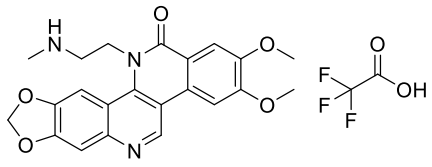
Product data sheet

MedKoo Cat#: 206482 Name: GENZ-644282 TFA salt CAS#: Unknown for TFA Chemical Formula: $C_{24}H_{22}F_3N_3O_7$ Molecular Weight: 521.45	
Product supplied as:	Powder
Purity (by HPLC):	≥ 98%
Shipping conditions	Ambient temperature
Storage conditions:	Powder: -20°C 3 years; 4°C 2 years.
	In solvent: -80°C 3 months; -20°C 2 weeks.

1. Product description:

Genz-644282, also known as SAR402674, is a non-camptothecin inhibitor of topoisomerase I with potential antineoplastic activity. Topoisomerase I inhibitor Genz-644282 binds to and inhibits the enzyme topoisomerase I, which may result in the inhibition of repair of single-strand DNA breaks, DNA replication, and tumor cell growth in susceptible tumor cell populations.

2. CoA, QC data, SDS, and handling instruction

SDS and handling instruction, CoA with copies of QC data (NMR, HPLC and MS analytical spectra) can be downloaded from the product web page under "QC And Documents" section. Note: copies of analytical spectra may not be available if the product is being supplied by MedKoo partners. Whether the product was made by MedKoo or provided by its partners, the quality is 100% guaranteed.

3. Solubility data

Solvent	Max Conc. mg/mL	Max Conc. mM
N/A	N/A	N/A

4. Stock solution preparation table:

Concentration / Solvent Volume / Mass	1 mg	5 mg	10 mg
1 mM	1.92 mL	9.59 mL	19.18 mL
5 mM	0.38 mL	1.92 mL	3.84 mL
10 mM	0.19 mL	0.96 mL	1.92 mL
50 mM	0.04 mL	0.19 mL	0.38 mL

5. Molarity Calculator, Reconstitution Calculator, Dilution Calculator

Please refer the product web page under section of "Calculator"

6. Recommended literature which reported protocols for in vitro and in vivo study

In vitro study

1. Sooryakumar D, Dexheimer TS, Teicher BA, Pommier Y. Molecular and cellular pharmacology of the novel noncamptothecin topoisomerase I inhibitor Genz-644282. Mol Cancer Ther. 2011 Aug;10(8):1490-9. doi: 10.1158/1535-7163.MCT-10-1043. Epub 2011 Jun 2. PMID: 21636699; PMCID: PMC3155218.
2. Kurtzberg LS, Roth S, Krumbholz R, Crawford J, Bormann C, Dunham S, Yao M, Rouleau C, Bagley RG, Yu XJ, Wang F, Schmid SM, Lavoie EJ, Teicher BA. Genz-644282, a novel non-camptothecin topoisomerase I inhibitor for cancer treatment. Clin Cancer Res. 2011 May 1;17(9):2777-87. doi: 10.1158/1078-0432.CCR-10-0542. Epub 2011 Mar 17. PMID: 21415217.

In vivo study

1. Kurtzberg LS, Roth S, Krumbholz R, Crawford J, Bormann C, Dunham S, Yao M, Rouleau C, Bagley RG, Yu XJ, Wang F, Schmid SM, Lavoie EJ, Teicher BA. Genz-644282, a novel non-camptothecin topoisomerase I inhibitor for cancer treatment. Clin Cancer Res. 2011 May 1;17(9):2777-87. doi: 10.1158/1078-0432.CCR-10-0542. Epub 2011 Mar 17. PMID: 21415217.

7. Bioactivity

Biological target:

Genz-644282 is a non-camptothecin topoisomerase I inhibitor, used for cancer research.

In vitro activity

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The induction and stability of Top1cc produced by Genz-644282 were evaluated in human colon cancer carcinoma HCT116 cells using the Immunocomplex of Enzyme (ICE) and alkaline elution assays. Figure 3A shows that Genz-644282 is more potent at trapping Top1-DNA covalent cleavage complexes than either CPT or TPT at the same concentration. Additionally, even metabolites of Genz-644282, Genz-649974, Genz-649975, and Genz-649978, are active and effective at trapping Top1 with Genz-649978 being less potent than the others (Fig. 3B).

Reference: Mol Cancer Ther. 2011 Aug; 10(8): 1490–1499. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3155218/

In vivo activity

Following i.v. administration of Genz-644282 (2 mg/kg) to nu/nu mice, the mean blood clearance, volume of distribution, and terminal half-life were 21.8 mL/min/kg, 5.44 L/kg, and 5.14 hours, respectively. An i.v. injection of Genz-644282 (2 mg/kg) to nu/nu mice bearing NCI-H460 human tumor xenografts resulted in plasma PK parameters of 104 mL/min/kg mean clearance, a 49.3-L/kg volume of distribution, and terminal half-life of 8.14 hours. The mean area under the curve (AUC) in tumor tissues (9,690 ng·h/mL) was approximately 30-fold higher than that observed in plasma (319 ng·h/mL), showing that Genz-644282 has a high penetration into tumor tissue in the xenograft model. For an analysis of the PK/PD relationship of Genz-644282, this study compared the exponential growth of tumors in control mice with tumor growth in the Genz-644282–treated mice. The growth decreased by a factor proportional to drug concentration. The estimated average tumor concentration of Genz-644282 at steady state ranged from 130 to 519 nmol/L, or 24- to 96-fold higher than the in vitro IC90 (5.4 nmol/L), thus predicting that the tumor would be responsive to treatment.

Reference: Clin Cancer Res. 2011 May 1;17(9):2777-87. https://clincancerres.aacrjournals.org/content/17/9/2777.long