Pixantrone

Cat. No.: HY-13727A

CAS No.: 144675-97-8

Molecular Formula: $C_{25}H_{27}N_5O_{10}$

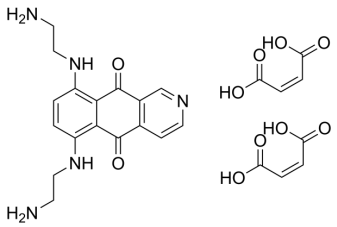
Molecular Weight: 557.51

Target: Topoisomerase

Pathway: Cell Cycle/DNA Damage

Storage: 4°C, sealed storage, away from moisture

* In solvent : -80°C, 6 months; -20°C, 1 month (sealed storage, away from moisture)



SOLVENT & SOLUBILITY

In Vitro

DMSO : 50 mg/mL (89.68 mM; Need ultrasonic)

H_2O : 8.33 mg/mL (14.94 mM; ultrasonic and warming and heat to 60°C)

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	1.7937 mL	8.9684 mL	17.9369 mL
5 mM	0.3587 mL	1.7937 mL	3.5874 mL
10 mM	0.1794 mL	0.8968 mL	1.7937 mL

Please refer to the solubility information to select the appropriate solvent.

In Vivo

1. Add each solvent one by one: PBS
   Solubility: 50 mg/mL (89.68 mM); Clear solution; Need ultrasonic
2. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: ≥ 0.83 mg/mL (1.49 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 0.83 mg/mL (1.49 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Pixantrone (BBR 2778) dimaleate is a topoisomerase II inhibitor and DNA intercalator, with anti-tumor activity.

IC_{50} & Target

Topoisomerase II

In Vitro

Pixantrone (0-10 μM, 72 h) dimaleate induces cell death in multiple cancer cell lines independent of cell cycle perturbation, with IC_{50}s of 37.3 nM, 126 nM and 136 nM for T47D, MCF-10A and OVCAR5 cells, respectively[1].

?Pixantrone (25-500 nM, 2 4 h) dimaleate induces DNA damage at high concentration of 500 nM and induces severe chromosomal aberrations and mitotic catastrophe in PANC1 cells[1].

?Pixantrone (100 nM, 24 h) dimaleate may disrupt chromosome segregation because of generating merotelic kinetochore attachments that cause chromosome non-disjunction[1].
?Pixantrone (0-100 μM, 72 h) dimaleate potently inhibits growth of human leukemia K562 cells, etoposide-resistant K/VP.5 cells, MDCK and ABCB1-transfected MDCK/MDR cells with IC_{50}s of 0.10 μM, 0.56 μM, 0.058 μM and 4.5 μM, respectively[2].
?Pixantrone (0.01-0.2 μM) dimaleate leads to a concentration-dependent formation of linear DNA through acting on topoisomerase Iiα and 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) dimaleate shows potent inhibitory activities against rat 97-116 peptide-specific T cell proliferation [4].

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

In Vivo

Pixantrone (i.v., 27 mg/kg, every 7 days, three times) dimaleate does not worsen pre-existing moderate degenerative cardiomyopathy, causes minimal cardiotoxic in mice following repeated treatment cycles and results in less mortality than Mitoxantrone (HY-13502) in Doxorubicin (HY-15142A)-pretreated mice[3].
?Pixantrone (i.v., 16.25 mg/kg, every week, three times) dimaleate modulates Lymph node cells (LNC) responses, affacts T cell subpopulations in TAChR-immunized Lewis rats and also shows preventive and therapeutic effect in experimental autoimmune myasthenia gravis (EAMG) rats[4].

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Cell Assay [1]

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 Administration [3][4]

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].

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- J Mol Med (Berl). 2019 Aug;97(8):1183-1193.
- Methods Mol Biol. 2018;1711:351-398.

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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.

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