

Product Data Sheet

Product Name: ESI-09
Cat. No.: GC11877

Chemical Properties

Cas. No. 263707-16-0

Chemical Name (1E)-2-(5-tert-butyl-1,2-oxazol-3-yl)-N-(3-chloroanilino)-2-oxoethanimidoyl cyanide

SMILES CC(C)(C)C1=CC(=NO1)C(=O)C(=NNC2=CC(=CC=C2)Cl)C#N

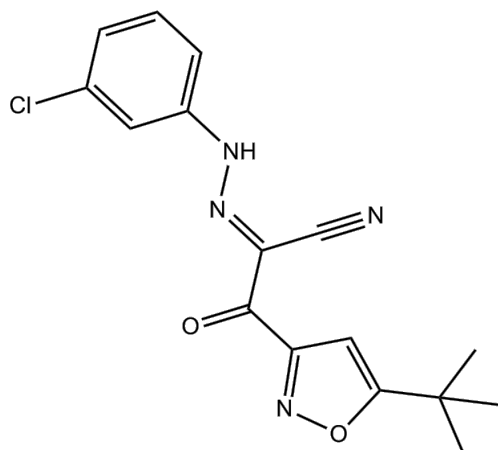
Formula $C_{16}H_{15}ClN_4O_2$ M.Wt 330.77

Solubility ≥ 33.1 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 PANC-1 cells (pancreatic ductal adenocarcinoma cell lines)

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Preparation Method PANC-1 cells were suspended and seeded in the opaque-walled multiple-well plates (5000 cells/100µl/well) and cultured overnight. Cells were treated with ESI-09 (1-10µM) alone, or treated with LiCl (1-10mM) + ESI-09 (1-10µM) in combinations for 48h. A total of 100µl of CellTiter-Glo® 2.0 reagent was added to each well and incubated for 10min to determine cell viability. The luminescence intensity was recorded using a microplate reader.

Reaction Conditions 1, 3, 5, and 10µM; 48h

Applications ESI-09 inhibited PANC-1 cell viability dose-dependently. Combination of LiCl and ESI-09 showed a significantly larger inhibitory effect toward PANC-1 cells, compared with LiCl or ESI-09 alone, a strong synergism between LiCl and ESI-09 in inhibiting PANC-1 cell viability.

Animal experiment [2]:

Animal models BALB/c-nu (nu/nu) mice bearing A549 cell xenografts

Preparation Method To generate tumor xenografts, A549 cells (5×10^6 cells) in 100µl of phosphate-buffered saline were injected into the subcutaneous flanks of nude mice. When the tumor volumes reached an average of approximately 100-150mm³, mice were treated with a monotherapy with ESI-09 (2mg/kg/day or 10mg/kg/day; 21 days; i.p.). At the end of the treatment period, blood samples were obtained by vena cava puncture under terminal anesthesia and the tumors were harvested and weighed. Plasma levels of CEA were measured using a human CEA ELISA kit.

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Dosage form 2mg/kg/day or 10mg/kg/day; 21 days; i.p.

Applications The monotherapy with ESI-09 at 2mg/kg/day or 10mg/kg/day significantly inhibited tumor growth by day 16. The plasma CEA levels were also significantly decreased in the mice treated with ESI-09 alone.

References:

- [1] WANG X, LUO C, CHENG X, et al. Lithium and an EPAC-specific inhibitor ESI-09 synergistically suppress pancreatic cancer cell proliferation and survival[J]. Acta Biochimica et Biophysica Sinica, 2017, 49(7): 573-580.
- [2] MAEDA Y, KIKUCHI R, KAWAGOE J, et al. Anti-cancer strategy targeting the energy metabolism of tumor cells surviving a low-nutrient acidic microenvironment[J]. Molecular Metabolism, 2020, 42: 101093.

Background

ESI-09 is a novel, cell-permeable, and specific inhibitor of the exchange protein directly activated by cAMP (EPAC), exhibiting IC₅₀ values of 3.2μM and 1.4μM for EPAC1 and EPAC2, respectively [1]. ESI-09 functions by blocking the guanine nucleotide exchange factor (GEF) activity of EPAC, thereby influencing downstream processes such as Akt phosphorylation and pancreatic cancer cell migration[2]. ESI-09 is commonly used to investigate the roles of EPAC proteins in cellular processes and disease models, such as pancreatic cancer and breast cancer[3].

In vitro, treatment of human non-small cell lung cancer A549 cell line with ESI-09 (2μM) for 48h in a glucose-free medium significantly reduced intracellular ATP content, increased the ADP/ATP ratio, and induced both apoptosis and necrosis[4]. Treatment of pancreatic cancer PANC-1 cells with ESI-09 (1-10μM) alone for 48h inhibited cell viability in a dose-dependent manner. The combination of 10mM LiCl and 10μM ESI-09 exhibited a synergistic effect, resulting in a significantly enhanced inhibition of PANC-1 cell viability[5]. Treatment of hippocampal neurons with ESI-09 (15μM) for 48h significantly reduced the percentage of polarized neurons and shortened axon length[6].

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In vivo, ESI-09 (2mg/kg/day or 10mg/kg/day) administered via intraperitoneal injection to mice bearing A549 tumor xenografts for 21 days significantly inhibited tumor growth from day 16 onwards and reduced plasma carcinoembryonic antigen (CEA) levels^[4]. Pretreatment of wild-type C57BL/6 mice with ESI-09 (10mg/kg/day) via intraperitoneal injection for 5 days, followed by intravenous inoculation with *Rickettsia australis* and continued ESI-09 administration for another 7 days, significantly alleviated disease severity and improved survival rate^[7].

References:

- [1] ALMAHARIQ M, TSALKOVA T, MEI F C, et al. A novel EPAC-specific inhibitor suppresses pancreatic cancer cell migration and invasion[J]. Molecular Pharmacology, 2013, 83(1): 122-128.
- [2] AHMED A, BOULTON S, SHAO H, et al. Recent advances in EPAC-targeted therapies: a biophysical perspective[J]. Cells, 2019, 8(11): 1462.
- [3] PARNELL E, PALMER T M, YARWOOD S J. The future of EPAC-targeted therapies: agonism versus antagonism[J]. Trends in Pharmacological Sciences, 2015, 36(4): 203-214.
- [4] MAEDA Y, KIKUCHI R, KAWAGOE J, et al. Anti-cancer strategy targeting the energy metabolism of tumor cells surviving a low-nutrient acidic microenvironment[J]. Molecular Metabolism, 2020, 42: 101093.
- [5] WANG X, LUO C, CHENG X, et al. Lithium and an EPAC-specific inhibitor ESI-09 synergistically suppress pancreatic cancer cell proliferation and survival[J]. Acta Biochimica et Biophysica Sinica, 2017, 49(7): 573-580.
- [6] MUÑOZ-LLANCAO P, HENRÍQUEZ D R, WILSON C, et al. Exchange protein directly activated by cAMP (EPAC) regulates neuronal polarization through Rap1B[J]. Journal of Neuroscience, 2015, 35(32): 11315-11329.
- [7] GONG B, SHELITE T, MEI F C, et al. Exchange protein directly activated by cAMP plays a critical role in bacterial invasion during fatal rickettsioses[J]. Proceedings of the National Academy of Sciences of the United States of America, 2013, 110(48): 19615-19620.

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