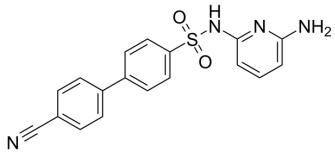
PF-915275

Cat. No.:	HY-18056
CAS No.:	857290-04-1
Molecular Formula:	$C_{18}H_{14}N_4O_2S$
Molecular Weight:	350.39
Target:	Others
Pathway:	Others
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 : ≥ 31 mg/mL (88.47 mM)

* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	2.8540 mL	14.2698 mL	28.5396 mL
5 mM	0.5708 mL	2.8540 mL	5.7079 mL
10 mM	0.2854 mL	1.4270 mL	2.8540 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: ≥ 0.83 mg/mL (2.37 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 0.83 mg/mL (2.37 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 0.83 mg/mL (2.37 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

PF-915275 is a potent, selective and orally active human 11β-hydroxysteroid dehydrogenase type 1 (11βHSD1) inhibitor with a K_i of 2.3 nM and an EC_{50} of 15 nM (in HEK293 cells). The dose-dependent effect of PF-915275 on conversion of cortisone to cortisol in primary human and monkey hepatocytes, with an EC_{50} of 20 and 100 nM, respectively[1][2][3].

IC_{50} & Target

Ki: 2.3 nM (11βHSD1); EC50: 15 nM (11βHSD1)[1]

In Vitro

PF-915275 is a potent inhibitor of 11βHSD1 (in vitro HEK293, EC_{50} of 15 nM) in this human 11βHSD1 overexpressed cell line when coincubated in the presence of 300 nM enzyme substrate. Consistent with the species differences between human and rodent observed in biochemical assays, PF-915275 is a poor inhibitor of 11βHSD1 in rat FAO hepatoma cells, with an EC_{50} of 14,500 nM. PF-915275 demonstrates species-dependent potency for inhibiting cellular conversion of cortisone to cortisol in dog, monkey, and human in primary hepatocytes, with activity in human hepatocytes/monkey hepatocytes/dog hepatocytes. PF-915275 does not significantly inhibit 11βHSD2 (only 1.5% inhibition when tested at 10 μM). The dose-dependent effect of PF-915275 on conversion of cortisone to cortisol in primary human and monkey hepatocytes, with an EC_{50} of 20 and 100 nM, respectively[1].

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

In Vivo

The inhibition of either cortisone or prednisone turnover with PF-915275 yields similar EC_{50} values to that in human hepatocytes (EC_{50} by PF-915275 is 18 and 13 nM using cortisone and prednisone substrates, respectively) in vivo 11βHSD1 activity[1].

PF-915275 dose-dependently inhibits 11βHSD1-mediated conversion of prednisone to prednisolone. A maximum of 87% inhibition is observed, with the highest tested dose of 3 mg/kg[1].

The half-life of PF-915275 is 22 hours in monkey[1].

PF-915275 (0.1-3 mg/kg; oral administration; for 8 hours; male cynomolgus monkeys) treatment shows a trend in dose-dependent lowering of fed plasma insulin after 8 h of dosing in these monkeys. Plasma insulin levels are significantly lowered (by 54 and 60%, respectively) at 1 and 3 mg/kg PF-915275 treatment. Plasma glucose or lipid levels are not altered with treatment[1].

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Animal Model:	Adult male cynomolgus monkeys (2-5 kg)[1]
Dosage:	0.1 mg/kg, 0.3 mg/kg, 1 mg/kg, 3 mg/kg
Administration:	Oral administration; for 8 hours
Result:	There was a trend in dose-dependent lowering of fed plasma insulin after 8 h of dosing in these monkeys. Plasma insulin levels were significantly lowered (by 54 and 60%, respectively).

REFERENCES

[1]. Bhat BG, et al. Demonstration of proof of mechanism and pharmacokinetics and pharmacodynamic relationship with 4'-cyano-biphenyl-4-sulfonic acid (6-amino-pyridin-2-yl)-amide (PF-915275), an inhibitor of 11 -hydroxysteroid dehydrogenase type 1, in cynomolg

[2]. Siu M, et al. N-(Pyridin-2-yl) arylsulfonamide inhibitors of 11beta-hydroxysteroid dehydrogenase type 1: Discovery of PF-915275. Bioorg Med Chem Lett. 2009 Jul 1;19(13):3493-7.

[3]. Courtney R, et al. Modulation of 11beta-hydroxysteroid dehydrogenase (11betaHSD) activity biomarkers and pharmacokinetics of PF-00915275, a selective 11betaHSD1 inhibitor. J Clin Endocrinol Metab. 2008 Feb;93(2):550-6.

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