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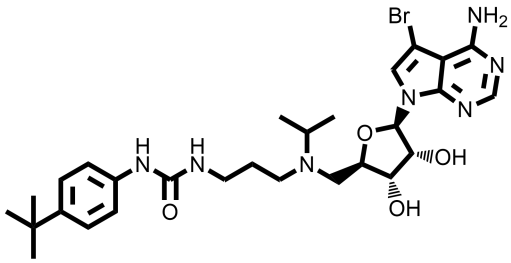
DOT1L inhibitor – SGC0946

Chemical Name: 1-(3-((((2R,3S,4R,5R)-5-(4-amino-5-bromo-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-3,4-dihydroxytetrahydrofuran-2-yl)methyl)(isopropyl)amino)propyl)-3-(4-(tert-butyl)phenyl)urea



Molecular Weight:	618.57
Formula:	$C_{28}H_{40}BrN_7O_4$
Purity:	≥ 98%
CAS#:	1561178-17-3
Solubility:	DMSO up to 100 mM
Storage	Powder: 4 °C 1 year DMSO: 4 °C 3 months -20 °C 1 year

Biological Activity:

SGC0946 is a highly potent and selective inhibitor of DOT1L methyltransferase. It selectively blocks binding of the cofactor, S-adenosylmethionine, to DOT1L, and inhibits the enzyme with an IC_{50} of 0.3 nM in a radioactive enzyme assay and is over 100-fold selective for other histone methyltransferases/HMTs. SGC0946 potently reduces H3K79 dimethylation with cellular IC_{50} of 2.6 nM in A431 cells, and 8.8 nM in MCF10A cells, which potently and selectively kills cells containing an MLL translocation. SGC0946 is much more potent than its close analog EPZ004777, and serves as an excellent chemical probe for investigating DOT1L and further development of DOT1L inhibitors for cancer therapy.

How to Use:

In vitro: SGC0946 was used at 1-5 μM final concentration in vitro and in cellular assays.

In vivo: SGC0946 was delivered via subcutaneously implanted mini-osmotic pumps capable of continuous infusion (drug load is ~50 mg/ml solution) for a period of 7 days in animal models.

Reference:

1. Yu W, et al. Catalytic site remodelling of the DOT1L methyltransferase by selective inhibitors. (2012) Nat Commun. 3:1288.
2. Yu W, et al. Bromo-deaza-SAH: A potent and selective DOT1L inhibitor. (2013) Bioorg Med Chem. 21(7):1787-94.