

Product Data Sheet

Product Name: OTX-015

Cat. No.: GC17973

Chemical Properties

Cas. No. 202590-98-5

SMILES CC1=C(SC2=C1C(=NC(C3=NN=C(N32)C)CC(=O)NC4=CC=C(C=C4)O)C5=CC=C(C=C5)Cl)C

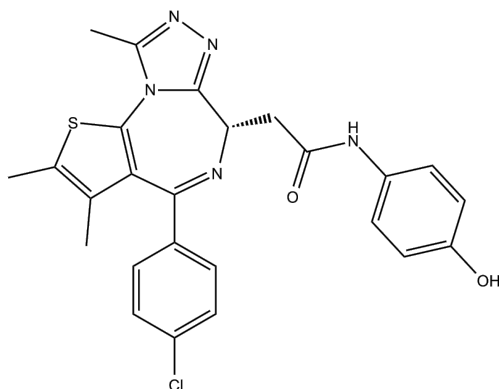
Formula $C_{25}H_{22}ClN_5O_2S$ M.Wt 491.99

Solubility ≥ 24.6 mg/mL in DMSO, ≥ 106 mg/mL in EtOH with gentle warming Storage Store at $-20^{\circ}C$

General tips For obtaining a higher solubility, please warm the tube at $37^{\circ}C$ and shake it in the ultrasonic bath for a while. Stock solution can be stored below $-20^{\circ}C$ 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]:

Cell lines $CD4^{+}$ T cells

Caution: Product has not been fully validated for medical applications. For research use only.

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CD4⁺ lymphocytes isolated from healthy donors were incubated with prostratin, Preparation Method OTX-015 or OTX-015/prostratin for 48 h and immunostained with anti-CD25, anti-CD69, anti-HLA-DR, anti-CD4, anti-CCR5 or anti-CXCR4 antibodies for 20 min at 4 °C.

Reaction Conditions 5 μM for 48 hours

Applications Primary CD4⁺ T cells were treated with OTX-015 for 48 h and evaluated for the expression of CD4, CCR5 and CXCR4 using flow cytometry. OTX-015 treatment did not cause an increase in the expression of these HIV receptors/co-receptors, suggesting that OTX-015 may not pose the risk of increasing the susceptibility of CD4⁺ T cells to HIV-1 infection during the reactivation of HIV-1 latency.

Animal experiment [2]:

Animal models Female nude Foxn1 mice 6-week-old

Preparation Method mice were randomized (nine animals/group) to one of the following experimental groups: vehicle (for OTX-015, water, twice daily, oral; for everolimus vehicle, 5% Tween-80/5% polyethylene glycol 400, thrice weekly, intraperitoneal); 50 mg/kg OTX-015, twice daily, oral; 2 mg/kg everolimus, thrice weekly, intraperitoneal; 50 mg/kg OTX-015 + 2 mg/kg everolimus, according to the single agent dosing schedules.

Dosage form 50 mg/kg OTX-015, twice daily, oral

Applications OTX-015-treated mice showed a substantial reduction in tumor mass with respect to the control group ($p < 0.05$) from 7 days after treatment start. The best T/C value was 41.3% recorded on day 23.

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- [1]. Lu P, et al. The BET inhibitor OTX-015 reactivates latent HIV-1 through P-TEFb. Sci Rep. 2016 Apr 12;6:24100
- [2]. Vázquez R, et al. The bromodomain inhibitor OTX-015 (MK-8628) exerts anti-tumor activity in triple-negative breast cancer models as single agent and in combination with RAD001. Oncotarget. 2017 Jan 31;8(5):7598-7613.

Background

OTX-015 inhibits the binding of BRD2, BRD3, and BRD4 to acetylated histone 4 in a concentration-dependent manner, with IC₅₀ values from 92-112nM [1].

OTX-015 significant growth inhibition was measured in six of nine AML cell lines and all four ALL cell lines: HEL IC₅₀ value as 248 nM, NB4 IC₅₀ value as 233 nM, NOMO-1 IC₅₀ value as 229 nM, KG1 IC₅₀ value as 198 nM, OCI-AML3 IC₅₀ value as 60 nM, Kasumi IC₅₀ value as 17 nM, JURKAT IC₅₀ value as 249 nM, BV-173 IC₅₀ value as 161 nM, TOM-1 IC₅₀ value as 133 nM, RS4-11 IC₅₀ value as 34 nM^[2]. GI₅₀ values obtained with OTX-015 in vitro in glioblastoma cell lines were equivalent to those achieved in plasma from patients treated at nontoxic doses in the ongoing Phase Ib clinical study in patients with hematologic malignancies, as described in a clinical pharmacokinetics evaluation. OTX-015 displayed higher potency (GI₅₀ 618.1 nM) in glioblastoma cell line panel. OTX-015 exerted antiproliferative effects and delayed tumor growth in lymphoma and neuroblastoma cells, together with a downregulation of C-MYC, MYCN and genes associated with superenhancers^[3].

OTX-015, offering a significant survival advantage in vivo in the orthotopic human glioblastoma model and slowing tumor progression in the heterotopic model with all administration regimens. Furthermore, no toxicity was seen with any of the OTX-015 dosing regimens, in direct contrast to treatment with temozolomide which induced pronounced weight loss. Synergistic and additive activity of OTX-015 in combination with several antitumor agents currently used to manage GBM patients, improving mouse survival with simultaneous combination of OTX-015 and temozolomide in the absence of toxicity, supporting the incorporation of OTX-015 as an epigenetic modulator in combination with temozolomide in glioblastoma ^[3].

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- [1]. J. Kay Noel, et al. Abstract C244: Development of the BET bromodomain inhibitor OTX015. Mol Cancer Ther November 2013 12; C244.
- [2]. Marie-Magdelaine Coudé, et al. BET inhibitor OTX015 targets BRD2 and BRD4 and decreases c-MYC in acute leukemia cells. Oncotarget. 2015 Jul 10; 6(19): 17698–17712.
- [3]. Berenguer-Daize C, et al. OTX015 (MK-8628), a novel BET inhibitor, displays in vitro and in vivo antitumor effects alone and in combination with conventional therapies in glioblastoma models. Int J Cancer. 2016;139(9):2047–2055.

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