

Product Data Sheet

Product Name: PYR-41
Cat. No.: GC15771

Chemical Properties

Cas. No. 418805-02-4

Chemical Name ethyl 4-[(4Z)-4-[(5-nitrofuran-2-yl)methylidene]-3,5-dioxypyrazolidin-1-yl]benzoate

SMILES CCOC(=O)C1=CC=C(C=C1)N2C(=O)C(=CC3=CC=C(O3)[N+](=O)[O-])C(=O)N2

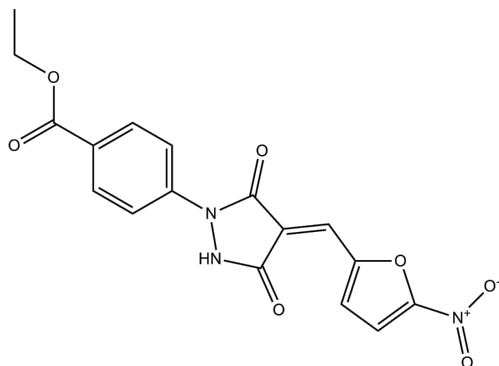
Formula $C_{17}H_{13}N_3O_7$ M.Wt 371.3

Solubility $\geq 18.55\text{mg/mL}$ 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 [1]:

Cell lines Dendritic cells

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

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Dendritic cells (DCs) were pre-treated with PYR-41 (5μM) for 30min before Preparation Method being co-incubated with or without Angiotensin II (100nM). Supernatants were harvested and frozen at -80°C before analysis for cytokines by ELISA kit.

Reaction
Conditions 5μM; 30min

Applications Angiotensin II treatment enhanced the secretion of IL-12, TNF-α, and IL-6, while high concentrations (5μM) of PYR-41 significantly reduced the secretion of these cytokines in the Angiotensin II-treated group.

Animal experiment [2]:

Animal models Male C57BL/6 mice

Mice were anesthetized with isoflurane inhalation, and their abdomens were shaved and cleaned with 10% povidone-iodine solution. An incision was made, and the cecum was ligated with 4-0 silk suture and punctured twice with a 22-gauge needle. Immediately after cecal ligation and puncture (CLP), the mice were administered either 20% DMSO in normal saline (vehicle) or 5mg/kg body Preparation Method weight of PYR-41 via intravenous injection. To prevent dehydration, mice received 0.5mL of normal saline subcutaneously immediately after surgery. At 20h post-CLP, blood and tissue samples were collected for various analyses. For the survival study, mice received a subcutaneous injection of the broad-spectrum antibiotic Primaxin (0.5mg/kg) after CLP. Survival was monitored for 10 days.

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Dosage form 5mg/kg; i.v.

Applications At 20h post-CLP, PYR-41 treatment significantly decreased serum levels of pro-inflammatory cytokines (TNF- α , IL-1 β , and IL-6) and organ injury markers (AST, ALT, and LDH). PYR-41 significantly improved lung tissue morphology, reduced myeloperoxidase activity, the number of apoptotic cells, and caspase-3 activation in the lungs of septic mice. The reduced I κ B protein levels in the lungs after CLP were restored by PYR-41 treatment. PYR-41 inhibited the expression of cytokines (IL-1 β and IL-6), chemokines (KC and MIP-2), and inflammatory mediators (COX-2 and iNOS) in the lungs of septic mice. Importantly, PYR-41 significantly increased 10-day survival in septic mice from 42% to 83%.

References:

- [1] Chen C, Meng Y, Wang L, et al. Ubiquitin-activating enzyme E1 inhibitor PYR-41 attenuates angiotensin II-induced activation of dendritic cells via the I κ B α /NF κ B and MKP-1/ERK/STAT-1 pathways[J]. Immunology, 2014, 142(2): 307-319.
- [2] Matsuo S, Sharma A, Wang P, et al. PYR-41, a ubiquitin-activating enzyme E1 inhibitor, attenuates lung injury in sepsis[J]. Shock, 2018, 49(4): 442-450.

Background

PYR-41 is an irreversible, cell-permeable inhibitor of ubiquitin-activating enzyme E1, with an IC₅₀ value less than 10 μ M and minimal effects on E2 and E3^[1, 2]. PYR-41 selectively and irreversibly binds to the cysteine residue of E1, effectively blocking the formation of the thioester bond between ubiquitin and E1, thereby inhibiting the upstream activation of the ubiquitin-proteasome pathway^[3].

In vitro, pretreatment of dendritic cells with PYR-41 (5 μ M) for 30min significantly reduced the increase in cytokine levels of IL-12, TNF- α , and IL-6 induced by angiotensin II^[4]. Treatment of MCF-7 breast cancer cells with PYR-41 (1 μ M) inhibited the rapid increase in AKT and p38/MAPK phosphorylation induced by 17 β -estradiol (E2), and suppressed the proliferative effect of E2 on MCF-

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7 cell colony formation^[5].

In vivo, intravenous administration of PYR-41 (5mg/kg) to septic mice significantly improved 10-day survival rate (from 42% to 83%), significantly reduced serum levels of pro-inflammatory cytokines (TNF- α , IL-1 β , and IL-6) and organ damage markers (AST, ALT, and LDH), and significantly improved lung morphology, reduced myeloperoxidase activity, apoptosis, and caspase-3 activation in lung tissue^[6]. Intraperitoneal administration of PYR-41 (5, 10mg/kg) to mice with angiotensin II-induced cardiac remodeling reduced angiotensin II-induced hypertension, cardiac hypertrophy, fibrosis, oxidative stress, and inflammation in a dose-dependent manner, and improved cardiac function^[7].

References:

- [1] Yang Y, Kitagaki J, Dai R M, et al. Inhibitors of ubiquitin-activating enzyme (E1), a new class of potential cancer therapeutics[J]. Cancer research, 2007, 67(19): 9472-9481.
- [2] Yoshida K, Kang W, Nakamura A, et al. Ubiquitin-activating enzyme E1 inhibitor PYR-41 retards sperm enlargement after fusion to the egg[J]. Reproductive Toxicology, 2018, 76: 71-77.
- [3] Ungermannova D, Parker S J, Nasveschuk C G, et al. Identification and mechanistic studies of a novel ubiquitin E1 inhibitor[J]. Journal of biomolecular screening, 2012, 17(4): 421-434.
- [4] Chen C, Meng Y, Wang L, et al. Ubiquitin-activating enzyme E 1 inhibitor PYR 41 attenuates angiotensin II-induced activation of dendritic cells via the I κ B α /NF- κ B and MKP 1/ERK/STAT 1 pathways[J]. Immunology, 2014, 142(2): 307-319.
- [5] Pesiri V, Totta P, Marino M, et al. Ubiquitin-activating enzyme is necessary for 17 β -estradiol-induced breast cancer cell proliferation and migration[J]. Iubmb Life, 2014, 66(8): 578-585.
- [6] Matsuo S, Sharma A, Wang P, et al. PYR-41, a ubiquitin-activating enzyme E1 inhibitor, attenuates lung injury in sepsis[J]. Shock, 2018, 49(4): 442-450.
- [7] Shu Q, Lai S, Wang X M, et al. Administration of ubiquitin-activating enzyme UBA1 inhibitor PYR-41 attenuates angiotensin II-induced cardiac remodeling in mice[J]. Biochemical and Biophysical Research Communications, 2018, 505(1): 317-324.

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