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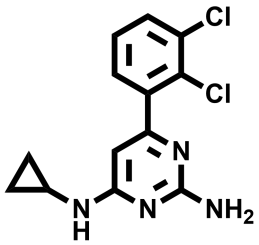
MTH1 Inhibitor TH588

Chemical Name: N^4-cyclopropyl-6-(2,3-dichlorophenyl)pyrimidine-2,4-diamine



Molecular Weight:	295.17
Formula:	$C_{13}H_{12}Cl_2N_4$
Purity:	≥98%
CAS#:	1609960-31-7
Solubility:	DMSO up to 50 mM
Storage	Powder: 4 °C 1 year DMSO: 4 °C 3 months -20 °C 1 year

Biological Activity:

TH588 is a novel potent, selective and cell permeable inhibitor of the nudix hydrolase family MTH1 protein with an IC50 of ~5 nM. Protein co-crystal structures demonstrate that TH588 binds in the active site of MTH1. It has excellent selectivity over other nudix family proteins and kinases present in the selectivity panel. The MTH1 protein sanitizes oxidized dNTP pools to prevent incorporation of damaged bases during DNA replication. Although MTH1 is non-essential in normal cells, the cancer cells require MTH1 activity to avoid incorporation of oxidized dNTPs. MTH1 inhibition by TH588 causes incorporation of oxidized dNTPs in cancer cells, leading to DNA damage, cytotoxicity and therapeutic responses in patient-derived mouse xenografts. TH588 is a good chemical tool to exemplify the non-oncogene addiction concept for anticancer treatment and validate MTH1 as a drug target.

How to Use:

In vitro: TH588 was used at 5-10 μM final concentration in various in vitro assays.

In vivo: TH588 was dosed to the mice by subcutaneous administration at 30 mg/kg once per day for 21 days. Formulation is 10% N-methylpyrrilidone, 90% PEG300.

Reference:

1. Gad H, et al. MTH1 inhibition eradicates cancer by preventing sanitation of the dNTP pool. (2014) Nature. 508(7495):215-21.