

## Product Data Sheet

Product Name: GCN2iB  
Cat. No.: GC32739

### Chemical Properties

Cas. No. 2183470-12-2

SMILES O=S(C1=CC(Cl)=CN=C1OC)(NC2=CC=C(F)C(C#CC3=CN=C(N)N=C3)=C2F)=O

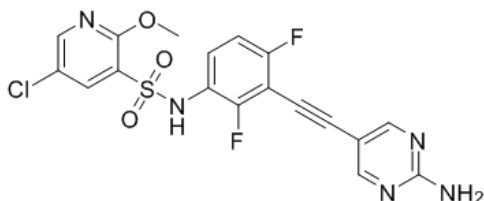
Formula  $C_{18}H_{12}ClF_2N_5O_3S$  M.Wt 451.83

Solubility DMSO : 16.67 mg/mL (36.89 mM); Water : < 0.1 mg/mL (insoluble) 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

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

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**Animal experiment:** Mice[1] A suspension of CCRF-CEM, HPB-ALL, MV-4-11, or SU.86.86 cells ( $1 \times 10^7$  cells/site) is subcutaneously injected into the right flanks of 6-week-old female SCID mice. Tumor volume is calculated as  $\text{volume} = L \times l^2 \times 1/2$ , where L represents the longest diameter across the tumor and l represents the corresponding perpendicular distance. Body weight is also measured. To assess the anti-tumor activity, mice with tumor mass  $\sim 200 \text{ mm}^3$  are sorted into treatment groups (N=5/group). The tumors are monitored and mice are euthanized when an endpoint is reached, or at the end of the study, whichever comes first. From the next day of randomization, GCN2 inhibitors (e.g., GCN2iB, 10 mpk, twice a day) or ASNase is orally or intraperitoneally administered to mice bearing the xenografts for 7 to 10 days, respectively. T/C (%), an index of anti-tumor activity, is calculated by comparing the mean change in tumor volume during the treatment period in the control and treated groups[1].

### References:

[1]. Nakamura A, et al. Inhibition of GCN2 sensitizes ASNS-low cancer cells to asparaginase by disrupting the amino acid response. Proc Natl Acad Sci U S A. 2018 Aug 14;115(33):E7776-E7785.

### Background

GCN2iB is an ATP-competitive inhibitor of a serine/threonine-protein kinase general control nonderepressible 2 (GCN2), with an  $IC_{50}$  of 2.4 nM.

GCN2iB shows an  $IC_{50}$  value of 2.4 nM for GCN2 and potent cellular activity. In a panel of 468 kinases, only GCN2 shows >99.5% inhibition, and three kinases (MAP2K5, STK10, and ZAK) show >95% inhibition at 1  $\mu\text{M}$  GCN2iB, demonstrating high kinase selectivity[1].

In the antitumor activity study of the CCRF-CEM xenografts, ASNase or GCN2iB alone does not significantly affect tumor growth. Notably, a combination of ASNase and GCN2iB elicit potent antitumor activity ( $P=0.0002$ ) with synergistic effects. In MV-4-11 and SU.86.86 xenografts, robust antitumor activity of the combination of GCN2iB and ASNase is observed with synergistic effect, respectively. ASNase/GCN2iB-treated tumors do not show significant growth even after drug

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cessation. The combination of ASNase and GCN2iB yield survival advantage compared with the vehicle treated control with synergistic effect[1].

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