G-5555 hydrochloride

Cat. No.: HY-19635A

CAS No.: 2319590-15-1

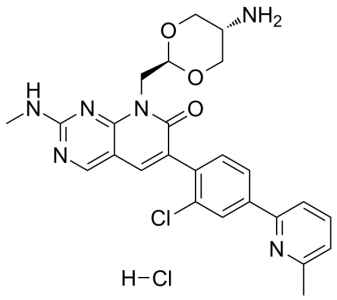
Molecular Formula: $C_{25}H_{26}Cl_2N_6O_3$

Molecular Weight: 529.42

Target: PAK

Pathway: Cell Cycle/DNA Damage; Cytoskeleton

Storage: 4°C, sealed storage, away from moisture
* In solvent : -80°C, 6 months; -20°C, 1 month (sealed storage, away from moisture)



SOLVENT & SOLUBILITY

In Vitro

DMSO : 100 mg/mL (188.89 mM; Need ultrasonic)
H_2O : 16.67 mg/mL (31.49 mM; Need ultrasonic)

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	1.8889 mL	9.4443 mL	18.8886 mL
5 mM	0.3778 mL	1.8889 mL	3.7777 mL
10 mM	0.1889 mL	0.9444 mL	1.8889 mL

Please refer to the solubility information to select the appropriate solvent.

In Vivo

1. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: ≥ 2.5 mg/mL (4.72 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.5 mg/mL (4.72 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

G-5555 hydrochloride is a potent and selective p21-activated kinase 1 (PAK1) inhibitor with a K_i of 3.7 nM.

IC_{50} & Target

PAK1	PAK2
3.7 nM (Ki)	11 nM (Ki)

In Vitro

G-5555 shows excellent kinase selectivity and inhibits only eight out of the 235 kinases tested other than PAK1 with inhibition >70%: PAK2, PAK3, KHS1, Lck, MST3, MST4, SIK2, and YSK1. The IC_{50}s of G-5555 against SIK2, PAK2, KHS1, MST4, YSK1, MST3 and Lck are 9, 11, 10, 20, 34, 43, 52 nM, respectively. In general, G-5555 demonstrates high selectivity for the group I PAKs. There is negligible activity for G-5555 against the hERG channel with IC_{50} more than 10 μM in a patch clamp assay[1]. In an array of 23 breast cancer cell lines, G-5555 has significantly greater growth inhibitory activity in cell lines that

	are PAK-amplified compared to non-amplified lines[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	G-5555 exhibits low blood clearance and an acceptable half-life. Good oral exposure (AUC=30 μM•h) and high oral bioavailability (F=80%) are achieved[1]. In an H292 non-small cell lunger cancer (NSCLC) xenograft study in mice, G-5555 inhibits phosphorylation of the PAK1/2 downstream substrate mitogen-activated protein kinase 1 (MEK1) S298 and, when administered at an oral dose of 25 mg/kg b.i.d., imparts 60% tumor growth inhibition in this model13 and a PAK1 amplified breast cancer xenograft model, MDAMB-175[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Kinase Assay [1]	The 10 μL assay mixtures contain 50 mM HEPES (pH 7.5), 0.01% Brij-35, 10 mM $MgCl_2$, 1 mM EGTA, 2 μM FRET peptide substrate, and PAK enzyme (20 pM PAK1; 50 pM PAK2; 90 pM PAK4). Incubations are carried out at 22°C in black polypropylene 384-well plates. Prior to the assay, enzyme, FRET peptide substrate and serially diluted test compounds (G-5555) are preincubated together in assay buffer (7.5 μL) for 10 minutes, and the assay is initiated by the addition of 2.5 μL assay buffer containing 4x ATP (160 μM PAK1; 480 μM PAK2; 16 μM PAK4). Following the 60-minute incubation, the assay mixtures are quenched by the addition of development reagent, and 1 hour later the emissions of Coumarin (445 nm) and Fluorescein (520 nm) are determined after excitation at 400 nm using an Envision plate reader[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1]	Mice: 3 mice in each of the two groups are administered 25 mg/kg oral suspension dose twice, with the second dose given 6 hours after the first dose. The dose volumes are 5 mL/kg for the IV group and 10 mL/kg for the PO groups. Following administration of G-5555 (12), 15 μL of blood is collected at each time point are stored at -70 to -80°C until analysis[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Acta Pharm Sin B. 2020 Apr;10(4):603-614.
- Elife. 2017 Mar 13;6:e22207.
- Endocr Relat Cancer. 2019 Aug;26(8):699-712.
- Endocr Relat Cancer. 2019 Aug;26(8):699-712.
- Exp Hematol. 2023 Sep 21;S0301-472X(23)01701-0.

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REFERENCES

[1]. Ndubaku CO, et al. Design of Selective PAK1 Inhibitor G-5555: Improving Properties by Employing an Unorthodox Low-pK a Polar Moiety. ACS Med Chem Lett. 2015 Oct 31;6(12):1241-6.

[2]. Rudolph J, et al. Chemically Diverse Group I p21-Activated Kinase (PAK) Inhibitors Impart Acute Cardiovascular Toxicity with a Narrow Therapeutic Window. J Med Chem. 2016 Jun 9;59(11):5520-41.

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

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