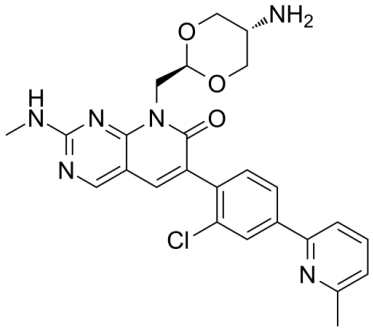
Data Sheet

Product Name:	G-5555
Cat. No.:	CS-5608
CAS No.:	1648863-90-4
Molecular Formula:	$C_{25}H_{25}ClN_6O_3$
Molecular Weight:	492.96
Target:	PAK
Pathway:	Cell Cycle/DNA Damage; Cytoskeleton
Solubility:	DMSO : 25 mg/mL (50.71 mM; ultrasonic and warming and heat to 80°C)



BIOLOGICAL ACTIVITY:

G-5555 is a potent p21-activated kinase 1 (**PAK1**) inhibitor with **K_i**s of 3.7 nM and 11 nM for PAK1 and PAK2, respectively. IC50 & Target: IC50: 11 nM (PAK2)[1]

Ki: 3.7 nM (PAK1)[1][2], 11 nM (PAK2)[2] **In Vitro:** G-5555 is a potent PAK1 inhibitor with a K_i of 3.7 nM. 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]. G-5555 potently inhibits PAK2, with a K_i of 11 nM. 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]. **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].

PROTOCOL (Extracted from published papers and Only for reference)

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**, etc.) 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 4× 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[1].

Animal Administration: G-5555 is prepared in corn oil and MCT (0.5% (w/v) methylcellulose/0.2% (w/v) Tween 80 in sterile water[1]. [1]Mice[1]

Three **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**, 15 μL of blood is collected at each time point are stored at -70 to -80°C until analysis[1].

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.

CAIndexNames:

Pyrido[2,3-d]pyrimidin-7(8H)-one, 8-[(trans-5-amino-1,3-dioxan-2-yl)methyl]-6-[2-chloro-4-(6-methyl-2-pyridinyl)phenyl]-2-(methylamino)-

SMILES:

ClC(C=C(C1=NC(C)=CC=C1)C=C2)=C2C3=CC4=CN=C(NC)N=C4N(C[C@@H]5OC[C@@H](N)CO5)C3=O

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