4 human colon carcinoma xenograft models. In the human HCT-116 colon cancer xenograft, TGD values were 14 days for irinotecan (60 mg/kg) and 34 days for Genz-644282 (2.7 mg/kg), giving maximum test to control ratios (T/Cs) of 23.7% and 16.8%, respectively [2]. Clinical trial: Dose-Escalation Study to Assess the Safety and Tolerability of Genz-644282 in Patients With Solid Tumors. Phase 1

Caution: Product has not been fully validated for medical applications. For research use only.

Tel: (909) 407-4943 Fax: (626) 353-8530 E-mail: tech@glpbio.com

Address: 10292 Central Ave. #205, Montclair, CA, USA