

Product Data Sheet

Product Name: GW441756

Cat. No.: GC14123

Chemical Properties

Cas. No. 504433-23-2

Chemical Name (3Z)-3-[(1-methylindol-3-yl)methylidene]-1H-pyrrolo[3,2-b]pyridin-2-one

SMILES CN1C=C(C2=CC=CC=C21)C=C3C4=C(C=CC=N4)NC3=O

Formula C₁₇H₁₃N₃O

M.Wt 275.3

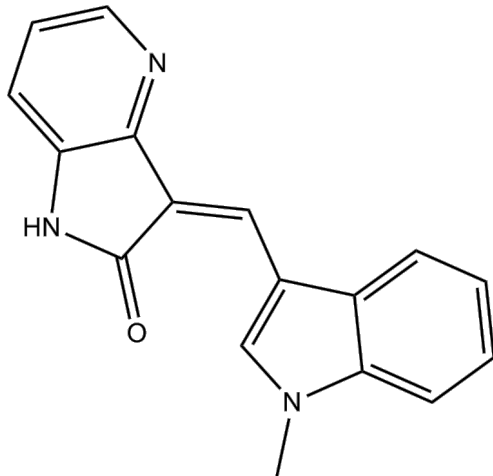
Solubility ≥ 13.75mg/mL in DMSO

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 RD-ES and SK-ES-1 (human Ewing sarcoma cell lines)

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

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Preparation Method	RD-ES and SK-ES-1 cells were treated with a range of doses of the specific TrkA receptor inhibitor GW441756 (0-15 μ M) for 72 hours.
Reaction Conditions	0-15 μ M; 72 hours.
Applications	GW441756 significantly reduced the proliferation of SK-ES-1 cells at all doses tested (IC_{50} =1.13 μ M) and reduced proliferation of RD-ES cells at doses of 1 μ M and above (IC_{50} =1.94 μ M). Furthermore, combined treatment of GW441756 with the TrkB selective inhibitor Ana-12 at low concentrations (0.1 μ M and 1 μ M) produced a more robust inhibition of cell proliferation than either inhibitor alone in both cell lines.
Animal experiment [2]:	
Animal models	Adult male Sprague Dawley rats with skin/muscle incision and retraction (SMIR)-induced chronic post-surgical pain
Preparation Method	An intrathecal catheter was implanted for drug delivery. The specific TrkA inhibitor GW441756 (1-100 μ M; 10 μ l) was administered intrathecally once daily from day 10 to day 14 after SMIR surgery. Behavioral tests (mechanical paw withdrawal threshold) were conducted.
Dosage form	1-100 μ M; 10 μ l; intrathecal injection; once daily for 5 consecutive days.

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Applications Repeated administration of GW441756 significantly reversed mechanical allodynia in SMIR rats with cumulative analgesic effects and without tolerance. GW441756 also suppressed the surgery-induced upregulation of Nav1.7, SGK1, and phospho-Nedd4-2 (p-Nedd4-2) proteins in the dorsal root ganglion (DRG).

References:

- [1] Heinen TE, Dos Santos RP, da Rocha A, et al. Trk inhibition reduces cell proliferation and potentiates the effects of chemotherapeutic agents in Ewing sarcoma. *Oncotarget*. 2016 Jun 7;7(23):34860-80.
- [2] Liu BW, Zhang J, Hong YS, et al. NGF-Induced Nav1.7 Upregulation Contributes to Chronic Post-surgical Pain by Activating SGK1-Dependent Nedd4-2 Phosphorylation. *Mol Neurobiol*. 2021 Mar;58(3):964-982.

Background

GW441756 is a potent inhibitor of tropomyosin receptor kinase A (TrkA) with an IC_{50} of 2nM, and GW441756 also exhibits inhibitory activity against leucine-rich repeat kinase 2 (LRRK2) with an IC_{50} of $2.2\mu M$ ^[1-2]. By inhibiting the TrkA receptor, GW441756 blocks the nerve growth factor (NGF) signaling pathway, thereby affecting cell proliferation, differentiation, and apoptosis, and can increase caspase-3 levels to induce apoptosis. GW441756 can be used in cancer research and neurobiology studies^[3-4].

In vitro, RD-ES and SK-ES-1 Ewing's sarcoma cells were treated with GW441756 (0-15 μM) for 72 hours. GW441756 significantly inhibited cell proliferation. When used in combination with the TrkB-selective inhibitor Ana-12, GW441756 produced a more robust anti-proliferative effect than either inhibitor alone^[5]. PC12 cells were pretreated with GW441756 (1 μM) for 4 hours, followed by stimulation with nerve growth factor (NGF; 50ng/mL) for 24 hours. GW441756 completely inhibited NGF-induced neurite outgrowth and blocked the enhancing effect of Rivastigmine on neurite growth^[6].

In vivo, in a CLP-induced sepsis model, mice received intraperitoneal injections of GW441756 (10mg/kg/day) for 22 days, starting 2 days before surgery. GW441756 completely abolished the

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protective effects of amitriptyline against neuronal loss, gliosis, cognitive dysfunction, and oxidative stress, and blocked amitriptyline's regulation of the Akt/GSK3 β signaling pathway and caspase-3 expression^[7]. In a rat model of chronic post-surgical pain induced by skin/muscle incision and retraction (SMIR), GW441756 (1-100 μ M; 10 μ l) was administered intrathecally once daily from day 10 to day 14 after surgery. GW441756 significantly alleviated mechanical allodynia and suppressed the upregulation of Nav1.7, SGK1, and p-Nedd4-2 proteins in the dorsal root ganglion^[8].

References:

- [1] Zhao F, Zou X, Li S, et al. BmK NSPK, a Potent Potassium Channel Inhibitor from Scorpion *Buthus martensii* Karsch, Promotes Neurite Outgrowth via NGF/TrkA Signaling Pathway. *Toxins* (Basel). 2021 Jan 5;13(1):33.
- [2] Wood ER, Kuyper L, Petrov KG, et al. Discovery and in vitro evaluation of potent TrkA kinase inhibitors: oxindole and aza-oxindoles. *Bioorg Med Chem Lett*. 2004 Feb 23;14(4):953-7.
- [3] Iimura A, Nishida E, Kusakabe M. Role of TrkA signaling during tadpole tail regeneration and early embryonic development in *Xenopus laevis*. *Genes Cells*. 2020 Feb;25(2):86-99.
- [4] Zhang J, Liu H, Zhang W, et al. Identification of lncRNA-mRNA Regulatory Module to Explore the Pathogenesis and Prognosis of Melanoma. *Front Cell Dev Biol*. 2020 Dec 17;8:615671.
- [5] Heinen TE, Dos Santos RP, da Rocha A, et al. Trk inhibition reduces cell proliferation and potentiates the effects of chemotherapeutic agents in Ewing sarcoma. *Oncotarget*. 2016 Jun 7;7(23):34860-80.
- [6] Terada K, Migita K, Matsushima Y, et al. Cholinesterase inhibitor rivastigmine enhances nerve growth factor-induced neurite outgrowth in PC12 cells via sigma-1 and sigma-2 receptors. *PLoS One*. 2018 Dec 17;13(12):e0209250.
- [7] Zhang L, Peng X, Ai Y, et al. Amitriptyline Reduces Sepsis-Induced Brain Damage Through TrkA Signaling Pathway. *J Mol Neurosci*. 2020 Dec;70(12):2049-2057.
- [8] Liu BW, Zhang J, Hong YS, et al. NGF-Induced Nav1.7 Upregulation Contributes to Chronic Post-surgical Pain by Activating SGK1-Dependent Nedd4-2 Phosphorylation. *Mol Neurobiol*. 2021 Mar;58(3):964-982.

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