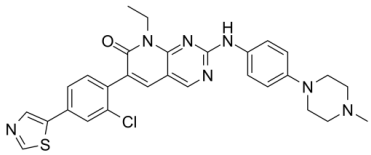
Data Sheet

Product Name:	FRAX597
Cat. No.:	CS-1977
CAS No.:	1286739-19-2
Molecular Formula:	C29H28ClN7OS
Molecular Weight:	558.10
Target:	PAK
Pathway:	Cell Cycle/DNA Damage; Cytoskeleton
Solubility:	H2O : < 0.1 mg/mL (insoluble); DMSO : 14.29 mg/mL (25.60 mM; Need ultrasonic)



BIOLOGICAL ACTIVITY:

FRAX597 is a potent group I p21-activated Kinases (**PAK**s) inhibitor with **IC_{50}** of 8, 13 and 19 nM for **PAK1**, **2** and **3**. IC50 & Target: IC50: 8 nM (PAK1), 13 nM (PAK2), 19 nM (PAK3), >10 μM (PAK4)[1] **In Vitro:** FRAX597 is determined to be a potent, ATP-competitive inhibitor of group I PAKs (PAK 1-3), with biochemical IC_{50} values as follows: PAK1 IC_{50}=8 nM, PAK2 IC_{50}=13 nM, PAK3 IC_{50}=19 nM. The IC_{50} toward PAK4, a member of group II PAKs is >10 μM. At a concentration of 100 nM FRAX597 displays a significant (>80% inhibition) inhibitory capacity toward YES1 (87%), RET (82%), CSF1R (91%), TEK (87%), PAK1 (82%), and PAK2 (93%). When measured using the Kinase Glo Assay in the presence of 20 nM protein and 1 μM ATP, FRAX597 displayed an IC_{50} value of 48 nM against wild type PAK1, while IC_{50} values against the V342F and V342Y PAK1 mutants are higher than 3 μM and 2 μM, respectively[1]. **In Vivo:** Analysis of the flux reading for the animals in the two cohorts demonstrates a significantly slower tumor growth rate in FRAX597-treated mice compared with control mice. After 14 days of treatment the animals are sacrificed and the tumors excised and weighed. FRAX597-treated cohort shows significantly lower average tumor weight compared with the control cohort (0.55 g versus 1.87 g, p=0.0001)[1].

PROTOCOL (Extracted from published papers and Only for reference)

Cell Assay: FRAX597 is dissolved in DMSO and stored, and then diluted with appropriate medium before use[1].[1]30,000 SC4 cells/well are plated in 12-well dishes in triplicate. Cell growth media with or without FRAX597 (1 μM) is replaced daily. At indicated time points, cells from individual wells are trypsinized and counted using a Coulter counter. Statistical analysis is performed using a Student's t test. For cell cycle analysis, cells are harvested, washed once with PBS and fixed in cold 70% ethanol. Fixed cells are resuspended in propidium iodide (PI) buffer (50 μg/mL PI, 250 mg/mL RNase A in PBS) and incubated overnight at 4°C in the dark. Cell cycle distribution is evaluated using Coulter Epics XL flow cytometer. Data are analyzed using WinMDI software[1]. **Animal Administration:** FRAX597 is dissolved in DMSO and then diluted with PBS or saline[1].[1]Mice[1]

$Nf2^{-/-}$ SC4 Schwann cells are transduced by lentiviruses carrying pLuc-mCherry and sorted by FACS. 5×10^4 cells are transplanted into the sciatic nerve sheath of NOD/SCID mice (8 weeks of age) by intraneural injection. Tumor progression is monitored weekly by bioluminescence imaging (BLI) on an IVIS-200 system. The representative images from bioluminescence imaging (BLI) of mice carrying orthotopic tumors treated with FRAX597 (100 mg/kg) or vehicle control at day 14 of treatment. NOD/SCID mice are injected intraneurally with 5×10^4 SC4/pLuc-mCherry cells and are enrolled into treatment after 10 days. Mice are treated daily for 14 days and imaged every 3 days to follow tumor development.

References:

[1]. Licciulli S, et al. FRAX597, a small molecule inhibitor of the p21-activated kinases, inhibits tumorigenesis of neurofibromatosis type 2 (NF2)-associated

Schwannomas. J Biol Chem. 2013 Oct 4;288(40):29105-14.

CAIndexNames:

Pyrido[2,3-d]pyrimidin-7(8H)-one, 6-[2-chloro-4-(5-thiazolyl)phenyl]-8-ethyl-2-[[4-(4-methyl-1-piperazinyl)phenyl]amino]-

SMILES:

O=C1C(C2=CC=C(C3=CN=CS3)C=C2Cl)=CC4=CN=C(NC5=CC=C(N6CCN(C)CC6)C=C5)N=C4N1CC

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