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Lieferung & Zahlungsart

siehe unsere Liefer- und Versandbedingungen

Zuschläge

- Mindermengenzuschlag
- Trockeneiszuschlag
- Gefahrgutzuschlag
- Expressversand

SZABO-SCANDIC HandelsgmbH

Quellenstraße 110, A-1100 Wien

T. +43(0)1 489 3961-0

F. +43(0)1 489 3961-7

mail@szabo-scandic.com

www.szabo-scandic.com

linkedin.com/company/szaboscandic

PF-AKT400

Cat. No.: HY-10721

CAS No.: 1004990-28-6

Molecular Formula: $C_{20}H_{22}F_2N_6O$

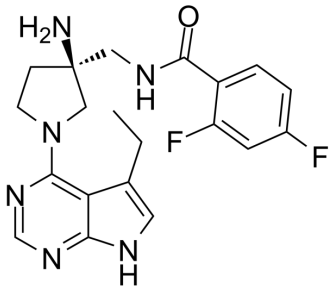
Molecular Weight: 400.43

Target: Akt

Pathway: PI3K/Akt/mTOR

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 : ≥ 100 mg/mL (249.73 mM)

* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	2.4973 mL	12.4866 mL	24.9732 mL
5 mM	0.4995 mL	2.4973 mL	4.9946 mL
10 mM	0.2497 mL	1.2487 mL	2.4973 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 (6.24 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.5 mg/mL (6.24 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (6.24 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

PF-AKT400 is a broadly selective, potent, ATP-competitive Akt inhibitor, displays 900-fold greater selectivity for PKBα (IC_{50} =0.5 nM) than PKA (IC_{50}=450 nM).

IC_{50} & Target

PKBα	PKA
0.5 nM (IC_{50})	450 nM (IC_{50})

In Vitro	PF-AKT400 (Compound 42) provides significantly enhanced selectivity for Akt relative to earlier leads such as spiroindoline 2. Free IC_{50} and EC_{50} values are estimated for phospho-S6 reduction (110 nM) and Akt hyperphosphorylation (216 nM), respectively. These values corresponded well to the cellular IC_{50} for PF-AKT400 in U87 cells measuring p-GSK-3α (310 nM)[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	PF-AKT400 is subsequently evaluated for modulation of Akt in tumors and in multiple in vivo mouse models of antitumor efficacy. It is active in a PC3 prostate carcinoma xenograft experiment, with 75% TGI observed at 100 mg/kg b.i.d. dosing for 10 days. In a colorectal carcinoma (Colo205) xenograft study, PF-AKT400 produces 60% TGI at 150 mg/kg b.i.d. after 10 days. Most intriguingly, in combination with Rapamycin (10 mg/kg, ip), 75 mg/kg b.i.d. (10 days) of PF-AKT400 results in 98% TGI in an additional PC3 prostate carcinoma xenograft study compared to 56% TGI and 66% TGI with PF-AKT400 and Rapamycin as single agents. To define the in vivo potency of PF-AKT400 (Compound 42) in the PC3 xenograft model, oral administration of 25, 75, and 100 mg/kg PF-AKT400 is performed with blood and tumor sampling over time. Immunoblot analysis of detergent-soluble extracts derived from PC3 tumors shows a significant reduction of S6 phosphorylation, and hyperphosphorylation of Akt upon treatment at doses that produced significant tumor growth inhibition. Plasma drug concentrations peak rapidly after oral administration of doses between 25-100 mg/kg (T_{max}=0.5 h). Peak PD responses of phospho-S6 and phospho-Akt are observed at approximately 2-4h and 1h post-administration of PF-AKT400, respectively. The time-course of PD marker response is well described by a PK/PD model at doses that ranged from no efficacy (25 mg/kg) to maximal efficacy (100 mg/kg)[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Kinase Assay [2]	A fluorescence polarization IMAP type assay is used. An amount of 15 µL of diluted PF-AKT400 (Compound 42) in DMSO is mixed with 60 µL of reaction buffer (10 mM Tris-HCl, pH 7.5, 10 mM $MgCl_2$, 0.1 mM EGTA, 0.01% Triton-X100, 1 mM DTT). Then 5 µL of the compound/buffer mixture, 10 µL of a solution containing 4 µM ATP and 40 nM fluorescent-labeled Crosstide (Tamara-labeled GRPRTSSFAEG peptide), and 5 µL of Akt1 protein (lacking the pleckstrin homology (PH) domain, containing an Asp at position 473, and prephosphorylated at Thr 308) in reaction buffer are combined. After a 90 min incubation, IMAP beads are added and plates are read (lamp filter, 544 nm; emission filter, 615 nm). The same procedure can be applied to full length Akt1 to provide similar results. All IC_{50} values are the geometric mean of at least n=2 determinations[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [2]	Mice[2] Studies to describe the PK/PD relationship for PF-AKT400 are performed in male SCID/Beige mice bearing subcutaneous PC3 prostate carcinoma xenografts. Once tumors reach about ~300mm^3 in size, PF-AKT400 is formulated in 0.5% methylcellulose vehicle and administered orally to 3 mice per dose group. Plasma and tumors are harvested over time, tumor lysates prepared, and the levels of phospho S6 reduction and phospho Akt induction are evaluated by immunoblot. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

REFERENCES

[1]. Chen SF, et al. Binding selectivity studies of PKBα using molecular dynamics simulation and free energy calculations. J Mol Model. 2013 Nov;19(11):5097-5112.

[2]. Freeman-Cook KD, et al. Design of selective, ATP-competitive inhibitors of Akt. J Med Chem. 2010 Jun 24;53(12):4615-4622.

Tel: 609-228-6898 Fax: 609-228-5909 E-mail: tech@MedChemExpress.com

Address: 1 Deer Park Dr, Suite Q, Monmouth Junction, NJ 08852, USA