

Product Data Sheet

Product Name: WNK463

Cat. No.: GC19383

Chemical Properties

Cas. No. 2012607-27-9

SMILES FC(F)(F)C1=NN=C(O1)C2=CN=C(N3CCC(N4C=NC=C4C(NC(C)(C)C)=O)CC3)C=C2

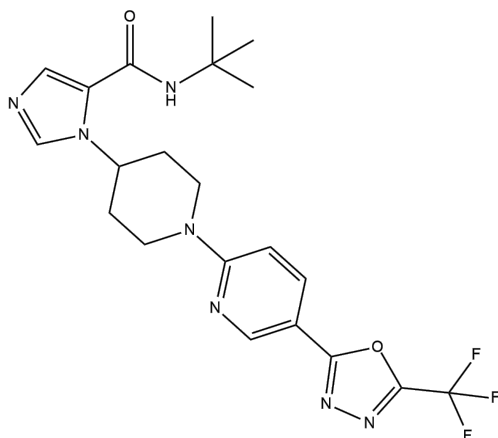
Formula $C_{21}H_{24}F_3N_7O_2$ M.Wt 463.46

Solubility DMSO : ≥ 30 mg/mL (64.73 mM) 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

HEK-293 cells

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

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Preparation method	Cells transfected with hKCC2 cDNA plasmids were treated with either WNK463 (1 μ M) or DMSO (0.1%) for 15 minutes at 37°C, three days post-transfection.
Reaction Conditions	1 μ M; 15 min
Applications	WNK463 decreased K ⁺ /Cl ⁻ cotransporter 2 (KCC2) phosphorylation and increased KCC2 activity in HEK-293 cells.
Animal experiment [1]:	
Animal models	C57BL/6 male mice (Alzet pump implantation surgeries)
Preparation method	Mini-osmotic pumps were loaded with 100 μ l WNK463 (8.57 mM) or DMSO (14.2%) and connected to brain infusion kit. The rate of drug delivery by the Alzet osmotic pumps was 0.25 μ l/h, resulting in final concentrations of 60 μ M WNK463 and 0.1% DMSO in the brain.
Dosage form	100 μ l WNK463 (8.57 mM) (0.857 μ mol); intra hippocampal infusion; 7 days
Applications	WNK463 reduces KCC2 phosphorylation <i>in vivo</i> .

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References:

[1]. Lee KL, Abiraman K, et.al. Inhibiting with-no-lysine kinases enhances K⁺/Cl⁻ cotransporter 2 activity and limits status epilepticus. *Brain*. 2022 Apr 29;145(3):950-963. doi: 10.1093/brain/awab343. PMID: 34528073; PMCID: PMC9050525.

Background

WNK463 inhibits the pan-With-No-Lysine (K) (WNK) kinase, demonstrating *IC*₅₀ values of 5 nM, 1 nM, 6 nM, and 9 nM for WNK1, WNK2, WNK3, and WNK4, respectively^[1-2].

WNK463 at 1 μM for 15 minutes decreased KCC2 phosphorylation at site 1007 and increased KCC2 activity in HEK-293 cells^[3]. WNK463(10 μM ;2h) significantly enhanced p38 activation in HeLa cells^[4]. Inhibition of WNK1 by WNK463(10 μM) leads to Ca²⁺ influx and permeability in lung endothelium via transient receptor potential vanilloid 4^[5].

WNK blockade by WNK463 (1 mg/kg; oral in water;3days) decreases TRPV4 activity and expression in the aldosterone-sensitive distal nephron (ASDN) in mice^[6]. WNK463 (8.57 mM, 100 μl, 0.857 μmol) administered via intra-hippocampal infusion for 7 days reduces KCC2-T1007 phosphorylation and restricts kainite (KA)-induced status epilepticus *in vivo*^[3]. WNK1–OSR1 axis inhibitors WNK463(11 μM,5 μL; p.o; twice a week for a month) combined with oligo-fucoidan attenuate hepatocellular carcinoma (HCC) proliferation^[7].

References:

[1]. Yamada K, Park HM, et.al. Small-molecule WNK inhibition regulates cardiovascular and renal function. *Nat Chem Biol*. 2016 Nov;12(11):896-898. doi: 10.1038/nchembio.2168. Epub 2016 Sep 5. PMID: 27595330.

[2]. Jonniya NA, Kar P. Investigating specificity of the anti-hypertensive inhibitor WNK463 against With-No-Lysine kinase family isoforms via multiscale simulations. *J Biomol Struct Dyn*. 2020 Mar;38(5):1306-1321. doi: 10.1080/07391102.2019.1602079. Epub 2019 Apr 24. PMID: 31017050.

[3]. Lee KL, Abiraman K, et.al. Inhibiting with-no-lysine kinases enhances K⁺/Cl⁻ cotransporter 2

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activity and limits status epilepticus. Brain. 2022 Apr 29;145(3):950-963. doi: 10.1093/brain/awab343. PMID: 34528073; PMCID: PMC9050525.

[4]. Liu Z, Demian W, et,al. Regulation of the p38-MAPK pathway by hyperosmolarity and by WNK kinases. Sci Rep. 2022 Aug 25;12(1):14480. doi: 10.1038/s41598-022-18630-w. PMID: 36008477; PMCID: PMC9411163.

[5]. Erfinanda L, Zou L, et,al. Loss of endothelial CFTR drives barrier failure and edema formation in lung infection and can be targeted by CFTR potentiation. Sci Transl Med. 2022 Dec 7;14(674):eabg8577. doi: 10.1126/scitranslmed.abg8577. Epub 2022 Dec 7. PMID: 36475904.

[6]. Tomilin VN, Pyrshev K, et,al. With-No-Lysine Kinase 1 (WNK1) Augments TRPV4 Function in the Aldosterone-Sensitive Distal Nephron. Cells. 2021 Jun 12;10(6):1482. doi: 10.3390/cells10061482. PMID: 34204757; PMCID: PMC8231605.

[7]. Hou CY, Ma CY, et,al. WNK1-OSR1 Signaling Regulates Angiogenesis-Mediated Metastasis towards Developing a Combinatorial Anti-Cancer Strategy. Int J Mol Sci. 2022 Oct 11;23(20):12100. doi: 10.3390/ijms232012100. PMID: 36292952; PMCID: PMC9602556.

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