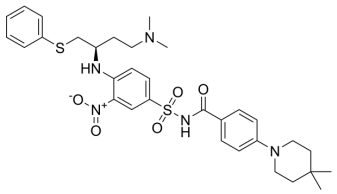
A-385358

Cat. No.:	HY-16014
CAS No.:	406228-55-5
Molecular Formula:	$C_{32}H_{41}N_5O_5S_2$
Molecular Weight:	639.83
Target:	Bcl-2 Family
Pathway:	Apoptosis
Storage:	Powder -20°C 3 years 4°C 2 years In solvent -80°C 2 years -20°C 1 year



SOLVENT & SOLUBILITY

In Vitro

DMSO : 50 mg/mL (78.15 mM; Need ultrasonic)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	1.5629 mL	7.8146 mL	15.6292 mL
	5 mM	0.3126 mL	1.5629 mL	3.1258 mL
	10 mM	0.1563 mL	0.7815 mL	1.5629 mL

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

In Vivo

1. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: 2.5 mg/mL (3.91 mM); Suspended solution; Need ultrasonic
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.5 mg/mL (3.91 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

A-385358 is a selective inhibitor of Bcl-X_L with K_is of 0.80 and 67 nM for Bcl-X_L and Bcl-2, respectively.

IC_{50} & Target

Bcl-xL	Bcl-2
0.8 nM (Ki)	67 nM (Ki)

In Vitro

A-385358 is a selective inhibitor of Bcl-X_L with K_is of 0.80 and 67 nM for Bcl-X_L and Bcl-2, respectively, in fluorescence polarization assays. Treatment of IL-3-deprived FL5.12/Bcl-X_L cells for 24 hours with A-385358 results in cell killing with an EC_{50} of 0.47±0.05 μM (n=68). This effect is accompanied by an increase in caspase-3 activity. Consistent with the greater affinity for the Bcl-X_L versus Bcl-2 hydrophobic grooves, the EC_{50} of A-385358 for IL-3-depleted FL5.12/Bcl-2 cells (1.9±0.1 μM; n=55) is 4-fold higher relative to the cytokine-deprived FL5.12/Bcl-X_L cells. In addition, A-385358 is more effective at

	stimulating cytochrome c release from mitochondria isolated from FL5.12/Bcl-X_L versus Bcl-2 cells[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	The combination of A-385358 given at 100 mg/kg/d plus the lower dose of paclitaxel produces a significant reduction in tumor growth (%T/C) compare with paclitaxel monotherapy. This combination also yields a >100% increase in time for tumors to reach 900 mm^3 (%ILS) compare with vehicle control. Maximal efficacy is observed during the dosing period for A-385358, with slow but steady increase in the tumor growth after termination of treatment. The combination of A-385358 at 75 mg/kg/d plus paclitaxel at 30 mg/kg/d is also well tolerated and inhibits tumor growth rate by nearly 80%. Significant effects on tumor growth relative to paclitaxel monotherapy are observed with doses as low as 50 mg/kg/d[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Kinase Assay [1]	FL5.12 cells suspended in EMB growth medium containing 4% fetal bovine serum (FBS) are incubated at 37°C for 1 hour in 10 μM A-385358. Compound concentration is determined by high-performance liquid chromatography before and after the 1-hour incubation following brief centrifugation. To analyze membrane-bound fractions following compound incubation, cells are washed once with 10 volumes of cold PBS and lysed with 4 mL of water. A-385358 concentration is determined from aliquots of lysate before and after centrifugation[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Cell Assay [1]	A549 cells (1×10^5) are plated in 96-well plates in medium containing 10% fetal bovine serum. Following attachment, A-385358 is added to one set of wells (final concentration of 50 μM in 10% FBS) and medium is added to another set. [^{3}H]Paclitaxel (5 μM; 0.5 μCi/mL final concentration) is added to all wells and the cells are incubated at 37°C for various periods of time. For washout experiments, cells are exposed first to [^{3}H]paclitaxel for 2 hours. The cells are washed once with medium and then incubated with fresh medium with or without 50 μM A-385358 at 37°C for various periods of time[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1]	For efficacy studies, male CD-1 nude mice are inoculated with a 1:5 dilution of tumor brei in 50% Matrigel and analysis is conducted. A-385358 is delivered in a vehicle containing 5% Tween 80, 20% propylene glycol, and 75% PBS (pH 3.8). Paclitaxel is formulated according to the recommendations of the manufacturer. For combination therapy of paclitaxel plus A-385358, both drugs are administered i.p. with the paclitaxel given several hours before treatment with A-385358 (except for immunohistochemistry studies looking at expression of MPM-2 and caspase-3 wherein the two drugs are given simultaneously)[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

REFERENCES

[1]. Shoemaker AR, et al. A small-molecule inhibitor of Bcl-XL potentiates the activity of cytotoxic drugs in vitro and in vivo. Cancer Res. 2006 Sep 1;66(17):8731-9.

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