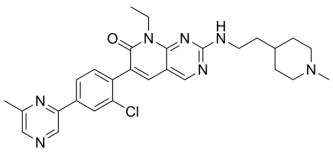
FRAX1036

Cat. No.:	HY-19538
CAS No.:	1432908-05-8
Molecular Formula:	$C_{28}H_{32}ClN_7O$
Molecular Weight:	518.05
Target:	PAK
Pathway:	Cell Cycle/DNA Damage; Cytoskeleton
Storage:	Powder -20°C 3 years 4°C 2 years In solvent -80°C 2 years -20°C 1 year



SOLVENT & SOLUBILITY

In Vitro

DMSO : 5.3 mg/mL (10.23 mM; Need warming)

Preparing Stock Solutions	Mass / Solvent / Concentration	1 mg	5 mg	10 mg
	1 mM	1.9303 mL	9.6516 mL	19.3032 mL
	5 mM	0.3861 mL	1.9303 mL	3.8606 mL
	10 mM	0.1930 mL	0.9652 mL	1.9303 mL

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

In Vivo

1. Add each solvent one by one: 50% PEG300 >> 50% saline
   Solubility: 10 mg/mL (19.30 mM); Suspended solution; Need ultrasonic

BIOLOGICAL ACTIVITY

Description

FRAX1036 is a PAK inhibitor with K_is of 23.3 nM, 72.4 nM, and 2.4 μM for PAK1, PAK2 and PAK4, respectively.

IC_{50} & Target

PAK1	PAK2	PAK4
23.3 nM (Ki)	72.4 nM (Ki)	2.4 μM (Ki)

In Vitro

FRAX1036 is a PAK inhibitor with K_is of 23.3 nM, 72.4 nM, and 2.4 μM for PAK1, PAK2 and PAK4, respectively. FRAX1036 (2.5 μM) incombination with docetaxel alters stathmin phosphorylation, induces the apoptotic marker cleaved PARP and increases kinetics of apoptosis in MDA-MB-175 and HCC2911 cells; also alters microtubule organization, mitosis and cell fate in U2OS cells. Moreover, FRAX1036 shows significantly effective inhibition on U2OS cells[1]. FRAX1036 (10 μM) affects the proliferation of non-small cell lung cancer (NSCLC) cells when added to KRAS prenylation inhibitors[2].

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Kinase Assay [1]

The activity/inhibition of human recombinant PAK1 (kinase domain), PAK2 (full length) or PAK4 (kinase domain) is estimated by measuring the phosphorylation of a FRET peptide substrate (Ser/Thr19) labeled with Coumarin and Fluorescein using Z'-LYTE^{TM} assay. The 10 μL assay mixtures containe 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 (FRAX1036, 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 5 μL of Z'-LYTE^{TM} development reagent, and 1 hour later the emissions of Coumarin (445 nm) and Fluorescein (520 nm) are determined after excitation at 400 nm. An emission ratio (445 nm/520 nm) is determined to quantify the degree of substrate phosphorylation[1].

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Cell Assay [1]

For caspase 3/7 activation apoptosis assays, cells are plated at 10,000 cells/well in 96-well plates for 24 hours prior to treating with DMSO, FRAX1036, and/or docetaxel. Caspase 3/7 reagent is added at a 1:1000 dilution. Cells are imaged at 10× magnification in an IncuCyte Zoom Live-content imaging system at 37°C, 5% CO_2. Images are acquired every 2 hours or 4 hours for 36 to 72 hours, two images/well. Data is analyzed using IncuCyte analysis software to detect and quantify green (apoptotic) cells/image. Each condition is performed in triplicate. Averages with SEM at each time point are plotted in Excel. A t-test is performed for the final time point comparing the combination of FRAX1036 and docetaxel with each single agent in Prism. The apoptotic index is calculated from the apoptosis assays by dividing the final apoptotic cell count by the total cell count. Averages with SEM are plotted in Excel, and a t-test is performed comparing the combination of FRAX1036 and docetaxel with each single agent in Prism[1].

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CUSTOMER VALIDATION

- Elife. 2017 Mar 13;6:e22207.
- bioRxiv. 2023 Apr 17.

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REFERENCES

[1]. Ong CC, et al. Small molecule inhibition of group I p21-activated kinases in breast cancer induces apoptosis and potentiates the activity of microtubule stabilizing agents. Breast Cancer Res. 2015 Apr 23;17:59.

[2]. Mortazavi F, et al. Significance of KRAS/PAK1/Crk pathway in non-small cell lung cancer oncogenesis. BMC Cancer. 2015 May 9;15:381.

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