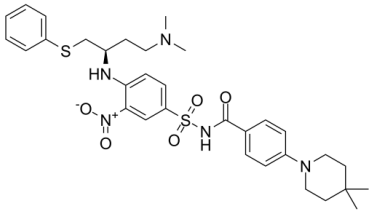
Data Sheet

Product Name:	A-385358
Cat. No.:	CS-0006108
CAS No.:	406228-55-5
Molecular Formula:	C32H41N5O5S2
Molecular Weight:	639.83
Target:	Bcl-2 Family
Pathway:	Apoptosis
Solubility:	DMSO : 125 mg/mL (195.36 mM; Need ultrasonic and warming)



BIOLOGICAL ACTIVITY:

A-385358 is a selective inhibitor of **Bcl-X_L** with **K_i**s of 0.80 and 67 nM for **Bcl-X_L** and **Bcl-2**, respectively. IC50 & Target: Ki: 0.80 nM (Bcl-X_L), 67 nM (Bcl-2) **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]. **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].

PROTOCOL (Extracted from published papers and Only for reference)

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]. **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]. **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].

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.

CAIndexNames:

Benzamide, N-[[4-[[(1R)-3-(dimethylamino)-1-[(phenylthio)methyl]propyl]amino]-3-nitrophenyl]sulfonyl]-4-(4,4-dimethyl-1-piperidinyl)-

SMILES:

O=C(NS(=O)(C1=CC=C(N[C@@H](CSC2=CC=CC=C2)CCN(C)C)C([N+]([O-])=O)=C1)=O)C3=CC=C(N4CCC(C)(C)CC4)C=C3

Tel: 732-484-9848 Fax: 888-484-5008 E-mail: sales@ChemScene.com

Address: 1 Deer Park Dr, Suite Q, Monmouth Junction, NJ 08852, USA