# Product Data Sheet

Product Name: ISRIB
Cat. No.: GC10581

## Chemical Properties

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|---|---|---|---|
| Cas. No. | 548470-11-7 | | |
| Chemical Name | (1Z,1'Z)-N',N''-((1r,4r)-cyclohexane-1,4-diyl)bis(2-(4-chlorophenoxy)acetimidic acid) | | |
| SMILES | ClC1=CC=C(OC/C(O)=N/[C@@]2([H])CC[C@@](/N=C(O)/COC3=CC=C(Cl)C=C3)([H])CC2)C=C1 | | |
| Formula | $C_{22}H_{24}Cl_2N_2O_4$ | M.Wt | 451.34 |
| Solubility | 6 mg/mL in DMSO with gentle warming | Storage | Store at -20°C |
| General tips | For obtaining a higher solubility , please warm the tube at 37 ℃ and shake it in the ultrasonic bath for a while.Stock solution can be stored below -20℃ 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 | ISRIB | | |

## Protocol

### Cell experiment [1]:

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| Cell lines | U2OS cells |
| Preparation Method | U2OS cells were treated with 200nM thapsigargin (Tg) for 1h, 250μM arsenite (Ars) for 30min, or 100nM Pateamine A (Pat A) for 30min, either in the presence or absence of 200nM ISRIB. Immunofluorescence analysis was then performed, with eIF2α visualized using a secondary Alexa Fluor 488 anti-rabbit antibody and cell nuclei visualized using DAPI. |


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| Reaction Conditions | 200nM; 30min, 1h |
| Applications | ISRIB prevents formation of stress granules exclusively triggered by eIF2α phosphorylation. |

**Animal experiment [2]:**

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| Animal models | Male C57B6/J wild-type (WT) mice |
| Preparation Method | All animals were randomly assigned to undergo either sham surgery or traumatic brain injury (TBI) surgery. After surgery, the animals were returned to their cages after recovering to normal behavior in a 37°C environment. Subsequently, one day prior to the start of behavioral testing (day 27 post-injury), the sham surgery group and the TBI group were further randomly divided into a vehicle control group and an ISRIB treatment group, and administered the drug via intraperitoneal injection (ISRIB dose: 2.5mg/kg). |
| Dosage form | 2.5mg/kg; i.p. |
| Applications | ISRIB treatment can effectively improve spatial learning and memory deficits occurring 28 days after focal brain injury, as well as behavioral impairments observed in the radial maze and water maze tests. |


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References:
[1] Sidrauski C, McGeachy A M, Ingolia N T, et al. The small molecule ISRIB reverses the effects of eIF2α phosphorylation on translation and stress granule assembly[J]. elife, 2015, 4: e05033.
[2]Chou A, Krukowski K, Jopson T, et al. Inhibition of the integrated stress response reverses cognitive deficits after traumatic brain injury[J]. Proceedings of the National Academy of Sciences, 2017, 114(31): E6420-E6426.

## Background

ISRIB is an inhibitor of the protein kinase R-like endoplasmic reticulum kinase (PERK) signaling pathway. ISRIB effectively reverses the phosphorylation of eukaryotic translation initiation factor 2 alpha (eIF2α), with an $IC_{50}$ value of 5nM[1]. ISRIB is an inhibitor of the integrated stress response (ISR), which restores protein synthesis suppressed under stress conditions by modulating eIF2α activity, thus exerting neuroprotective effects and improving cognitive function[2, 3].

In vitro, treatment of U2OS cells with ISRIB (200nM) specifically blocked the formation of stress granules (SGs) induced by eIF2α phosphorylation[4]. Pretreatment of the myeloid leukemia cell line K562 with ISRIB (0-1000nM) for 2h significantly reduced the mRNA levels of ISR markers (CHOP and GADD34)[5].


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In vivo, ISRIB (2.5mg/kg) administered intraperitoneally to a mouse model of traumatic brain injury (TBI) significantly improved spatial learning and memory performance in the Morris water maze test[6]. ISRIB (0.25mg/kg) administered intraperitoneally to prion-infected mice reduced the levels of transcription factor ATF4 in the brain and partially restored protein synthesis rates, preventing hippocampal neuronal loss and reducing typical prion-related spongiform encephalopathy[7].

References:

[1] Sidrauski C, Acosta-Alvear D, Khoutorsky A, et al. Pharmacological brake-release of mRNA translation enhances cognitive memory[J]. elife, 2013, 2: e00498.
[2] Ilyin N P, Nikitin V S, Kalueff A V. The Role of the Integrated Stress Response (ISR) in Neuropsychiatric Disorders[J]. Journal of Evolutionary Biochemistry and Physiology, 2024, 60(6): 2215-2240.
[3] Costa-Mattioli M, Walter P. The integrated stress response: From mechanism to disease[J]. Science, 2020, 368(6489): eaat5314.
[4] Sidrauski C, McGeachy A M, Ingolia N T, et al. The small molecule ISRIB reverses the effects of eIF2α phosphorylation on translation and stress granule assembly[J]. elife, 2015, 4: e05033.
[5] Dudka W, Hoser G, Mondal S S, et al. Targeting integrated stress response with ISRIB combined with imatinib treatment attenuates RAS/RAF/MAPK and STAT5 signaling and eradicates chronic myeloid leukemia cells[J]. BMC cancer, 2022, 22(1): 1254.
[6] Chou A, Krukowski K, Jopson T, et al. Inhibition of the integrated stress response reverses cognitive deficits after traumatic brain injury[J]. Proceedings of the National Academy of Sciences, 2017, 114(31): E6420-E6426.
[7] Halliday M, Radford H, Sekine Y, et al. Partial restoration of protein synthesis rates by the small molecule ISRIB prevents neurodegeneration without pancreatic toxicity[J]. Cell death & disease, 2015, 6(3): e1672-e1672.


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