

## Product Data Sheet

Product Name: HA15  
Cat. No.: GC19188

### Chemical Properties

Cas. No. 1609402-14-3

SMILES CC(NC1=NC(C2=CC=CC(NS(=O)(C3=C4C=CC=C(N(C)C)C4=CC=C3)=O)=C2)=CS1)=O

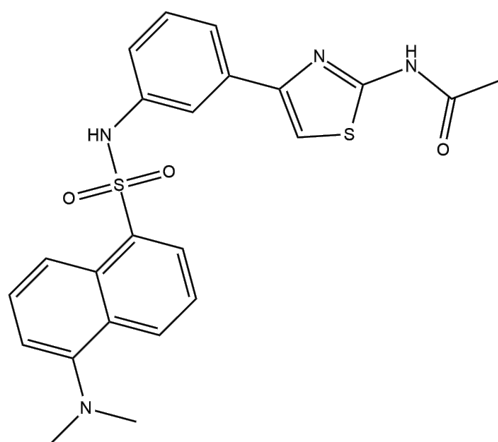
Formula  $C_{23}H_{22}N_4O_3S_2$  M.Wt 466.58

Solubility DMSO :  $\geq 50$  mg/mL (107.16 mM); Water :  $< 0.1$  mg/mL (insoluble) Storage Store at  $-20^{\circ}\text{C}$

General tips For obtaining a higher solubility, please warm the tube at  $37^{\circ}\text{C}$  and shake it in the ultrasonic bath for a while. Stock solution can be stored below  $-20^{\circ}\text{C}$  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 [1]:

Cell lines Resistant melanoma cell lines A375

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

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A375 cells were treated with indicated concentrations (1-10 $\mu$ M) of HA15. After 24h, viable cells were counted using the trypan blue dye exclusion method.

**Preparation Method** For trypan blue staining, 200 $\mu$ l of cells was aseptically transferred to a 1.5ml clear Eppendorf tube and incubated for 3min at room temperature with an equal volume of 0.4% trypan blue solution. Viable cells were counted and the results are expressed as the percentage of the value of control cells.

**Reaction Conditions** 1-10 $\mu$ M, 24h

**Applications** HA15 decreases melanoma cell viability in a dose-dependent manner compared with control conditions (DMSO), with an IC<sub>50</sub> of 1-2.5 $\mu$ M in A375 cells.

### Animal experiment [2]:

**Animal models** Malignant pleural mesothelioma (MPM) mouse model

**Preparation Method** Suspensions of tumor cells (in PBS) mixed with 1:1 with BD Matrigel Basement Membrane Matrix were subcutaneously inoculated in left and right flanks (BE261T cells: 1 $\times$ 10<sup>6</sup>/injection). When tumors were palpable, mice were randomly assigned to treatment groups: (1) control; (2) Cisplatin (3.75mg/kg) plus Pemetrexed (83mg/kg) (i.p., once weekly) for five weeks; (3) HA15 (0.7mg/mouse, i.p., 5 days/week) for five weeks. Mice weight and tumor size were measured every three days. Tumor size was calculated as follows: (length  $\times$  width  $\times$  width)/2. At the endpoint, blood samples were collected through cardiac puncta and subjected to the determination of transaminase activities.

**Dosage form** 0.7mg/mouse, 5 days/week, 5 weeks, i.p.

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**Applications** HA15 treatment delayed tumor growth in patient-derived xenograft models compared to the vehicle treatment.

### References:

- [1] Cerezo M, Lehraiki A, Millet A, et al. Compounds Triggering ER Stress Exert Anti-Melanoma Effects and Overcome BRAF Inhibitor Resistance. *Cancer Cell*. 2016 Jun 13;29(6):805-819.
- [2] Xu D, Yang H, Yang Z, et al. Endoplasmic Reticulum Stress Signaling as a Therapeutic Target in Malignant Pleural Mesothelioma. *Cancers (Basel)*. 2019 Oct 8;11(10):1502.

### Background

HA15 is a molecule that specifically targets BiP/GRP78/HSPA5, binding to and inhibiting its ATPase activity, which leads to the dissociation of BiP from PERK, IRE1 $\alpha$ , and ATF6, thereby triggering endoplasmic reticulum stress<sup>[1][2][3]</sup>. HA15 has demonstrated anti-tumor effects in a variety of human cancers, including melanoma, breast, pancreas, and adrenocortical carcinoma<sup>[2]</sup>.

HA15 (1-10 $\mu$ M, 24h) decreases melanoma cell viability in a dose-dependent manner compared with control conditions (DMSO), with an IC<sub>50</sub> of 1-2.5 $\mu$ M in A375 cells<sup>[1]</sup>. HA15 (10 $\mu$ M, 48h) induces typical dilated endoplasmic reticulum cisternae in A375 cells<sup>[1]</sup>. HA15 (1, 5 and 10 $\mu$ M; 48h) induces apoptosis in A375 cells by increasing the levels of the cleaved and activated form of caspase 9 and decreasing the levels of the zymogenic form of caspase 3<sup>[1]</sup>.

HA15 (0.7mg/mouse, 5 days/week, 5 weeks, i.p.) treatment delayed tumor growth in malignant pleural mesothelioma (MPM) mouse model<sup>[2]</sup>. HA15 (0.5mg/kg twice weekly, 3 weeks, i.p.) in combination with BTZ, was more effective at inhibiting tumor growth than BTZ alone in a multiple myeloma mouse model<sup>[4]</sup>.

### References:

- [1] Cerezo M, Lehraiki A, Millet A, et al. Compounds Triggering ER Stress Exert Anti-Melanoma Effects and Overcome BRAF Inhibitor Resistance. *Cancer Cell*. 2016 Jun 13;29(6):805-819.
- [2] Xu D, Yang H, Yang Z, et al. Endoplasmic Reticulum Stress Signaling as a Therapeutic Target in Malignant Pleural Mesothelioma. *Cancers (Basel)*. 2019 Oct 8;11(10):1502.
- [3] Ruggiero C, Doghman-Bouguerra M, Ronco C, et al. The GRP78/BiP inhibitor HA15 synergizes

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with mitotane action against adrenocortical carcinoma cells through convergent activation of ER stress pathways. Mol Cell Endocrinol. 2018 Oct 15;474:57-64.

[4] Chen Y, Tao Y, Hu K, et al. GRP78 inhibitor HA15 increases the effect of Bortezomib on eradicating multiple myeloma cells through triggering endoplasmic reticulum stress. Heliyon. 2023 Sep 2;9(9):e19806.

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