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## Product Data Sheet

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Product Name: BM 957  
 Cat. No.: GC33407

### Chemical Properties

Cas. No. 1391107-54-2

SMILES O=C(C1=C(C)N(CC)C(C2=CC=C(Cl)C=C2)=C1C3=CC=CC(N4CCN(C5=CC=C(NS(=O)(C6=CC=C(N[C@H](CCN7CCC(O)CC7)CSC8=CC=CC=C8)C(S(=O)(C(F)(F)F)=O)=C6)=O)C=C5)CC4)=C3)O

Formula C<sub>52</sub>H<sub>56</sub>ClF<sub>3</sub>N<sub>6</sub>O<sub>7</sub>S<sub>3</sub> M.Wt 1065.68

Solubility Soluble in DMSO Storage Store at -20°C

General tips For obtaining a higher solubility , please warm the tube at 37 °C and shake it in the ultrasonic bath for a while. Stock solution can be stored below -20°C 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

### Protocol

**Cell experiment:** 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].

**Caution: Product has not been fully validated for medical applications. For research use only.**

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### Animal experiment:

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<sup>3</sup>) 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<sup>3</sup>) 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<sup>3</sup> in the vehicle treated group in both experiments[1].

### 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.

### Background

BM 957 is a potent Bcl-2 and Bcl-xL inhibitor, with  $K_{is}$  of 1.2, <1 nM and IC<sub>50</sub>s of 5.4, 6.0 nM respectively.

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<sub>50</sub> 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<sub>50</sub> values of 6.0 and 3.9 nM, respectively ( $K_i$  values < 1 nM). BM 957 has IC<sub>50</sub> values of 21 nM and 22 nM, respectively, in these two cancer cell lines (H1417 and H146 cell lines). All these compounds

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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].

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].

[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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