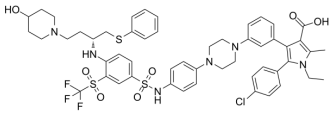
BM 957

Cat. No.:	HY-18106
CAS No.:	1391107-54-2
Molecular Formula:	$C_{52}H_{56}ClF_3N_6O_7S_3$
Molecular Weight:	1065.68
Target:	Bcl-2 Family
Pathway:	Apoptosis
Storage:	Please store the product under the recommended conditions in the Certificate of Analysis.



BIOLOGICAL ACTIVITY

Description	BM 957 is a potent Bcl-2 and Bcl-xL inhibitor, with K_is of 1.2, <1 nM and IC_{50}s of 5.4, 6.0 nM respectively.

IC_{50} & Target	Bcl-2 5.4 nM (IC_{50})	Bcl-xL 6.0 nM (IC_{50})	Bcl-2 1.2 nM (Ki)	Bcl-xL <1 nM (Ki)

In Vitro	BM 957 (Compound 30) with ethyl and compound 31 with isopropyl bind to both Bcl-2 and Bcl-xL with very high affinities. While BM 957 and 31 bind to Bcl-2 with IC_{50} values of 5.4 and 4.0 nM, respectively (K_i values=1.2 and 0.8 nM, respectively), they bind to Bcl-xL with IC_{50} values of 6.0 and 3.9 nM, respectively (K_i values < 1 nM). BM 957 has IC_{50} values of 21 nM and 22 nM, respectively, in these two cancer cell lines (H1417 and H146 cell lines). All these compounds induce cell death in a dose-dependent manner but have different potencies. While BM 957 and 31 are several times more potent than 1 and 2. BM 957 at 10 nM, 28 at 100 nM and 2 at 30 nM all induce clear cleavage of PARP and activation of caspase-3 and have similar effects. Hence, the potencies for these three compounds in induction of cleavage of PARP and activation of caspase-3 in the H146 cells are consistent with their potencies in induction of cell death[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	It is found that 28 at 50 mg/kg, BM 957 at 25 mg/kg and 31 at 10 mg/kg, daily, intravenous dosing, 5 days a week for 2 weeks are well tolerated in SCID mice and the animals have less than 10% of weight loss. Higher doses of these compounds (75 mg/kg for 28, 50 mg/kg for 30 and 25 mg/kg for 31) cause more than 10% of weight loss. Mice bearing H146 tumors are given a single i.v. dose of 28 at 50 mg/kg or BM 957 at 25 mg/kg. It showed that although compound 28 at 50 mg/kg effectively inhibits tumor growth, it fails to induce tumor regression. In contrast, BM 957 at 25 mg/kg is capable of achieving complete tumor regression. Of 7 mice treated with BM 957, all mice are tumor-free at day 47 and five (71%) remained tumor-free on day 58. Similar to the data obtained from our MTD experiment, both compounds 28 and BM 957 are well tolerated in tumor-bearing animals. All treated animals experienced less than 10% weight loss compared to the vehicle control and all regained their weight quickly after the treatments are finished. This in vivo experiment thus establish that BM 957 achieves complete and durable tumor regression in the H146 xenograft tumor model and is more efficacious than 28[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Cell Assay [1]	Two cancer cell lines (H1417 and H146 cell lines) are used. Induction of cell death by compounds (e.g., BM 957) in the H146 cell line. Cells are treated with different concentrations of the compounds (e.g., BM 957: 10, 30, 100 nM) for 24 hr. Cell

	viability is determined using a trypan blue exclusion assay[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1]	Mice[1] Induction of cleavage of PARP and caspase-3 in H146 xenograft tumors by compounds 28 and BM 957. SCID mice bearing H146 xenograft tumors (100-200 mm^3) are treated with vehicle control, single dose of 28 (50 mg/kg, i.v.) or BM 957 (25 mg/kg, i.v.). SCID mice bearing xenograft tumors (100 mm^3) are treated with vehicle control, compound 28 at 50 mg/kg, i.v. or BM 957 at 25 mg/kg, i.v., daily, 5 days a week for two weeks. The tumor growth inhibition for both compounds is statistically highly significant with p=0.0033 for compound 28 versus vehicle control and p=0.0006 for BM 957 versus vehicle control, respectively, when the mean tumor volume reaches 750 mm^3 in the vehicle treated group in both experiments[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

REFERENCES

[1]. Chen J, et al. Structure-based discovery of BM-957 as a potent small-molecule inhibitor of Bcl-2 and Bcl-xL capable of achieving complete tumor regression. J Med Chem. 2012 Oct 11;55(19):8502-14.

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