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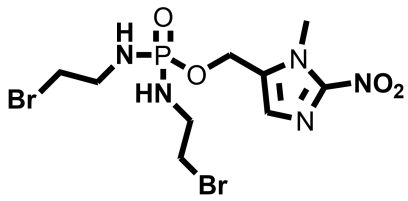
Hypoxia-activated Pro-drug – TH-302

Chemical Name: (1-methyl-2-nitro-1H-imidazol-5-yl)methyl N,N-bis(2-bromoethyl)phosphordiamidate



Molecular Weight:	449.04
Formula:	$C_9H_{16}FBr_2N_6O_4P$
Purity:	≥ 98%
CAS#:	918633-87-1
Solubility:	DMSO up to 50 mM
Storage	Powder: 4°C 1 year DMSO: 4°C 3 month -20°C 1 year

Biological Activity:

TH-302 is a highly potent and selective hypoxia-activated pro-drug targeting hypoxic regions of solid tumors with an IC_{50} of 19 nM. It is stable to liver microsomes. However, under hypoxic conditions, it is selectively and irreversibly converted to its active phosphoramidate-based, DNA-crosslinking, bis-alkylator. TH-302 inhibits H460 cells and HT29 cells with IC_{90} of 0.1 μM and 0.2 μM, respectively. It shows much enhanced potency in H460 spheroids compared to H460 monolayer cells under normoxia. TH-302 exhibits potent cytotoxicity to both human and murine MM cells with hypoxic selectivity and dose dependency, and induces G0/G1 cell-cycle arrest under hypoxic conditions. It inhibits primary tumor growth in multiple xenograft models. TH-302 is currently in a phase II clinical trial for the treatment of soft tissue sarcoma.

How to Use:

In vitro: TH-302 was used at 1 μM concentration in vitro and cellular assays.

In vivo: TH-302 was intraperitoneally (IP) dosed to mice at 50 mg/kg once per day to inhibit tumor growth.

Reference:

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2. Hu J, et al. Targeting the multiple myeloma hypoxic niche with TH-302, a hypoxia-activated prodrug. (2010) Blood. 116(9):1524-7.
3. Weiss GJ, et al. Phase 1 study of the safety, tolerability, and pharmacokinetics of TH-302, a hypoxia-activated prodrug, in patients with advanced solid malignancies. (2011) Clin Cancer Res. 17(9):2997-3004.
4. Meng F, et al. Molecular and cellular pharmacology of the hypoxia-activated prodrug TH-302. (2012) Mol Cancer Ther. 11(3):740-51.
5. Sun JD, et al. Selective tumor hypoxia targeting by hypoxia-activated prodrug TH-302 inhibits tumor growth in preclinical models of cancer. (2012) Clin Cancer Res. 18(3):758-70.
6. Moyer MW. Targeting hypoxia brings breath of fresh air to cancer therapy. (2012) Nat Med. 18(5):636-7.