Product Data Sheet

Product Name: Genz-644282
Cat. No.: GC15853

Chemical Properties

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cas No.</td>
<td>529488-28-6</td>
</tr>
<tr>
<td>Chemical Name</td>
<td>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</td>
</tr>
</tbody>
</table>
| Canonical SMILES  | O=C1N(C([H])([H]))([H])N([H])C([H])([H])([H])C(C(N=C2([H]))=C3([H]))=C([H])C4=C30C([H])([H])=
                        C50C([H])([H])([H])=
                        C50C(N=C2([H]))=C3([H])=C([H])C4=C30C([H])([H])=
                        C50C([H])([H])([H])=[H] |
| Formula           | C_{22}H_{21}N_{3}O_{5}                                              |
| 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.

Structure
Protocol

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 x 103/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 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 t least two independent experiments[1].

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 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:

Background

Description: IC50 Value: 1.2 nM [1] Genz-644282 [8,9-dimethoxy-5-(2-N-methylaminoethyl)-2,3-methyleneoxo-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 IC(50) 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) 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