Product Data Sheet

Product Name: Pixantrone
Cat. No.: GC12503

Chemical Properties

Cas. No.	144510-96-3		
Chemical Name	6,9-bis((2-aminoethyl)amino)benzo[g]isoquinoline-5,10-dione		
SMILES	NCCNC1=C(C(C2=CC=NC=C2C3=O)=O)C3=C(NCCN)C=C1		
Formula	$C_{17}H_{19}N_5O_2$	M.Wt	325.37
Solubility	Soluble in DMSO	Storage	Store at -20°C
General tips	For obtaining a higher solubility , please warm the tube at 37 ℃ and shake it in the ultrasonic bath for a while.Stock solution can be stored below -20℃ 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	Pixantrone		

Protocol

Cell experiment:

Briefly, cells seeded into 96-well plates are treated with increasing concentrations of either pixantrone or doxorubicin for 72 hours. After this time, MTS reagent is added to cells and incubated at 37°C for a further 4 hours. Cell proliferation is then determined by measuring the absorbance at 490 nm. All data points are normalized to untreated cells. All treatments are performed in triplicate and performed a minimum of 3 times[1].

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Animal experiment:

Mice[3]To evaluate the potential cardiotoxicity of Pixantrone in doxorubicin-pretreated mice, doxorubicin 7.5 mg/kg is administered intravenously every 7 days for 3 weeks (1 cycle) to a group of CD1 females. Six weeks later, these mice receive either 0.9% saline (vehicle), doxorubicin 7.5 mg/kg, Pixantrone 27 mg/kg, or mitoxantrone 3 mg/kg intravenously every 7 days for 3 weeks (2 cycles). Animals are sacrificed after the first cycle at 8 weeks, and after the second cycle at 16 weeks. In addition, to evaluate the potential cardiotoxicity of Pixantrone as a single agent compared with doxorubicin and mitoxantrone, CD1 female mice receive a single or a double cycle of vehicle, doxorubicin 7.5 mg/kg, Pixantrone 27 mg/kg, or mitoxantrone 3 mg/kg. These animals are sacrificed after the first and second cycles (at 8 and 16 weeks, all groups), during week 14 (Pixantrone-treated group only) and during week 22 (Pixantrone- and vehicle-treated groups)[3].Rats[4]For the studies on Pixantrone efficacy on EAMG, TAChR-immunized rats are randomly assigned to different treatment groups: 1) preventive Pixantrone group, starting 4 days after immunization, with 16.25 mg/kg Pixantrone, administered i.v. via tail vein, once a week for three times; 2) therapeutic Pixantrone group, starting 4 wk after immunization, with 16.25 mg/kg Pixantrone, administered i.v. via tail vein, once a week for three times; 3) therapeutic MTX group (1.2 mg/kg, i.v. via tail vein, once a week for three times); and 4) vehicle group (sterile saline, i.v. via tail vein, once a week for three times). The doses of Pixantrone and MTX used in this study are in both cases equal to one-fourth of the LD10 for single i.v. injection in rats. Treatment assignation is performed at day 4 after TAChR immunization (preventive schedule) in coincidence of the acute phase of EAMG, or at onset of clinical signs (therapeutic schedule), which occurs after 4 wk. Animals are sacrificed after deep anesthesia obtained by carbon dioxide; low-grade anesthesia with chloral hydrate administered i.p. is used for TAChR immunization and drug treatments[4].

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References:

[1]. Beeharry N, et al. Pixantrone induces cell death through mitotic perturbations and subsequent aberrant cell divisions. Cancer Biol Ther. 2015;16(9):1397-406.
[2]. Hasinoff BB, et al. Mechanisms of Action and Reduced Cardiotoxicity of Pixantrone; a Topoisomerase II Targeting Agent with Cellular Selectivity for the Topoisomerase IIα Isoform. J Pharmacol Exp Ther. 2016 Feb;356(2):397-409.
[3]. Cavalletti E, et al. Pixantrone (BBR 2778) has

reduced cardiotoxic potential in mice pretreated with doxorubicin: comparative studies against doxorubicin and mitoxantrone. Invest New Drugs. 2007 Jun;25(3):187-95.
[4]. Ubiali F, et al. Pixantrone (BBR2778) reduces the severity of experimental autoimmune myasthenia gravis in Lewis rats. J Immunol. 2008 Feb 15;180(4):2696-703.

Background

Pixantrone is a topoisomerase II inhibitor and DNA intercalator, with anti-tumor activity. Pixantrone is a topoisomerase II inhibitor. Pixantrone induces cell death in multiple cancer cell lines independent of cell cycle perturbation, with IC50s of 37.3 nM, 126 nM and 136 nM for T47D, MCF-10A and OVCAR5 cells, respectively. Pixantrone induces DNA damage at high concentrations (500 nM) but not at concentrations (100 nM) sufficient to kill PANC1 cells. Pixantrone (25 or 100 nM) induces severe chromosomal aberrations and mitotic catastrophe in PANC1 cells. Pixantrone (100 nM) may disrupt chromosome segregation because of generating merotelic kinetochore attachments that cause

chromosome non-disjunction[1]. Pixantrone potently inhibits growth of human Leukemia K562 cells, etoposide-resistant K/VP.5 cells, MDCK and ABCB1-transfected MDCK/MDR cells, with IC50s of 0.10 μM, 0.56 μM, 0.058 μM and 4.5 μM, respectively. Pixantrone (0.01-0.2 μM) leads to a concentration-dependent formation of linear DNA through acting on topoisomerase IIα. Pixantrone produces semiquinone free radicals in an enzymatic reducing system, although not in a cellular system, most likely due to low cellular uptake[2]. Pixantrone (0.01-10 μM) shows potent inhibitory activities against rat 97-116 peptide-specific T cell proliferation[4].

Pixantrone (27 mg/kg) does not worsen pre-existing moderate degenerative cardiomyopathy in doxorubicin-pretreated mice, by i.v. one dose every 7 days repeated thrice (q7d × 3). Pixantrone (27 mg/kg) causes minimal cardiotoxic in mice following repeated treatment cycles. Moreover, Pixantrone results in less mortality than mitoxantrone in doxorubicin-pretreated mice[3]. Pixantrone (16.25 mg/kg i.v, q7d × 3) modulates Lymph node cells (LNC) responses, and affacts T cell subpopulations in TAChR-immunized Lewis rats. Pixantrone also shows preventive and therapeutic effect in experimental autoimmune myasthenia gravis (EAMG) rats[4].

Reference:

[1]. Beeharry N, et al. Pixantrone induces cell death through mitotic perturbations and subsequent aberrant cell divisions. Cancer Biol Ther. 2015;16(9):1397-406.

[2]. Hasinoff BB, et al. Mechanisms of Action and Reduced Cardiotoxicity of Pixantrone; a Topoisomerase II Targeting Agent with Cellular Selectivity for the Topoisomerase IIα Isoform. J Pharmacol Exp Ther. 2016 Feb;356(2):397-409.

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