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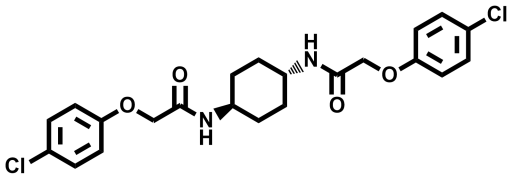
ISRIB (trans-isomer) --- Inhibitor of "Integrated Stress Response" (ISR)

Chemical Name: N,N'-((1r,4r)-cyclohexane-1,4-diyl)bis(2-(4-chlorophenoxy)acetamide)



Molecular Weight:	451.34
Formula:	$C_{22}H_{24}Cl_2N_2O_4$
Purity:	≥98%
CAS#:	1597403-47-8
Solubility:	DMSO up to 100 mM
Storage	Powder: 4 °C 1 year DMSO: 4 °C 3 months -20 °C 1 year

Biological Activity:

In cells, distinct stress conditions activate different downstream kinases, including PERK, that converge on phosphorylating the α-subunit of initiation factor 2 (eIF2α). This collection of signaling pathways is termed the 'integrated stress response' (ISR). **Trans-ISRIB** is a potent and selective small molecule inhibitor of PERK signaling (IC_{50} ~5 nM) that can potently reverse the effects of eIF2α phosphorylation. ISRIB reduces the viability of cells subjected to PERK-activation by chronic endoplasmic reticulum (ER) stress. The deleterious synergistic effect between ER-stress and ISRIB may be generally advantageous to kill cancer cells, especially those derived from secretory lineages that have increased secretory load and increased basal levels of ER stress (including myelomas, and pancreatic and breast cancers). Importantly, by acting downstream of eIF2α phosphorylation, ISRIB blocks multiple stress effectors. eIF2α phosphorylation is also implicated in memory consolidation. Remarkably, ISRIB-treated mice display significant enhancement in spatial and fear-associated learning. Thus, memory consolidation is inherently limited by the ISR, and ISRIB releases this brake. ISRIB may serve as an invaluable tool in deciphering higher order brain functions and perhaps be further developed as a therapeutic agent effecting memory impairment.

How to Use:

In vitro: Trans-ISRIB was used at 0.2 μM final concentration in various in vitro assays.

In vivo: Trans-ISRIB could be dosed to the mice by intraperitoneal injection at 2.5-5 mg/kg administration single dose. Trans-ISRIB displayed a half-life in plasma of 8 hr and readily crossed the blood-brain barrier, quickly equilibrating with the central nervous system.

Reference:

1. Sidrauski C, et al. Pharmacological brake-release of mRNA translation enhances cognitive memory. (2013) Elife. 2:e00498.