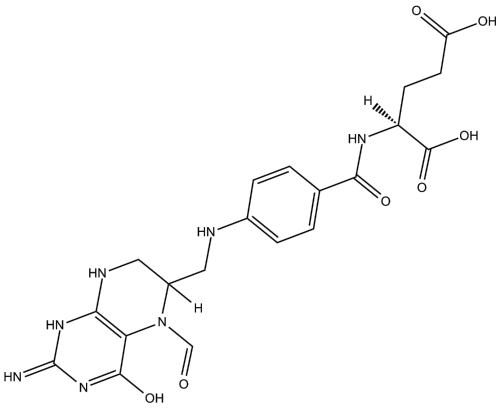
Product Data Sheet

Product Name: Folinic acid
Cat. No.: GC14331

Chemical Properties

Cas. No.	58-05-9		
Chemical Name	(2S)-2-(4-(((5-formyl-4-hydroxy-2-imino-1,2,5,6,7,8-hexahydropteridin-6-yl)methyl)amino)benzamido)pentanedioic acid		
SMILES	N=C1NC(NCC(N2C=O)([H])CNC3=CC=C(C(N[C@@](C(O)=O)([H])CCC(O)=O)=O)C=C3)=C2C(O)=N1		
Formula	$C_{20}H_{23}N_7O_7$	M.Wt	473.44
Solubility	<4.73mg/mL in DMSO, Limited solubility in Water	Storage	Store at -20°C, protect from light, stored under nitrogen
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 [1]:

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Cell lines	V79 Chinese hamster lung fibroblast cell line
Preparation Method	Folinic acid was dissolved in distilled water at 2mg/mL and diluted immediately prior to use. The concentration selection for Folinic acid (5 or 50μg/mL). The cultures were exposed to MTX (5-100mg/mL; 6h) and were post-treated with Folinic acid for 40h.
Reaction Conditions	5μg/mL and 50μg/mL; 40h
Applications	MTX alone induced a concentration-dependent increase in the percentage of micronucleated binucleated cells (MNBN) and aberrant cells (Abs), as well as a decrease in the nuclear division index (NDI) and mitotic index (MI). The addition of Folinic acid at 50μg/mL significantly reduced % MNBN (40-68%) and % Abs (36–77%). Inhibition was also seen at 5μg/mL Folinic acid (20% to 54% for MNBN and 20 to 61% for Abs).

Animal experiment [2]:

Animal models	HCT116 xenograft mouse model
Preparation Method	HCT116 cells were inoculated subcutaneously on the right flank of immunodeficient NOD scid gamma (NSG) mice. Mice were injected intraperitoneally with the vehicle control (PBS), 0.5mg/kg bortezomib, 80mg/kg Folinic acid, or the combination twice per week. Tumor size and mouse body weight were measured during the treatment.
Dosage form	80mg/kg; i.p.; twice a week for 2 weeks

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Applications	There were no significant differences in animal body weight. Folinic acid treatment had no effect on tumor growth, but bortezomib treatment suppressed tumor growth significantly. The combination of bortezomib and Folinic acid inhibited tumorigenesis to a greater extent than bortezomib alone.

References:
[1] Keshava C, Keshava N, Whong WZ, Nath J, Ong TM. Inhibition of methotrexate-induced chromosomal damage by folinic acid in V79 cells. Mutat Res. 1998;397(2):221-228.
[2] Wang S, Wang L, Zhou Z, et al. Leucovorin Enhances the Anti-cancer Effect of Bortezomib in Colorectal Cancer Cells. Sci Rep. 2017;7(1):682.

Background

Folinic acid (FA) is an ubiquitous member of biological folate pools, usually comprising 10-20% of total cellular folates. Folic acid is commonly used as a protective agent in combination with methotrexate (MTX), an anticancer compound, to mitigate the cytotoxic effects induced by MTX[1]. Folinic acid also serves as a sensitizer of 5-fluorouracil (5-FU)/FdUrd through inhibition of thymidylate synthase in tumor cells, thus potentiating the antitumor activity of 5-fluorouracil[4].

In vitro, Folinic acid (5 and 50μg/mL; 40h) reduced MTX-induced cytogenetic damage in V79 cells, as evidenced by decreased percentages of micronucleated binucleated cells (MNBN) and aberrant cells (Abs), alongside increased nuclear division index (NDI) and mitotic index (MI)[1]. Folinic acid (0.1-10μM; 72h) concentration-dependently enhances FdUrd (0.03μM) cytotoxicity in both DLD-1 and HCT116 cells[3]. Folinic acid (10μM; 24-48h) in combination with bortezomib (3-300nM) significantly enhances cytotoxicity and caspase-related apoptosis in HCT116 and HT29 cells[4].

In vivo, Folinic acid (1.5, 20, or 50mg/kg/dose; p.o.; twice daily), administered 6h after each daily TMX dose (25, 35, or 45mg/kg/d; p.o.), is able to protect rats against the toxicity induced by repeated daily TMX administration[1]. Folinic acid (7mg/kg; i.p.; every other day for 3 weeks) is able to reverse the inhibitory effect of MTX on skeletal growth in juvenile male Balb/c mice[2]. Folinic acid (80mg/kg; i.p.; twice a week for 2 weeks) in combination with bortezomib (0.5mg/kg) is able to induce apoptosis and inhibit tumor growth to a greater extent than bortezomib alone in HCT116 xenograft mouse model[4]. Topical administration of 2.5% Folinic acid facilitates cutaneous wound healing in rats,

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manifested by enhanced re-epithelialization, neovascularization, collagen deposition, and progressive mast cell increase[5].

References:

[1] Keshava C, Keshava N, Whong WZ, Nath J, Ong TM. Inhibition of methotrexate-induced chromosomal damage by folinic acid in V79 cells. Mutat Res. 1998;397(2):221-228.
[2] Iqbal MP, et al. Effect of methotrexate and folinic acid on skeletal growth in mice. Acta Paediatr. 2003 Dec;92(12):1438-44.
[3] Tsukihara H, Tsunekuni K, Takechi T. Folic Acid-Metabolizing Enzymes Regulate the Antitumor Effect of 5-Fluoro-2'-Deoxyuridine in Colorectal Cancer Cell Lines. PLoS One. 2016;11(9):e0163961.
[4] Wang S, Wang L, Zhou Z, et al. Leucovorin Enhances the Anti-cancer Effect of Bortezomib in Colorectal Cancer Cells. Sci Rep. 2017;7(1):682.
[5] Duman N, Duman R, Tosun M, et al. Topical folinic acid enhances wound healing in rat model. Adv Med Sci. 2018;63(2):347-352.

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