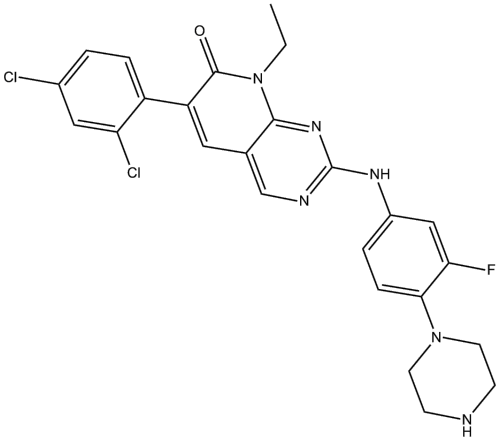
Product Data Sheet

Product Name: FRAX486
Cat. No.: GC16075

Chemical Properties

Cas. No.	1232030-35-1		
Chemical Name	6-(2,4-dichlorophenyl)-8-ethyl-2-((3-fluoro-4-(piperazin-1-yl)phenyl)amino)pyrido[2,3-d]pyrimidin-7(8H)-one		
SMILES	O=C1C(C2=CC=C(Cl)C=C2Cl)=CC3=CN=C(NC4=CC=C(N5CCNCC5)C(F)=C4)N=C3N1CC		
Formula	$C_{25}H_{23}Cl_2FN_6O$	M.Wt	513.39
Solubility	<2.59 mg/mL in DMSO, <2.62 mg/mL in ETOH, <2.56 mg/mL in Water	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

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Cell experiment: WPMY-1 cells are plated with a density of 50,000/well on a 16-well chambered coverslip. After 24 h, cells are treated with FRAX486 (1, 5, 10 μM), IPA3 (1, 5, 10 μM), or DMSO. After further 24 h, the medium is changed to a 10 mM 5-ethynyl-2'-deoxyuridine (EdU) solution in FCS-free medium containing inhibitors or solvent. 20 h later, cells were fixed with 3.7% formaldehyde. EdU incorporation is determined using the "EdU-Click 555" cell proliferation assay. In this assay, incorporation of EdU into DNA is assessed by detection with fluorescing 5-carboxytetramethylrhodamine (5-TAMRA). Counterstaining of all nuclei is performed with DAPI. Cells are analyzed by fluorescence microscopy (excitation: 546 nm; emission: 479 nm)[1].

Animal experiment: Mice[2] The fasted male C57BL/6 mice are used. For FRAX486, i.v. dose is 3 mg/kg using a 1 mg/mL solution in 20% (wt/vol) 2-hydroxypropyl-β-cyclodextrin in water, and per oral administration (o.s.) (PO) dose is 30 mg/kg in a 3 mg/mL solution in water. For the in vivo experiment, FRAX486 is intraperitoneally administered [10 μg/BW (g)] once daily from P35 to P60, which provides brain levels at >175 nM.

References:

[1]. Wang Y, et al. P21-Activated Kinase Inhibitors FRAX486 and IPA3: Inhibition of Prostate Stromal Cell Growth and Effects on Smooth Muscle Contraction in the Human Prostate. PLoS One. 2016 Apr 12;11(4):e0153312.
[2]. Hayashi-Takagi A, et al. PAKs inhibitors ameliorate schizophrenia-associated dendritic spine deterioration in vitro and in vivo during late adolescence. Proc Natl Acad Sci U S A. 2014 Apr 29;111(17):6461-6.

Background

IC50: 14, 33, 39 and 575 nM for PAK1, PAK2, PAK3 and PAK4 respectively

FRAX486 is a p21-activated kinase (PAK) inhibitor.

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PAKs are known as effector proteins for the Rho GTPases Cdc42 and Rac. Both in vitro and in vivo studies have showed PAKs play critical roles for cytoskeletal organization and in various aspects of cell growth and development.

In vitro: Previous study showed in WPMY-1 cells, FRAX486 could dose-dependently induce the degeneration of actin filaments, which was accompanied by proliferation rate attenuation. Moreover, the FRAX486 cytotoxicity in WPMY-1 cells was found to be both time- and concentration-dependent. In addition, the effects of FRAX486 on actin organization, survival, and proliferation were observed at 1-5 μM in WPMY-1 cells, and complete inhibition of PAK1-3 might be expected, whereas PAK4 might be inhibited only partially at these concentrations [1].

In vivo: Animal study found that FRAX486 was able to cross the blood-brain barrier (BBB) and the brain therapeutical FRAX486 concentrations were detected as early as 1 h and remained as long as 24 h, with the maximum concentration (Cmax) at 8 h. Moreover, FRAX486 could reduce hyperactivity and stereotypical movements, both of which were phenotypes characterizing the Fragile X syndrome mouse model [2].

Clinical trial: Up to now, FRAX486 is still in the preclinical development stage.

References:
[1] Wang Y,et al. P21-Activated Kinase Inhibitors FRAX486 and IPA3: Inhibition of Prostate Stromal Cell Growth and Effects on Smooth Muscle Contraction in the Human Prostate. PLoS One. 2016 Apr 12;11(4):e0153312.
[2] Dolan BM,Duron SG,Campbell DA,Vollrath B,Shankaranarayana Rao BS,Ko HY,Lin GG,Govindarajan A,Choi SY,Tonegawa S. Rescue of fragile X syndrome phenotypes in Fmr1 KO mice by the small-molecule PAK inhibitor FRAX486. Proc Natl Acad Sci U S A. 2013 Apr 2;110(14):5671-6.

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